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* TH = Thursday, FR = Friday, SA = Saturday
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The presenting author's name is underlined.

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- Basic/Clinical Science Sessions
- Clinical Practice Sessions
- Translational Sessions
- Special Sessions
- Educational Symposia
- Oral Abstract Sessions
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TH-OR01
Heart-Specific LIM Protein (CSRP3) as a Novel Cardiorenal Connector in Acute Cardiorenal Syndrome-Related CKD Progression
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Background: Cardiorenal syndrome type 1 (CRS1) is acute kidney injury (AKI) caused by acute cardiovascular disease. Our translational CRS1 model, cardiac arrest and cardiopulmonary resuscitation (CA-CPR) causes AKI-CKD transition characterized by reduced GFR, increased fibrosis, renovascular hypertrophy, and elevated blood pressure—CSRP3-induced AKI-CKD CRRACK. Heart specific LIM protein (CSRP3) is sequestered into blood stream by acute cardiac injury, and taken up by renal proximal tubular cells via megalin mediated endocytosis. We hypothesized that cardiac CSRP3 mediates CRRACK.

Methods: We generated inducible cardiac CSRP3 KO mice (iCSRP3KO, csrp3 fl/fl myh6 cre-esr1). CA/CPR (8min cardiac arrest) or 8min ischemia reperfusion injury (IRI) was performed to C57BL6 mice, inducible proximal tubules megalin KO mice (iMegKO), or iCSRP3KO mice. IRI mice were injected 5ug CSRP3 or PBS. GFR, αSMA expression, and renovascular wall thickness were analyzed at 49 days. Research-designed human kidney proximal tubular epithelial cell (PTEC) was used in vitro.

Results: iCSRP3KO mice did not express CSRP3 in myocardium. SnRNA sequencing of CA/CPR kidney and bulk RNA sequencing of CSRP3 treated PTEC demonstrated similar alteration of fibrosis and myogenesis related genes. CSRP3-treated IRI mice (CSRP3-IRI) demonstrated reduced GFR (785.0±96.6 vs 933.4±148.6 (ug/ml/100g), p<0.05), increased fibrosis (V SMA/V kidney: 2.3±2.09 μg vs 1.4±0.40, p<0.05) and renovascular hypertrophy (thickness index: 0.6±0.03 vs 0.5±0.03, p<0.01) compared with PBS-treated IRI mice. These CSRP3 induced phenotypic changes were attenuated by pharmacological megalin inhibition in CSRP3-IRI mice or iMegKO/CA-CPR mice. Compared with littermate control, deletion of cardiac CSRP3 ameliorated CA/CPR induced GFR loss (845.4±75.5, p<0.05) and BP elevation (122.8±13.3 vs 148.6±96.6, p<0.05) (Mean±/SD, Student's t-test).

Conclusions: Cardiac CSRP3 mediates renal fibrosis and myogenesis leading to CRRACK. We report a novel mechanism of CRS1 induced AKI-CKD transition.

Funding: Veterans Affairs Support

TH-OR02
The Epidermal Growth Factor Receptor Is an Essential Mediator of Interstitial Fibrosis Development Following AKI
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Background: In the kidney, tubulointerstitial fibrosis can result from incomplete recovery from acute kidney injury (AKI), toxic injury or other inflammatory insults. Activation of the Epidermal Growth Factor Receptor (EGFR) has been implicated as a potential mediator of interstitial fibrosis but underlying mechanisms of EGFR’s actions have not been previously addressed.

Methods: To delete EGFR selectively in the fibroblast/pericyte population, we generated PDGF-Rβ-Cre;ERT2; mCherry (WT) and PDGF-Rβ-Cre;ERT2; mCherry; EGFRβ (FibEGFRβ/−/) mice. Models of acute kidney injury included ischemia/reperfusion, UUO and fociate and adenine nephropathy. In vitro studies utilized immortalized mouse fibroblasts.

Results: In all models of acute injury, FibEGFRβ/−/ mice developed less tubulointerstitial fibrosis and isolated fibroblasts had decreased collagen mRNA expression. Fibroblast EGFR expression played an essential role in fibroblast migration and proliferation after injury. In cultured mouse fibroblast cells, EGFR activation induced proliferation but decreased expression of SMAβ3 and myofibroblast markers. TGF-β did not induce proliferation but reversed EGFR’s inhibition and stimulated myofibroblast differentiation. SnRNAseq confirmed decreased markers of fibroblast proliferation and cell motility and numbers of myofibroblasts in FibEGFRβ/−/ mice.

Conclusions: These studies provided evidence for a heretofore undescribed and important role for EGFR in kidney fibroblasts and pericytes as a specific mediator of interstitial fibrosis in response to kidney injury by stimulating peri- and fibroblast migration and proliferation.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR03
Prevention of Ischemia-Reperfusion Injury (IRI)-Induced AKI by Maintaining Na+/K+ ATPase Activity
Nadzihula N. Zheleznyov, Tamara A. Wahbeh, Lei Wang, Jie Zhang, Jin Wei, Nathan Hall, Nohely Hernandez Soto, Bo Chen, Wei Chen, Ruisheng Liu.

Background: IRI impairs Na+/K+ ATPase pump function leading to cellular death. We developed a method using a 3rd Generation Synchronization Modulation Electric field (SMEF) to optimize Na/K ATPase activity during ischemia (Sci Trans Med. 2022). Now, advanced to a 4th Generation SMEF, we have incorporated dual-energy transformation functions and power injections for ATP generation, hypothesizing that it will more efficiently combat ischemia-reperfusion-induced acute kidney injury (AKI).

Methods: Male and female C57BL/6J mice were divided into 3 groups: sham control, AKI without 4th-SMEF, and AKI with 4th-SMEF. A right nephrectomy was performed, followed by warm ischemia induction by clamping of the left renal pedicle (20 min in males vs. 25 min in females). In the 4th-SMEF group, an electric field was applied to the left kidney pre-clamping. Plasma creatinine (Day 1,3,7), Glomerular Filtration Rate (day 7), KIM-1, and Na/K pump activity and expression were evaluated. A histological kidney tissue examination was conducted.

Results: The 4th-SMEF reduced plasma creatinine by 92% in males (4th-SMEF:0.21±0.10 mg/dL, untreated AKI 1.2±0.6 mg/dL) and 98% in females (4th-SMEF:0.34±0.3 mg/dL, untreated AKI 1.8±0.4 mg/dL), displaying similitude to sham groups. This outperforms the previous 3rd-SMEF approach, decreasing plasma creatinine by only 40% (Chen, 2022). GFR showed 60% improvement in males (4th-SMEF:255 µl/min, untreated AKI:110 µl/min) and 55% improvement in females (4th-SMEF:220±/min, untreated AKI:98±/min). KIM-1 marker in the AKI-untreated group, the sham, and 4th-SMEF-treated groups showed: (271±30 mg/ml, 60±9 mg/ml, and 66±21 mg/ml) respectively. Baseline Na/K expression is higher in females. AKI groups of both genders exhibited reduced activity, expression, and association, alongside cellular relocation. With 4th-SMEF, both genders reached equalized Na/K pump activity and degradation reduction. Histology conveyed diffuse renal tubular necrosis and casts comprising necrotic cells and debris in AKI groups. In contrast, the 4th-SMEF treatment essentially normalized the histopathologic changes aided cellular relocation.

Conclusions: 4th-SMEF prevented AKI by equally normalizing Na+K pump activity in both genders of mice, leading to similar prevention of IRI-induced AKI.

Funding: NIDDK Support

TH-OR04
Analysis of the Immune Cell Landscape Identifies Immunosenescence as a Therapeutic Target in Rhabdomyolysis-Induced AKI
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Background: Rhabdomyolysis (RM) accounts for 10% of the acute kidney injury (AKI) cases. The role of macrophages in the development of RM-AKI lesions has clearly been established, but a high resolution understanding of the changes in the immune landscape could help to improve targeted strategies.

Methods: Single-cell RNA sequencing was used in the murine glycol-erinduced RM-AKI model to dissect the transcriptomic characteristics of CD45+ live cells sorted from kidneys 2 days after injury. A combination of senolytics (dasatinib and quercetin) was administered to mice exposed or not to RM-AKI.

Results: Unsupervised clustering of nearly 17,000 single-cell transcripts identified 7 known immune cell clusters. Sub-clustering of the mononuclear phagocyte cells (MPC), including monocytes, macrophages and dendritic cells, revealed 9 distinct cell sub-populations differentially modified with RM. One macrophage cluster was particularly interesting since it behaved as a critical node in a trajectory connecting one MCHIIhigh cluster only present in control to 2 MCHIIlow clusters only present RM-AKI. Because this crucial cluster expressed senescence hallmark genes, the effect of combined dasatinib and quercetin (DQ) senolytics treatment was evaluated. DQ treatment in RM-AKI improved kidney function and blocked the known phenotypic switch from F4/80high to F4/80low.

Conclusions: scRNAseq identified novel renal myeloid subtypes after RM-AKI and unmasked a transition macrophage population affected by cellular senescence processes. This work provides a proof-of-concept that immunosenescence occurs during AKI and that senolytics deserve attention as potential nephroprotective drugs.
Novel Anti-Inflammatory Effects of IL-1 Receptor in Kidney Myeloid Cells Following AKI

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Background: Acute kidney injury (AKI) is a leading cause of organ failure in hospitalized and critically ill patients. Following AKI, the canonical pro-inflammatory cytokine interleukin-1β (IL1β) is released predominantly from activated myeloid cells and binds to the interleukin-1 receptor 1 (IL1R1). IL1R1 activation is known to amplify the immune response and exacerbate AKI. However, the specific role of IL-1R1 on myeloid cells during AKI is poorly understood. Our objective was to study the function of myeloid cell IL-1R1 during AKI. As IL1R1 is known to signal through the pro-inflammatory Toll-like receptor (TLR)/MyD88 pathway, we initially hypothesized that myeloid cell IL1R1 activation would exacerbate AKI.

Methods: IL1R1 was selectively depleted in CD11c+ myeloid cells with CD11cCre/+ / Il1r1fl/fl mice. IL1R1fl/fl and littermate controls were co-cultured with IL1R1−/− or LPS) exhibited higher mRNA levels of inflammatory markers.

Results: Surprisingly, compared to IL1R1−/− mice, IL1R1fl/fl mice displayed exaggerated ER-induced kidney injury, as indicated by elevated levels of serum creatinine (mean ± SD: 1.24 ± 0.85 vs. 2.06 ± 1.17 mg/dl, p<0.05), and histologic injury scoring. In support of these findings, in vitro co-culture studies showed that RT co-cultured with IL1R1−/− BMDC, which exhibited higher mRNA levels of the kidney injury marker neutrophil gelatinase-associated lipocalin (NGAL) than those with IL1R1-/- BMDC. Furthermore, we observed that IL1R1 activation on IL1R1−/− BMDC preferentially augmented expression of anti-inflammatory mediators tumor necrosis factor alpha receptor alpha induced protein 3 (A20) and interleukin-1 receptor antagonist (IL1Ra) in IL1R1-/- BMDC, effects that were abrogated by IL1R1 activation would exacerbate AKI.

Conclusions: Our findings suggest a novel function of IL1R1 is to serve as a critical negative feedback regulator of IL1 signaling in CD11c+ cells to dampen inflammation and limit AKI. Our results lend further support for cell-specific, as opposed to global, targeting of immunomodulatory agents.

Funding: NIDDK Support, Other NIH Support - NIGMS, Veterans Affairs Support

Spatial Multi-Omic Atlas of Pyelonephritis

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Background: Pyelonephritis (PN) causes renal injury, inflammation, and scar formation. Over 80% of PN episodes are due to uropathogenic Escherichia coli (UPEC). The molecular mechanisms of acute kidney injury and renal fibrosis in PN patients are poorly understood, hindering the development of effective therapies.

Methods: We infected female C3H/HeOu mice via transurethral inoculation with UPEC. Spatial transcriptomics (5T, Vismax 10x genomics, and PIPseq) of single-cell RNA-sequencing (scRNA-seq) was performed on kidney tissue sections at 5, 17, and 28 days post infection. The integrative analysis encompassed pathological evaluation, cell type annotation, spatial deconvolution, differential gene expression, cell-cell communication, pseudotime inference, and signaling pathway exploration, aiming to unravel the dynamic structure and molecular changes during PN.

Results: We characterized 20,831 spatial spots with deconvoluted cell-type compositions at six timepoints. We profiled 40,224 single cells representing 18 major cell types and identified infected proximal tubule cells with distinct cell-cycle and cell-signaling signatures. This approach revealed that both T cell-mediated and innate responses target different subsets of tissue abscesses that were specific to the infection and associated with fibrotic injury, repair, and remodeling. These abscesses exhibited increased levels of colonization between leukocytes, fibroblasts, and endothelial cells after infection, along with activations in leukocyte migration and proliferation, T cell activation, TNF-α signaling, and cell-cell adhesion. Signaling analyses unveiled unique spatial dependencies in hypoxia, apoptosis, proinflammatory responses, profibrotic and proliferative processes. The marginal regions of the renal abscess displayed dramatically increased activation in NF-κB, TNF-α, EGFR, and P53 signaling pathways, but decreased STAT and Wnt pathway activity.

Conclusions: Our study provides an integrative map of the spatial gene expression and gene-regulation networks involved in maintaining kidney homeostasis and anti-fibrotic responses during PN. We believe our findings will contribute to the advancement of mechanistic insights and potential therapeutic strategies to treat PN.

Funding: NIDDK Support

The Kidney-Gut-Brain Axis in AKI

Jihyun Yang,1 Young Eun Choi,2 Sungyeon Kim,2 Suk Min Chung,2 Yookyung Jang,1 Ko Yoon Sook,1 Lee Hee Young,1 Tai yeon Koo,2 Sewon D. Kim,2 Myung-Gyu Kim,1 Sang-Kyung Jo.1 Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea; 2Korea University, Seongbuk-gu, Republic of Korea.

Background: Although epidemiological studies suggest that long-term survivors of dialysis requiring AKI have had increased risk of dementia, its underlying mechanisms remain uncertain. Based on recent data showing kidney-gut crosstalk mediated by immune modulation in AKI, we hypothesized that gut dysbiosis and aberrant gut immune response might contribute to the cognitive dysfunction following AKI.

Methods: In mouse long-term AKI survival model (1yr after kidney ischemia-reperfusion injury (IRI)), we initially hypothesized that myeloid cell IL1R1 activation would exacerbate AKI. By using RankCre, and RanknaCre (Regnase3fl/fl) mice. Upon these mice, we applied a range of kidney injury models involving unilateral ischemia-reperfusion and nephrocalcinosis. Furthermore, scRNA-seq and RNA-seq were utilized to examine the role of Regnase3 in RTEC. Through in silico, we found that Regnase3 is highly expressed in the kidney and brain in long-term AKI mouse model.
of RTEC. Regnase3 targets pre-RNA and modulates alternative splicing by increasing skipped exon events and decreasing the probability of retained intron events.

Conclusions: Regnase3 contributes to kidney injury but the impact of it is contingent upon the specific cell lineage in question. The RankCre-Regnase3fl/fl leads to an exacerbation of kidney injury by increasing pro-inflammatory M2 recruitment, whereas the Pax8Rta-TetCre-Regnase3fl/fl leads to an improvement after injury through its effects on cell death and RTEC repair.

TH-OR09

Role of YB-1 in the Early Pathogenesis of Acute Respiratory Distress Syndrome (ARDS) and Associated Renal Damage

Anna Lett,1 Daniela Herrnert,1 Vera Jankowski,2 Yingying Gao,3 Xiayan Liu,4 Marcus Schultz,2 Jürgen Floege,1 Stefan Uhlig,1 Tammo Ostendorf,1 Lucy K. Reiss,1 Ute Raafstedt,1 1Universitätsklinikum Aachen Klinik fü R Nierener- und Hochdruckkrankheiten rheumatologische und immunologische Erkrankungen, Aachen, Germany; 2Department of Intensive Care, Amsterdam University Medical Centres, Amsterdam, Netherlands; 3Universitätsklinikum Aachen Institut für Molekulare Herz Kreislauf Forschung, Aachen, Germany; 4Institute of Pharmacology and Toxicology, Medical Faculty, RWTH Aachen, Aachen, Germany.

Background: Acute respiratory distress syndrome (ARDS) is a life-threatening lung impairment that is associated with a mortality of 25% up to 45%. It is caused by acute inflammation and currently patients with ARDS can only be stabilized by mechanical ventilation and intensive care. Acute kidney injury (AKI) is the most common extra-renal organ dysfunction associated with ARDS, affecting more than 35% of the patients. Proteins with alarm function, such as the highly conserved Y-box binding protein (YB-1), are good candidates for early progression of ARDS and the crosstalk between lung and kidney. YB-1 functions as a translation or transcription factor and is also involved in renal injury.

Methods: Mice were mechanically ventilated in a mouse intensive care unit (MICU). The role of YB-1 in murine ARDS and its effect on the kidneys was evaluated in a two-hit- (intratracheal (i.t.) application of hydrochloric acid & ventilation) and a triple-hit- (hydrochloric acid i.t., lipopolysaccharide (LPS) i.t., & ventilation) model in heterozygous Yb1-deficient (Yb1+) mice and after i.t. application of recombinant YB-1 protein. In addition, tracheal secretion, urine and serum from ARDS patients were analyzed for (post-translationally modified) extracellular YB-1 by mass spectrometry.

Results: In both models, Yb1+ mice were protected in terms of pulmonary inflammatory parameters. In the two-hit model, the improved lung function in the Yb1+ mice deteriorated to wild-type (WT) level by additional i.t. application of recombinant YB-1. Interestingly, however, heterozygous YB-1 deficiency in the kidneys led to more inflammatory responses, i.e. (i.t. instillation of LPS) with subsequent evidence of lung injury. Extracellular YB-1 in murine and human ARDS was post-translationally modified, and mass spectrometric analysis of ARDS patient samples showed a correlation of guanidinylated YB-1 levels in tracheal secretion/serum and disease severity.

Conclusions: Taken together, YB-1 expression in ARDS mouse models displays opposite effects on the inflammatory process in the primarily damaged lung and the secondarily affected kidney. In addition, the intratracheal or extracellular localization of YB-1 also determines its protective or destructive character.

Funding: Government Support - Non-U.S.

TH-OR10

Injured Tubular Epithelia-Derived CCN1 Promotes the Mobilization of Fibroblasts Toward the Injury Sites at the Acute Phase After Kidney Injury

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Background: Renal fibrosis is associated with the progression of renal injury. Conversely, the function of fibroblasts is indispensable for the reconstruction of normal tissue structure following injury in various organs. Consequently, the humoral factors that prompt fibroblasts to migrate to the injury site at an appropriate time point are deemed indispensable. Hence, the precise mechanisms that influence fibroblasts and promote migration to the tissue-injured site remain unclear.

Methods: To exploit on the paracrine effects on fibroblasts (NRK49F), we subjected them to treatment with conditioned medium (CM) derived from either normal or injured tubular epithelial cells (NRK52E). Based on the transcriptomics data, we identified Cellular Communication Network Factor 1 (CCN1) signaling as a candidate and analyzed its impact on kidney injury.

Results: The CM from injured NRK52E expedited NRK49F chemotaxis and proliferation. Based on the transcriptional analysis, we identified and validated CCN1 expression in fibroblasts surrounding injured tubular epithelial cells as well as the expression in fibroblasts originating from tubule-derived fibroblasts in the injured kidneys. Fibroblasts treated with CM from injured NRK52E with CRISPR-mediated CCN1 knockout (CCN1-/-) reduced migration and proliferation of fibroblasts from injured kidneys. Fibroblasts treated with CM from injured NRK52E with CRISPR-mediated CCN1 knockout (CCN1-/-) reduced migration and proliferation of fibroblasts from injured kidneys. Fibroblasts treated with CM from injured NRK52E with CRISPR-mediated CCN1 knockout (CCN1-/-) reduced migration and proliferation of fibroblasts from injured kidneys.

Conclusions: The CM from injured NRK52E accelerated fibroblast migration toward the injured kidneys. This acceleration was not observed in the CM from CRISPR-treated NRK52E with CCN1 knockout, suggesting that mobilized fibroblasts by tubule-derived CCN1 may impede the expansion of tubular injury.

Background: The kidney plays a critical role in maintaining systemic homeostasis, yet our current understanding of species differences, health states, and changes in disease states remains limited. Owing to the kidney’s complex cellular architecture, single-cell transcriptomics can provide pivotal insight into these processes.

Methods: We processed seven large renal single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics datasets derived from healthy and disease-affected mouse, rat, and human samples. Following meticulous quality controls, we harmonized gene symbols and integrated data using deep generative modeling (seV). A variety of computational tools were utilized to comprehend cell type conservations as well as species and disease state-specific changes.

Results: We present the first comprehensive, fully integrated interspecies renal single-cell atlas, comprising more than 140 samples and over 1 million cells - the largest kidney cell atlas to date. Our atlas uncovers over 100 distinct cell states, providing a detailed understanding of conserved biological functions, marker genes, species-specific differences, and cellular adaptations in response to disease. Conserved cell types were also conserved upon positioning using spatial transcriptomics data. By employing the concept of Differentially Expressed Gene Ontology terms (DEGOs) – which focus on mean expression values for functional gene sets rather than individual genes – we highlighted the conserved renal physiology at the single-cell and spatial level. We observed notably fewer heterogeneity tubule S3 segment cells in the human kidney compared to rodents. We identified a conserved injured proximal tubule subset with its unique markers. Additionally, we discovered novel cell types in the loop of Henle cluster expressing developmental process-related gene signatures.

Conclusions: This comprehensive kidney single-cell atlas serves as a valuable resource for discerning a consistent set of cell types across species with standardized cell terminology. It enables a deeper understanding of kidney biology and paves the way for developing novel therapeutic strategies.

Funding: NIDDK Support

TH-OR12

Extracellular miRNAs as Predictors of CKD Progression

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Background: Kidney fibrosis is final common pathway downstream of most renal injuries that contributes to progressive chronic kidney disease (CKD). Noncoding RNAs represent potentially useful fibrosis through the repression and/or expression of matrix genes and TGF-β signaling. We hypothesized that specific circulating microRNAs (miRNAs) are indicators of underlying kidney fibrosis and can serve as early biomarkers for CKD progression.

Methods: The study was performed using patient samples/clinical data from the Chronic Renal Insufficiency Cohort (CRIC) cohort (n= 3,471). The slowest and fastest progressors of CKD were defined based on the largest and smallest negative slope of eGFR change over time, using within-subject ordinary least-squares regression of follow-up eGFR readings. Next Generation Sequencing (NGS) was performed to identify miRNAs associated with CKD progression. Circulating RNAs from plasma samples were isolated and sequencing was performed on NovaSeq platform (Illumina, Inc). The raw counts, mapping, and differential expression analysis was done using R Bioconductor packages. The top 500 genes with highest variance were used for principal component analysis and 35 genes with highest variance across samples were selected for hierarchical clustering. The biological effects, mechanisms and functions of identified miRNAs were analyzed using Ingenuity Pathway analysis.

Results: Global extracellular miRNA expression analysis showed presence of 1,888 miRNAs in plasma. Differential analysis using generalized linear models (GLMs) in edger was performed to identify the miRNA associated with rapid progression adjusting for sex, ethnicity, diabetes status, UAC Ratio and EGFR levels. Expression of 8 miRNAs were enriched (p=1.19E-179, p=1.19E-179, p=1.19E-179, p=1.19E-179, p=1.19E-179, p=1.19E-179, p=1.19E-179, p=1.19E-179) varied significantly between fast and slow progressor groups. This differential expression of miRNAs between the two groups was significantly modulated by ethnicity and diabetic status of patient. Biomimetic analysis showed pivotal role of these miRNAs in variety of important cell activities such as apoptosis, organ fibrosis, autophagy, metastasis etc.

Conclusions: This study identifies extracellular miRNAs that can serve as indicator of CKD progression. Identification of specific miRNA pathways for CKD progression will enhance diagnostic, enable risk stratification and lead to targeted interventions.

Funding: NIDDK Support
TH-OR13
Alternative Splicing in CKD
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Background: Alternative splicing (AS) is a process that can lead to variable genotype expression. The primary forms are exon skipping, intron inclusion, alternative 5' and 3' splice sites. The role of alternative splicing of VEGF has been shown to play an important role in chronic kidney disease (CKD) development, however a comprehensive assessment of VEGF AS motifs has not been undertaken yet.

Methods: Human kidney tissue (n=410) was collected from nephrectomies of healthy subjects and patients with diabetic or hypertensive CKD. Clinical demographics information was collected via honest broker and histopathology was analyzed in an unbiased manner to be nephroitic in renal models. RNA was extracted from the tubular compartment and sequenced. RNA-seq reads were aligned to the human genome using STAR 2.7.3. Outliers identified by Mahalanobis distance. Aligned BAM files were sorted and indexed using Samtools v1.17 and junctions were extracted using RegTools v 1.0. Differential splicing for was analyzed separately using leafcutter v 0.2.7 and adjusted for age, sex, race, and RNA quality indices (RNA integrity number, 5'-3' bias, 5'rsibosomal, total reads).

Results: When comparing healthy samples to those with eGFR of less than 60 cc/ min/1.73m2 (CKD stage 3-5), we identified 31 intron cluster alternative splicing events at an adjusted p-value of 0.05. 26 of these were previously annotated. Pathway analysis using gene ontology (GO) terms showed enrichment for cell death and metabolic pathway. When comparing samples with less than 10% fibrosis to those with greater than 10% fibrosis, we identified 239 alternative differential splicing clusters. 23 of these were previously annotated. Pathway analysis using GO terms demonstrated these genes were enriched in the metabolic and immune pathways.

Conclusions: Large number of differential splicing events were observed compared to controls with enrichment in the metabolic and immune pathway genes.

TH-OR14
Adenine Accumulation Induced by Hypoxia in Kidney Organoids
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Background: Kidney disease progression is thought to result from a multitude of metabolic and genetic changes, including hypoxia and adenine. Adenine-rich diet has previously shown to induce nephrotic in rodent models. Recently, a pathway contributing to endogenous adenine production was identified (manuscript in revision). We explored the association between adenine, kidney hypoxia and kidney injury using a human kidney organoid system with multi-omic analysis.

Methods: Kidney organoids generated from human pluripotent stem cells and sectioned and evaluated by MALDI-mass spectrometry imaging (MSI) using DAN matrix (Collagen I) and growth arrest (p21cip1) were quantified by immunofluorescence (IF), and increased activated myofibroblasts. IF confirmed increased renal fibrosis at D7 in TG vs WT (Collagen1 1.1 ± 0.3 vs 3.1 ± 0.5, p<0.005). By D42, scRNAseq analysis demonstrated clearance of cdkn1a+ senescent epithelium, recruited leukocytes and increased activated myofibroblasts. IF confirmed increased renal fibrosis at D7 in TG vs WT (Collagen1 1.1 ± 0.3 vs 3.1 ± 0.5, p<0.005).

Intracellular Fibrosis >0.1

Conclusions: Our results demonstrate that epithelial senescence is profibrotic in absence of injury to other cell types. Of importance, metabolic and immunologic indices in the adult male allow detection of disease progression and prevent ongoing fibrosis. Understanding how these pathways are lost with age and chronic injury may lead to new routes to promote clearance of profibrotic senescent epithelium.

TH-OR15
Induced Senescent Cells Recruit Leukocytes and Permit Their Own Clearance from Healthy Young Kids
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Background: Increasing evidence links senescent epithelia to fibrosis and functional loss in experimental and human kidney disease. Whether senescent cells themselves are sufficient to initiate and sustain kidney fibrosis is unknown. We hypothesised that induction of epithelial senescence alone, in absence of other renal injuries, is sufficient to initiate and sustain fibrosis.

Methods: We generated a Pax4creERT2;tm2dm2 fl/fl mouse (‘TG’) via a cross of two established strains and treated these and wild type (WT) mice with tamoxifen by oral gavage to induce epithelial restricted senescence via tm2dm2 deletion. Markers of fibrosis (Collagen I) and growth arrest (p21cip1) were quantified by immunofluorescence (IF), and total collagen by picrosiris red. Full transcriptomic analysis was undertaken using scRNA-seq (10X).

Results: Tamoxifen resulted in p21cip1 induction in renal epithelia in TG but not in wild WT mice by IF (10.45 ± 2.9 vs 3.15 ± 0.7, p<0.05). On scRNA-seq, TG (but not WT) kidneys contained transcriptionally distinct, cdkn1a+ epithelia, recruited leukocytes and increased activated myofibroblasts. IF confirmed increased renal fibrosis at D7 in TG vs WT (Collagen1 1.1 ± 0.3 vs 3.1 ± 0.5, p<0.005). By D42, scRNAseq analysis demonstrated clearance of cdkn1a+ senescent epithelium, normalisation of leukocyte counts and resolution of myofibroblast activation in TG kidneys, with confirmation by IF; showing no difference in p21cip1 levels between WT and TG mice (2.4 ± 1.4 vs 4 ± 1.1, p>0.7) and no progressive fibrosis.

Conclusions: Our results demonstrate that epithelial senescence is profibrotic in absence of injury to other cell types. Of importance, metabolic and immunologic indices in the adult male allow detection of disease progression and prevent ongoing fibrosis. Understanding how these pathways are lost with age and chronic injury may lead to new routes to promote clearance of profibrotic senescent epithelium.

TH-OR16
Identification of Noninvasive Biomarkers Reflecting Cellular Mechanisms of Endothelin A (ETA) Receptor Activity and Atrasentan Response in CKD
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Background: Endothelin pathway activation contributes to disease progression across multiple CKD etiologies. Atrasentan is a potent and selective endothelin A receptor (ETA) antagonist that has demonstrated rapid and sustained reductions in proteinuria, preservation of kidney function and improved kidney outcomes in diabetic kidney disease patients. Single cell transcriptomic characterization of a preclinical mouse model of IgA nephropathy revealed specific ETA, activity and atrasentan responses associated with proximal tubular failed repair (FR-PTs). We conducted an analysis of patient-matched kidney biopsies and biofluids from the NURTuRE cohort with the aim to identify non-invasive biomarkers of ETA receptor activity and atrasentan responses in CKD mechanism.

Methods: Serum (n=99) and urine samples (n=22) from the NURTuRE biobank were assayed using Olink and SomaScan proteomics platforms, respectively. Patient-matched kidney biopsies for each sample were analyzed by RNA-Seq and scored for a gene signature reflecting atrasentan responses in the gddY mouse model. Correlation analysis of 16/173 serum and 12/174 urine proteins with kidney mRNA expression and atrasentan response scores suggested candidate non-invasive biomarkers for further validation (r ≥ 0.4 and p < 0.05).

Results: Proteomic analysis identified 173 serum and 174 urine proteins significantly correlated with atrasentan response score in CKD patients. Strong positive correlation of 16/173 serum and 12/174 urine proteins with kidney mRNA expression suggests these proteins could originate from the kidney. Importantly, the majority of the respective genes were expressed by FR-PTs or immune cells, likely reflecting
mechanisms of ETA activation and atrasentan response in the kidney inflammatory and fibrotic environment.

Conclusions: This study identified potential biomarkers reflecting cellular mechanisms of ETA activation and atrasentan response in the NURTuRE CKD cohort. These biomarkers may be useful in assessing and differentiating cellular responses in atrasentan-treated CKD patients. To validate these initial findings, serum and urine collected at baseline and following treatment in the AFFINITY iGan cohort are currently being analyzed.

Funding: Commercial Support - Chinox Therapeutics, Evotec SE

TH-OR17
LACTB Is a Kidney C Mitochondrial Metabolism

Background: Genome-wide association studies (GWAS) have identified hundreds of loci where genetic variants are associated with kidney function. However, the causal variants, genes, cell types, and disease mechanisms remain mostly unknown.

Methods: We integrated GWAS, human kidney expression of quantitative trait analysis using Bayesian colocations, transcriptome-wide association studies, and summary-based Mendelian randomization studies to identify likely causal genes for kidney function. We used single-cell RNA and ATACseq data to identify causal cell types. Finally, we generated mice with genetic deletion to study kidney disease mechanisms.

Results: We identified serine beta lactamase-like protein (LACTB) as a kidney disease risk gene. LACTB is expressed in kidney tubule cells. LACTB knockout mice were more susceptible to acute and chronic kidney injury induced by cisplatin and folic acid. LACTB knockout mice had lower cardiopulmonary levels and abnormal mitochondria morphology, causing elevated mitochondrial injury and activation of the cytosolic nucleotide sensing pathways (cGAS-STING) with an increment of inflammation. Cardiolipin is a crucial lipid for maintaining mitochondrial morphology and function. Additionally, we discovered that as a protease, LACTB cleaves PLA2G6, an enzyme involved in cardiolipin biosynthesis, generating a more active fragment that promotes cardiolipin production.

Conclusions: In summary, the integration of GWAS, epigenome analysis, mouse models, and cultured cell systems has identified LACTB as a causal gene for kidney disease. LACTB plays a crucial role in regulating cardiolipin metabolism, mitochondrial function, and inflammation.

Funding: NIDDK Support

TH-OR18
Glutathione-Specific γ-Glutamylcysteine Transferase 1 (CHAC1) Is a Kidney Disease Risk Gene by Controlling Ferroptosis

Background: Despite GWAS identified over 800 loci associated with kidney function, the specific genes, cell types, and mechanisms influenced by these genetic variants largely remain unexplored. In our research, we leveraged human kidney gene expression and methylation quantitative trait data, as well as human kidney single nuclear expression of quantitative trait analysis using Bayesian colocations, transcriptome-wide association studies, and summary-based Mendelian randomization studies to identify likely causal genes for kidney function. We used single-cell RNA and ATACseq data to identify causal cell types. Finally, we generated mice with genetic deletion to study kidney disease mechanisms.

Methods: We integrated GWAS, human kidney expression of quantitative trait analysis using Bayesian colocations, transcriptome-wide association studies, and summary-based Mendelian randomization studies to identify likely causal genes for kidney function. We used single-cell RNA and ATACseq data to identify causal cell types. Finally, we generated mice with genetic deletion to study kidney disease mechanisms.

Results: We identified serine beta lactamase-like protein (LACTB) as a kidney disease risk gene. LACTB is expressed in kidney tubule cells. LACTB knockout mice were more susceptible to acute and chronic kidney injury induced by cisplatin and folic acid. LACTB knockout mice had lower cardiopulmonary levels and abnormal mitochondria morphology, causing elevated mitochondrial injury and activation of the cytosolic nucleotide sensing pathways (cGAS-STING) with an increment of inflammation. Cardiolipin is a crucial lipid for maintaining mitochondrial morphology and function. Additionally, we discovered that as a protease, LACTB cleaves PLA2G6, an enzyme involved in cardiolipin biosynthesis, generating a more active fragment that promotes cardiolipin production.

Conclusions: In summary, the integration of GWAS, epigenome analysis, mouse models, and cultured cell systems has identified LACTB as a causal gene for kidney disease. LACTB plays a crucial role in regulating cardiolipin metabolism, mitochondrial function, and inflammation.

Funding: NIDDK Support

TH-OR19
Calprotectin Is Associated with Vascular Calcification and Cardiovascular Complications During CKD
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Background: In patients with chronic kidney disease (CKD), vascular calcification is considered a major risk factor of cardiovascular (CV) mortality. The mechanisms of vascular calcification are complex and treatment options remain limited. Serum proteome analysis could help identify novel actors and potential therapeutic targets.

Methods: In this observational, European, multicenter study, we included 112 CKD3-4 patients from Spain, 171 dialysis patients from Toulouse and La Reunion (France), 188 CHD5 patients from Sweden. Serum proteome analysis was performed using LC-MS/MS on a subset of 66 CKD3-4 patients. Circulating calprotectin concentration was validated in the serum or plasma from the full cohorts by ELISA. Calprotectin was associated with CV outcome (2-4 years of follow-up) or with vascular calcification score assessed by Von Kossa staining on a piece of epigastric artery collected during renal transplantation surgery. The effect of calprotectin on calcification was measured in primary human vascular smooth muscle cells (VSMCs) and mouse aortic rings. The anticalcific potential of calprotectin inhibitor paquinimod was studied in a 5/6 subtotal nephrectomy mouse model.

Results: We identified using serum proteome analysis and further validation by ELISA that calprotectin, a circulating damage-associated molecular pattern protein, was associated with vascular calcification, CV outcome and mortality in CKD and dialysis patients. In primary human VSMCs and mouse aortic rings, calprotectin exacerbated calcification. Treatment with paquinimod inhibited the pro-calcifying effect of calprotectin. Paquinimod also ameliorated calcification induced by serum of uremic patients in primary human VSMCs. Finally, treatment with paquinimod blocked vascular calcification in mice with chronic renal failure induced by 5/6 subtotal nephrectomy.

Conclusions: We identified calprotectin as a key factor associated with vascular calcification, CV outcome and mortality in CKD patients. Blockade of calprotectin by paquinimod might be a promising strategy to reduce the burden of vascular calcification in CKD.
Conclusions: In conclusion, glomerular damage increases filtration of PCSK9 and concomitantly megalin degradation, resulting in escalated proteinuria. Targeting PCSK9 may be beneficial to attenuate proteinuria-induced kidney injury in CKD.

Funding: Private Foundation Support

TH-OR21

Prediction of Kidney Failure Using Multiple Data Domains in Glomerulonephropathy: A CureGN Study
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Methods: Sequential ridge regression models using demographics (I), social determinants of health (SDOH; II), clinical (III), and pathology features (IV) were fitted to predict time to kidney failure (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m² or treatment by dialysis or transplant). Discrimination was assessed by integrated area under the curve (iAUC); variables were ranked by absolute value of standardized coefficients.

Results: The kidney failure rate was 2.9 per 100 person years in 2,544 CureGN participants. 36 predictors were included (7 base, 2 socioeconomic, 27 clinical). Discrimination was similar between models I and II (iAUC=0.89) and higher for model III (iAUC=0.91). eGFR, urine protein to creatinine ratio, age, Black race, and FSGS were highly ranked across models I-III; the ranking of Black race was lower in model III (Figure). Medicaid as primary insurance, hypertension, renin angiotensin system inhibitor use, and serum albumin and urea nitrogen levels were highly ranked in model III. In model IV (n=670), interstitial fibrosis/tubular atrophy (IFTA), presence of tubular microcysts, and sclerotic glomeruli ranked as top predictors, displacing Black race, and reducing ranking of age and FSGS.

Conclusions: Machine learning improves prediction of kidney failure through incorporation of novel data domains. In CureGN, addition of these data improved prediction for kidney failure across conventional diagnostic categories and detected novel predictors that displaced traditional risk factors.

Funding: NIDDK Support

TH-OR22

Plasma Metabolic Profiles and Clinical Outcomes in Focal Segmental Sclerosis (FSGS) and Minimal Change Disease (MCD)
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Background: Metabolomics is a powerful approach to investigate the relationship between disease mechanisms and patients’ phenotype. However, the association between plasma metabolic profiles and clinical outcomes of focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) has not been studied well.

Methods: Plasma samples from 135 FSGS/MCD participants in the Nephrotic Syndrome Study Network (NEPTUNE) were studied. Samples were collected within 45 days from kidney biopsy. Untargeted metabolomics data were obtained using liquid chromatography mass spectrometry (LC-MS). We performed rigorous preprocessing to identify metabolites, remove outliers, and impute missing values. Outcomes with our interest were time to complete remission of proteinuria (UPCR<0.3) and, time to composite renal outcome (40% decline of eGFR or ESKD). Metabolites associated with clinical outcomes were selected by Cox-Elastic Net algorithm. Among the selected metabolites, a hypergeometric test was performed to identify the enriched metabolite categories.

Results: Among the 135 participants, 85 (63.0%) were male, 49 (36.3%) were pediatric and 81 (60.0%) were FSGS. Median UPCR level was 1.65, and 42 (31.1%) demonstrated nephrotic range proteinuria (UPCR>3.5). Median eGFR levels was 84.2

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
at the time of sample collection. During the follow-up period (median: 51 months), 47 achieved complete remission and 33 reached to composite renal outcome (CRO) metabolomics data, 371 high-quality named metabolites were analyzed. Cox-Elastic Net models selected 21 and 47 endogenous metabolites that associated with time to complete remission and eGFR decline or ESKD, respectively. Among 87 metabolite categories, hypergeometric tests revealed that Fatty esters and were associated with complete remission while Bile acids were associated with eGFR decline or ESKD.

**Conclusions:** Specific combinations of plasma metabolites, particularly included as lipids and lipid derivatives, were associated with clinical outcomes in FSGS/MCD, which could help to understand disease mechanisms and can be potential biomarkers to improve treatment strategies.

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

**TH-OR23**

**Idiopathic Glomerulopathy Is Associated with APOL1**

**High-Risk Genotypes or Mendelian Variants in Most Affected Individuals in a Highly Admixed Population**

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**Background:** Collapsing glomerulopathy (CG) is most often associated with fast progression to chronic kidney disease requiring renal replacement therapy (CKD-RRT). Its incidence is apparently higher in Brazil than in other countries, however the reason for this occurrence is unknown.

**Methods:** We performed an integrated analysis of clinical, histological, therapeutic, causative genetic and ancestry data in a highly genetically-admixed cohort with 70 idiopathic CG (ICG) patients, including children and adults. Genetic analyses included targeted-gene panel or whole exome sequencing and a high-density SNP array for ancestry assessment.

**Results:** The disease onset occurred at 23 (17.31) years and 51.4% of patients progressed to CKD-RRT 36 months after diagnosis. Causative genetic bases were identified in 58.6% of patients. Among these cases, 80.5% harbored APOL1 high-risk genotypes (HRG) and 19.5% causative Mendelian variants (MV). Self-reported non-White patients presented more frequently HRG. MV was an independent risk factor for progression to CKD-RRT at 36 months (HR: 2.583, 95%CI 1.151-7.076, p=0.024) and the end of follow-up (HR: 2.355, 95%CI 1.018-5.447, p=0.045). Older age at kidney biopsy and remission were independent protective factors against progression to CKD-RRT at 36 months (HR: 0.961, 95%CI 0.927-0.996, p=0.029; and HR: 0.230, 95%CI 0.085-0.623, p=0.004, respectively), and remission also at the end of follow-up (HR: 0.155, 95%CI 0.069-0.351, p=0.001). All HRG patients manifested CG at 9-44 years of age whereas in those with APOL1 low-risk genotype the disease arose throughout life. HRG associated with Asian ancestry accounted for 29% of those with CG in Brazil. Novel causative MVs were identified in COLA45, COQ2, and PLCE1 and previously described causative MVs in MYH9, TRPC6, COQ2, COLA43, and TTC21B. Three patients displayed HRG combined with a VUS (ITG54, LAM5 or PTPRO). MVs was associated with worse kidney prognosis.

**Conclusions:** Our data revealed that the genetic status plays a major role in ICG pathogenesis, accounting for more than half of cases in a highly-admixed Brazilian population.

**TH-OR24**

**Anti-Nephrin Antibody as a Potential Etiology in Primary Focal Segmental Glomerulosclerosis (FSGS)**

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**Background:** Minimal change disease (MCD) and primary FSGS have long been pondered to have shared pathogenesis representing a spectrum of different stages of podocyte injury and repair. Recent discovery of anti-nephrin antibodies (Ab) in MCD led us to hypothesize that anti-nephrin Ab may also be present in primary FSGS.

**Methods:** We retrospectively reviewed all native kidney biopsies performed at BWH from 1/2018-4/2022. We identified 52 cases of primary FSGS (diffuse or focal) with +IgG and were associated with complete remission while Bile acids were associated with eGFR decline or ESKD.

**Results:** Among the 52 cases, 14 had +IgG on IF (27%). There was no difference in the presence of collapsing lesion (36% vs. 45%, P=0.6), percentage of segmental sclerosis (7% vs. 8%, P=0.6) and IFTA (18% vs. 20%, P=0.7) between +IgG and -IgG groups. There was a trend towards enrichment of tip lesions in the +IgG group (21% vs. 11%, P=0.3). Among the 40 pts with available clinical data at biopsy, median proteinuria was significantly higher in the +IgG group compared to -IgG group (13 vs 8 g, P<0.01). Five pts with +IgG had anti-nephrin Ab tested during active disease and all were positive (Table 1); all 5 biopsies showed colocalization of the punctate IgG with nephrin (Figure 1).

**Conclusions:** Punctate IgG deposition that colocalizes with nephrin is also observed in patients with primary FSGS and correlates with circulating anti-nephrin Ab. This suggests that anti-nephrin Ab-mediated podocyte dysfunction may be a shared pathogenesis mechanism among MCD and primary FSGS.

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**Table 1**

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**Figure 1. Punctate IgG deposition with nephrin colocalization.**
TH-OR26

eGFR Decline in Patients with IgA Nephropathy Treated with Nefecon or Placebo: Results from the 2-Year NeflGard Phase 3 Trial

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Background: The novel targeted-release budesonide formulation Nefecon is designed to treat immunoglobulin A (IgA) nephropathy (IgAN) by downregulating IgA1 production in the distal ileum. 9-month data from the first 199 patients (pts) in the Phase 3 NeflGard trial demonstrated significant urine protein-creatinine ratio (UPCR) reduction and estimated glomerular filtration rate (eGFR) preservation with Nefecon vs placebo in pts with IgAN, as reported previously (Barratt J et al. Kidney Int 2023;103:391–402). Here, we present data for the complete study population from the full 2-year trial (9 months of treatment and 15 months of follow-up) comparing eGFR decline (measured as a confirmed 30% reduction in eGFR from baseline) in pts treated with Nefecon 16 mg/day vs placebo.

Methods: Pts (≥18 years) with primary IgAN, eGFR 35–90 mL/min/1.73 m², proteinuria ≥24 h despite renin–angiotensin system blockade, and blood pressure <140/90 mmHg, were eligible. A 30% reduction from baseline in eGFR (Chronic Kidney Disease Epidemiology Collaboration formula) was confirmed by 2 values.

Results: 364 pts were included in the full analysis set. The proportion of pts with a confirmed 30% eGFR reduction was lower in the Nefecon vs placebo arm (Figure). The time to a confirmed 30% reduction in eGFR from baseline (hazard ratio [HR] 0.45 [95% confidence interval 0.26–0.75]; p=0.0014 [1-sided]). A pre-specified supplementary analysis with rescue medication use included as an event yielded a similar result (HR 0.51). Baseline UPCR (<1.5 and ≥3.0 g/g, and stable GFR) within the 12 month period. Consistent with the short period of follow-up, no patients achieved CR. Serum albumin increased in 11/15 (73%) patients in C1 and 7/10 (70%) patients in C2.

Conclusions: In high-risk patients with high unmet need (previously relapsing or refractory to IST, among the highest eGFR titer in a therapeutic clinical study to date), Nefecon resulted in rapid, deep, and durable pALR2 responses with associated improvements in proteinuria and serum albumin. Depleting CD20–CD38+ plasma cells is a promising therapeutic strategy for treatment of PMN, including patients with high pALR2 titer.

Funding: Commercial Support - Human Immunology Biosciences Inc, MorphoSys AG

TH-OR27

Safety and Efficacy of Felzarz in Primary Membranous Nephropathy (PMN): Final Analysis of the M-PLACE Study

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Background: PMN, a common cause of nephrotic syndrome with serious sequelae, is characterized by deposition of pathergic autoantibodies forming immune complexes between podocytes and the basement membrane. Felzarz (Felza), a fully human IgG1 anti-CD38 mAb, binds to CD38 antigen and depletes plasmablasts and plasma cells, the source of pathogenic pALR2.

Methods: M-PLACE (NCT04145440), a PI/h2a multi-national study, assessed safety and efficacy of felza in 2 adult cohorts with pALR2+ PMN requiring immunosuppressive therapy (IST). Cohort 1 (C1) enrolled newly diagnosed or relapsed patients and Cohort 2 (C2) enrolled IST-refractory patients. Nine infusions (16 mg/kg) were given over 5 months with a total observation period of 12 months.

Results: Among 31 patients (C1: n=18; C2: n=13), baseline characteristics include (Mean (SD)); Age 57.5 (11.8) yrs, serum pALR2 titer 247.1 (259.3) U/mL, UPCR 6.2 (2.2) g/g, and serum albumin 26.8 (4.96) g/L. Most frequently reported TEAEs were infusion reactions in 9 patients (29.0%); 5 patients (16.1%) had serious TEAEs. Twenty-three patients (74%) achieved immunological response of ≥50% pALR2 reduction, with 8 (26%) achieving complete immunological response (pALR2 changes shown in Fig. 1). Of the patients who received >5 Felza doses and no other IST, 7/15 (47%) patients in C1 and 2/11 (18%) patients in C2 achieved partial remission (UPCR reduction > 50%, UPCR < 3.0 g/g, and stable GFR) within the 12 month period. Consistent with the short period of follow-up, no patients achieved CR. Serum albumin increased in 11/15 (73%) patients in C1 and 7/10 (70%) patients in C2.

Conclusions: In high-risk patients with high unmet need (previously relapsing or refractory to IST, among the highest pALR2 titer in a therapeutic clinical study to date), Felza resulted in rapid, deep, and durable pALR2 responses with associated improvements in proteinuria and serum albumin. Depleting CD20–CD38+ plasma cells is a promising therapeutic strategy for treatment of PMN, including patients with high pALR2 titer.

Funding: Commercial Support - Human Immunology Biosciences Inc, MorphoSys AG

TH-OR28

Remission, Glucocorticoid Toxicity, Health-Related Quality of Life, and Safety Outcomes in Patients with Renal Involvement in the ADVOCATE Trial

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Background: In the Phase 3 ADVOCATE trial comparing avacopan to a prednisone taper, 81% of patients with ANCA-associated vasculitis (AAV) had renal involvement based on the Birmingham Vasculitis Activity Score. This renal subgroup had a baseline mean estimated glomerular filtration rate of 45.1 mL/min/1.73 m².

Methods: This post hoc analysis evaluated remission, glucocorticoid (GC) use, GC toxicity index (GTI), health-related quality of life (HRQoL by SF-36), and safety in patients with baseline renal involvement for those treated with avacopan (N=134) versus a prednisone taper (N=134).

Results: Compared to the overall study population, for this subgroup the mean age was similar (62 vs 61 years), but there was a slightly higher proportion of patients with GPA diagnosed AAV (74% vs 69%), myeloperoxidase-ANCA (63% vs 57%), microscopic polyangiitis (52% vs 45%), and use of cyclophosphamide (39% vs 35%). The avacopan group achieved a higher sustained remission rate at week 52 (67.9% vs 56.7%) while receiving a (mean/median) 2.4-/5.3-fold less total GC dose than the prednisone taper group (Table 1). The GTI cumulative worsening and aggregate improvement scores were lower at weeks 13 and 26 in the avacopan group compared to the prednisone group. At weeks 26 and 52 the avacopan group reported a greater improvement in SF-36 physical and mental component summary scores. Serious adverse events occurred in 60% (2 deaths) and 49% (3 deaths) of patients in the avacopan and prednisone groups, respectively.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: In the ADVOCATE trial, patients with AAV and baseline renal involvement treated with azathioprine achieved higher sustained remission rates while receiving less GCs, experiencing less GC-related toxicity, and reporting greater improvements in HRQoL versus those treated with a prednisone taper.

Funding: Commercial Support - Amgen

TH-OR29
Repeat Kidney Biopsies from the AURORA 2 Study of Voclosporin in Active Lupus Nephritis
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Background: Voclosporin is approved for the treatment of adults with active lupus nephritis (LN). Addition of voclosporin to MMF and low-dose glucocorticoids in the Phase 3 global AURORA studies led to significantly earlier and greater reductions in proteinuria while maintaining stable renal function. To characterize the long-term renal impact of voclosporin at the histologic level, we analyzed repeat kidney biopsies from a small subgroup of patients in these studies.

Methods: Patients in AURORA 1 who had biopsy-proven LN, UPCR ≥1.5 g/g (≥2 g/g for Class V), and eGFR ≥45 mL/min/m2 were randomized to voclosporin or control for 1 year in AURORA 1 and continued the same blinded therapy for 2 additional years in AURORA 2; all patients received MMF and low-dose glucocorticoids. A subset of patients had a kidney biopsy prior to screening and a repeat biopsy after approximately 18 months of therapy. Histopathologic grading according to NIH indices for LN activity and chronicity were assessed.

Results: Repeat biopsy samples were collected from 16 patients in the voclosporin arm and 10 patients in the control arm. Baseline mean activity scores were similar between arms, with scores improving with treatment in both arms. Mean chronicity scores were also similar between arms at baseline and remained stable over time in most patients. Measures of renal function remained stable in both arms over the 3-year follow-up. Voclosporin-treated patients had numerically greater mean reductions from baseline in UPCR year-on-year compared to patients in the control arm. Measures of renal function remained stable in both arms over the 3-year follow-up.

Conclusions: As expected, mean activity scores improved in both treatment arms. Importantly, exposure to voclosporin was not associated with chronic injury, with the mean index remaining stable at follow-up. Similar to the overall population, patients treated with voclosporin showed greater reductions in UPCR over 3 years of treatment; safety outcomes from this small subgroup were also consistent with outcomes in AURORA 1.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

TH-OR30
Kidney-Related Outcomes in Patients with Active Lupus Nephritis Treated with Obinutuzumab: A Post Hoc Analysis of the Phase 2 NOBILITY Trial
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Background: Preservation of long-term kidney function is a major therapeutic goal in lupus nephritis (LN). In the randomized, double-blind, placebo-controlled, Phase 2 NOBILITY trial (NCT02556652; PMID: 34615636), patients with proliferative LN receiving obinutuzumab with standard-of-care therapy showed clinically meaningful improvement in complete and overall renal responses at Weeks 52, 76 and 104 compared to those receiving placebo and standard-of-care therapy. We conducted a post hoc analysis of NOBILITY to assess kidney-related outcomes.

Methods: Cox regression analysis was conducted for the time to first kidney-related event (death, doubling of serum creatinine or treatment failure), LN flare and first 30% and 40% eGFR decline from baseline. The eGFR slope was assessed in a linear mixed-effects model.

Results: Obinutuzumab significantly reduced the risk of kidney-related events or death (HR, 0.40; 95% CI, 0.20 to 0.80), LN flare (HR, 0.43; 95% CI, 0.20 to 0.95) and first eGFR decline of 30% (HR, 0.20; 95% CI, 0.06 to 0.61) and 40% (HR, 0.09; 95% CI, 0.01 to 0.73) (Fig. 1). Risk of sustained eGFR decline of 30% and 40% was numerically lower, and a significant difference in attenuation of eGFR slope decline was observed between patients receiving obinutuzumab and standard-of-care therapy and those receiving placebo and standard-of-care therapy (annual slope difference, 4.10 mL/min/year; 95% CI, 0.14 to 8.08).

Conclusions: Obinutuzumab, in addition to increasing the possibility of achieving a complete renal response, numerically reduced the risk of kidney-related events. Obinutuzumab sequence time to first kidney-related event, time to LN flare and eGFR slope decline in a post hoc analysis, suggesting that obinutuzumab in combination with standard-of-care therapy may positively impact kidney-related outcomes. Obinutuzumab is being evaluated in patients with active proliferative LN in the global registrational Phase 3 REGENCY trial (NCT04221477).

Funding: Commercial Support - This study was funded by Genentech, Inc., a member of the Roche Group. Editorial assistance was provided by Health Interactions, Inc., and funded by F. Hoffmann-La Roche Ltd.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
levels, as well as a decrease in the fractional excretion of phosphate. These alterations were normalized by treatment with rapamycin. Normal mice with UNX or SNX exhibited increased renal FGF-1 expression and activation of the PI3K/AKT/mTOR pathway. Furthermore, these mice showed a reduction in renal Klotho expression and an increase in circulating FGF23 and phosphate. Both of these alterations were restored with rapamycin administration. In renal mice from CKD patients, we observed a positive correlation between the expression of PTEN, KLOTHO, and glomerular filtration rate (GFR).

Conclusions: The overactivation of the PI3K/AKT/mTOR pathway in PTEC contributes to elevated levels of intact FGF23 in these mice and prevents reductions in renal Klotho levels, potentially benefiting kidney disease patients.

Funding: Government Support - Non-U.S.

TH-OR32

Spatial Genomics Localized Neprhon Segment-Specific FGF23 and CKD Klotho-Dependent and -Independent Transcriptional Reprogramming Lainey M. Hibbard, Sheng Liu, Rafiu Agoro, Yamil Marambio, Kayleigh N. Jennings, Steven S. Welc, Jun Wan, Kenneth E. White. Indiana University School of Medicine, Indianapolis, IN.

Background: FGF23 acts in the kidney via Klotho (KLO) to control phosphate metabolism. However, in CKD, KL is lost and FGF23 is pathologically increased, disrupting mineral homeostasis. KL is expressed in multiple nephron segments, thus localization of FGF23 actions in the nephron remain unclear. Herein, we tested for novel FGF23 bioactivity localized with KL, as well as hypothesized that CKD alters FGF23/KL signaling and causes spatially unique transcriptional reprogramming.

Methods: Using spatial transcriptomics (ST) was performed on kidney sections from normal mice injected with FGF23 (250 ng/kg) for 1 or 4 h, and male mice with adriamycin induced CKD (0.2% for 4 weeks).

Results: The FGF23-injected and CKD kidney sections had >6900 genes/sequencing spot and formed 12 and 10 UMAP cell clusters, respectively. Mapping nephron segment markers showed clear demarcation of cortical and medullary gene expression. ST P1/S2 marker Slc2a5a was highly expressed in the cortex and S3 marker Ecil3 localized to the outer stripe of the medulla (OSOM). FGF23 increased MAPK-dependent transcription factor Erk1 more than 4 h. The vitamin D metabolic enzyme Cyp24a1 and Cyp27b1 mRNAs were increased or decreased, respectively. At 4 h and overlapped with KL, ST data was validated by qPCR and independent scRNAseq data from FGF23-injected mice. We also identified novel changes in response to FGF23, including increased cortical Cyp4b1 at 4 h, which CKD decreased. Mice with CKD had reduced KL mRNA and increased Cyp30b1. Consistent with CKD fibrosis, Col1a1, -12, -3a1, and -4a1 were ubiquitously increased, although Co3a1 was more focused to the inner stripe of the medulla (ISOM).

Further, pro-fibrotic Tgfb1 broadly increased, whereas its target Mmp7 increased in the ISOM. In contrast, damage and injury markers C3 and Havcr1 were restricted to the cortex and OSOM, respectively. Finally, evidence of wider immune infiltration was present in CKD with elevated neutrophil marker Lcn2, and macrophage markersCd68 and Ptprc.

Conclusions: Using ST, we identified unbiased, spatially identifiable effects of FGF23 bioactivity in kidney, including new potential FGF23 targets. We also localized pathologic KL-dependent and -independent CKD gene alterations that differentially occur in distinct cell populations.

Funding: NIDDK Support, Other NIH Support - R01-HL145528

TH-OR33

Role of mir-122 on FGF23 Cleavage Jane J. Thomas, John C. Von Drasek, Guillaume Courbon, Jaden J. Spindler, Aline Martin, Valentin David. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: In chronic kidney disease (CKD), iron deficiency and inflammation contribute to elevated levels of intact fibroblast growth factor 23 (iFGF23) by increasing FGF23 production. Proteolytic cleavage of intact fibroblast growth factor 23 (fFGF23) yields C-terminal FGF23 peptides (Cter-FGF23) that play a role in tissue iron deficiency anemia (IDA) and inflammation. O-glycosylation of fFG23 cleavage site by GALNT3 protects iFGF23 from cleavage, but the regulation of GALNT3 is unknown. We found that IDA increases the expression of mir-122-5p (miR122), which is a predicted inhibitor of fFG23. We hypothesized that inhibition of GALNT3 by miR122 results in increased iFGF23 cleavage in IDA.

Methods: Since mir122 is mainly produced by the liver, we generated mice harboring a conditional deletion of mir122 in hepatocytes (mir122ceKO) by crossing mir122 floxed mice with mice expressing a Cre recombinase driver in liver. We generated PT-PTerm-cre recombinase, in wild-type (WT) and Dmp1 knockout (Dmp1cKO) mouse model of ARHR.

Results: We deleted Fgf23 specifically in osteocytes (Fgf23+/−) using a Dmp1−/− recombinase, in wild-type (WT) and Dmp1−/− mice. In addition, we fed WT and Dmp1−/− mice a diet containing either 0.5% (NP) or 2% Pi (HP). In parallel, we cultured male mice with UNX or SNX exhibited further reduced levels of iron and transferrin saturation, but this did not aggravate the severe hypophosphatemia in these mice due to a positive correlation between the expression of PTEN, KLOTHO, and glomerular filtration rate (GFR).

Conclusions: Our results demonstrate that iron deficiency increases mir122, which inhibits osseous Galnt3 expression and results in increased FGF23 cleavage, elevated Cter-FGF23 but reduced iFGF23. mir122 could be a potential therapeutic target to reduce iFGF23 and thus improve adverse outcomes in early stages of CKD.

Funding: NIDDK Support

TH-OR34

Direct Effects of FGF23 on Osteoblasts Contribute to Bone Defects in Dmp1KO Mice Independently of Phosphate Dominik Kneutrup, Guillaume Courbon, Hao-Hsuan Spindler, Rachel S. Hassan,1 Nareen Khalaili,1 Rachel Levin,1 Oded Volovelsky,1 Morris Nechama,1,2,1 Tally Naveh-Mani,1 Hadassah Hebrew University Medical Center, Jerusalem, Israel; 2Jerusalem Collage of Technology LV Institute, Jerusalem, Israel.

Background: Fibroblast growth factor 23 (FGF23) is a phosphate (Pi)-regulating hormone produced in bone. Hereditary hypophosphatemic disorders are associated with FGF23 excess that leads to hypophosphatemia, impaired skeletal growth, rickets and osteomalacia. The blockade of FGF23 signaling to correct serum Pi levels has become a superior therapeutic strategy to Pi supplementation in X-linked hypophosphatemia, but remains untested in autosomal recessive hypophosphatemic rickets (ARHR). In this study, we focus on the effects of reducing circulating FGF23 levels using osteocyte-specific deletion of Fg23 (FGF23−/−) to the effects of dietary Pi supplementation in the Dmp1 knockout (Dmp1−/−) mouse model of ARHR.

Methods: We deleted Fgf23 specifically in osteocytes (Fgf23−/−) using a Dmp1−/− recombinase, in wild-type (WT) and Dmp1−/− mice. In addition, we fed WT and Dmp1−/− mice a diet containing either 0.5% (NP) or 2% Pi (HP). In parallel, we cultured primary osteoblasts isolated from WT, Fgf23−/− (Dmp1−/−) and Dmp1−/−Fgf23−/− mice and analyzed the direct impact of FGF23 and DMP1 on osteoblast differentiation and activity.

Results: Compared with WT mice and concurrent with successful Fg23 deletion, Fg23−/− mice showed reduced serum FGF23 levels and increased serum Pi levels, whereas Dmp1−/− mice displayed highly increased serum FGF23 levels, hypophosphatemia, impaired growth, rickets and osteomalacia. In contrast, Dmp1−/− Fgf23−/− mice showed a near complete correction of FGF23 excess, which fully restored serum Pi levels, but only partially corrected the bone phenotype. Compared to NP diet, NP diet increased circulating FGF23 levels, PTH levels, and phosphaturia in WT mice. HP-Dmp1−/− mice remained hypophosphatemic and showed exacerbated FGF23 production, hyperparathyroidism, and phosphaturia, resulting in a worsened bone phenotype. In vitro, we found that FGF23 directly impairs osteoblast differentiation and that DMP1 deficiency contributes to impaired mineralization independently of FGF23 or Pi levels.

Conclusions: To conclude, our data suggest that the direct effects of FGF23 and DMP1 on osteoblasts need to be considered to effectively correct ARHR-associated mineral and bone disorders, independently of hypophosphatemia.

Funding: NIDDK Support

TH-OR35

The Essential Roles of miRNA and mTORC1 in Parathyroid Function and in Maintaining Parathyroid Glands in the Adult

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Background: Secondary hyperparathyroidism (SHP) of CKD is a leading cause of morbidity and mortality. The molecular mechanisms governing basal PTH levels and SHP are undefined. We have shown that the parathyroid mTORC1 pathway is activated in CKD-SHP and that ablation of the miRNA processing enzyme Dicer and hence miRNA prevents CDK-SHP with no effect on basal serum PTH.

Methods: We generated mice with parathyroid (PT) specific KO of Dicer, mtorc1, tuberous sclerosis complex 1 (Tsc1) or double Dicer−/− Tsc1−/− KO and TdTomato expression to identify the glands by fluorescent microscopy. Parathyroid sections were IF stained.

Results: Despite normal serum PTH, adult PT-Dicer−/− mice had no intact parathyroid glands, unlike controls. The glands were present at birth but soon after only clumps of parathyroid cells remained, indicating that Dicer and miRNA are not essential for parathyroid embryogenesis but rather for maintaining intact glands later in life. To overcome CDK-SHP, we generated PT-tetorC1 mice that had parathyroid cell clumps from early after birth but normal serum PTH, resembling PT-Dicer−/− mice. In contrast, PT-Tsc1−/− mice with mTORC1 hyper-activation due to deletion of its inhibitor, had vastly larger (x10) glands and increased serum PTH and calcium levels. IF staining for parathyroid specific and proliferation markers supported the KO phenotypes. Importantly, a double PT-Dicer−/− Tsc1−/− mouse had intact parathyroid glands similar to controls, indicating that Tsc1 ablation over-rides the parathyroidesis of Dicer KO.

Conclusions: miRNAs are essential for PTH stimulation in CKD induced SHP. Both miRNA and mTORC1 maintain intact glands in the adult.
TH-OR36
The Role of Osteopontin and Osteocyte-Derived Factors in Secondary Hyperparathyroidism-Induced Muscle Dystrophy
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Background: Secondary hyperparathyroidism (SHPT) leads to harmful effects, including muscle dystrophy. We have previously shown that parathyroidectomy (PTX) improves muscle function, but not muscle mass. We hypothesized that this improvement is related to muscle inflammatory modulation. Osteopontin (OPN), a bone matrix protein, is stimulated by PTH and phosphate, and regulates the immune system at different levels.

Methods: We prospectively enrolled 30 patients on dialysis (39 yrs, 62% female) referred for PTX. Muscle phenotyping involved tissue analysis by immunohistochemistry, multiplex protein quantification, and gene expression; DXA for body composition; and HRpQCT imaging, we observed that PA modified the skeletal response to PTH. When PA levels were low, higher PTH levels were associated with catabolic effects on bone. Significant and independent predictors of Tb volumetric density were male, age, PA, and PTH. We found a significant decrease in systemic and muscle OPN concentrations. Higher muscle OPN expression was noted at baseline compared to controls (11 vs 2.9%* and PTX led to a marked reduction (11 vs 3%*). Systemic and muscle cytokines concentrations also decreased. Muscle, but not systemic, RANKL and sclerostin concentrations decreased after PTX.

Results: MBD, DXA, physical evaluation, and tissue analysis are shown in Table1. We found a significant decrease in systemic and muscle OPN concentrations. Higher muscle OPN expression was noted at baseline compared to controls (11 vs 2.9%* and PTX led to a marked reduction (11 vs 3%*).

Conclusions: Our findings suggest that muscle OPN and osteocyte-derived factors might play a role in CKD-associated sarcopenia. In addition to its role in mineralization, OPN may foster muscle tissue inflammation, which is blunted after PTX. Based on these results, new pathways are revealed as therapeutic targets for uremic sarcopenia.

Funding: Government Support - Non-U.S.

TH-OR37
Bone Quality in Uremic Patients: Interactions Between Parathyroid Hormone (PTH) and Propionic Acid
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Background: Chronic kidney disease (CKD) associated hyperparathyroidism (HPT) results in impaired bone quality and strength. While calcitriol deficiency partially drives elevations in parathyroid hormone (PTH), skeletal resistance to PTH also contributes to progressive HPT. In mice with normal kidney function, short-chain fatty acids (SCFAs) produced by the gut microbiome, were shown to moderate PTH effects on bone. Interactions between SCFAs and PTH on bone quality in humans with CKD are unknown. We hypothesized that SCFAs moderate the skeletal effects of PTH in CKD.

Methods: In a cross-sectional study of 60 CKD patients with double label transiliac crest bone biopsies, we measured parameters of dynamic histomorphometry, PTH and 24 SCFAs (Metabolon, Inc). Ages were 29-88 yrs, 13% were on dialysis and 40% were male. High resolution peripheral quantitative computed tomography (HRpQCT; resolution 60 μm) imaging of the radius and tibia for cortical (Ct) and trabecular ( Tb) geometry, density and microarchitecture were performed in a subset of 45 patients. SCFAs were dichotomized at the median. Generalized linear regression models were used to evaluate relationships between bone outcomes, PTH, SCFA, SCFA-PTH and SCFA-sex interactions.

Results: We found that the SCFA, propionic acid (PA), modified relationships between PTH and bone outcomes. In contrast to low levels of PA, high levels of PA and PTH were associated with thinner osteoid (β=3.32, SE 1.58, p=0.041) on histomorphometry, thicker cortices at the radius (β=12.50, SE 3.45, p=0.001) and tibia (β=24.46, SE 8.34, p=0.006) and greater Tb volumetric density (β=26.59, SE 11.28, p=0.024) at the radius by HRpQCT.

Conclusions: In conclusion, in a cohort of CKD patients with bone biopsy and HRpQCT imaging, we observed that PA modified the skeletal response to PTH. When PA levels were elevated, higher PTH was associated with better bone quality. In contrast, when PA levels were low, higher PTH levels were associated with catabolic effects on bone quality. Prospective studies are needed to investigate whether PA has a therapeutic role in the management of renal osteodystrophy.

Funding: NIDDK Support, Private Foundation Support, Clinical Revenue Support

TH-OR38
Calcium Isotope Ratios in Serum: A Novel Biomarker of Bone and Vessel Calcium Balance in Patients on Dialysis
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Background: Disregulated mineral homeostasis in CKD can cause bone demineralization and vascular calcification. We have shown that non-radioactive calcium (Ca) isotopes, 44/42Ca serum and bone correlated positively increases when bone formation exceeds resorption and vice versa. We studied bone and arterial biopsies to determine the sensitivity of 44/42Ca serum in estimating BCaB and vascular calcification.

Methods: 44/42Ca serum and bone correlated positively

Results: BAP, TRAP5-b ratio and osteoblastic markers P1NP and inversely with osteoid.

Conclusions: 44/42Ca serum quantitatively determines changes in bone Ca balance (BCaB). Isotopically light 42Ca is preferentially incorporated into bone, so 44/42Ca decreases when bone formation exceeds resorption and vice versa. We studied bone and arterial biopsies to determine the sensitivity of 44/42Ca serum in estimating BCaB and vascular calcification.

Methods: 44/42Ca serum and bone correlated positively

Results: BAP, TRAP5-b ratio and osteoblastic markers P1NP and inversely with osteoid.

Conclusions: 44/42Ca serum quantitatively determines changes in bone Ca balance (BCaB). Isotopically light 42Ca is preferentially incorporated into bone, so 44/42Ca decreases when bone formation exceeds resorption and vice versa. We studied bone and arterial biopsies to determine the sensitivity of 44/42Ca serum in estimating BCaB and vascular calcification.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
\[ \delta^{13} \text{Ca}_{\text{bone}} \quad (p<0.01, 95\% \text{CI} -1.35 \text{ to } -0.26), \text{BAP/TRAP5-b ratio} \quad (p=0.04, 95\% \text{CI} 0.04 \text{ to } 0.26) \text{ and osteoid area} \quad (p=0.03, 95\% \text{CI} -1.11 \text{ to } -0.09), \text{together predicting 79\% of the variability in } \delta^{13} \text{Ca}_{\text{bone}}. \]

**Conclusions:** \[ \delta^{13} \text{Ca}_{\text{bone}} \] is a significant and independent marker of BCaB, correlating with bone histology, and may provide a more sensitive and non-invasive measure of BCaB than bone biomarkers or DXA.

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

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**TH-OR39**

**Role of Plasma Inorganic Pyrophosphate in Calciphylaxis: A Prospective Study**

**Api Chevcharat,1 Houda Bouchouari,1 Scott Krinsky,2 Jennifer Howe,2 Jeanfranco Torcatti,2 Borut Cizman,2 Yves Sabbagh,2 Sagar U. Nigwekar.1**

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**Background:** Calciphylaxis is a devastating disorder characterized by painful skin lesions caused by calcific microvascular occlusion and no approved treatment. In experimental models and genetic disorders, deficiency of pyrophosphate (PPi) is linked with vascular calcification and neointimal proliferation. This study was conducted to investigate the influence of plasma PPI on severity and outcomes in calciphylaxis.

**Methods:** In this prospective study, we enrolled 70 patients with calciphylaxis. Plasma PPI levels were measured using an ATP Sulfurylase/Luminescence-based method at enrollment (n=70) and at 6-week follow up (n=36). We examined the associations of 1) PPI levels at enrollment with skin lesion count, pain severity (assessed by Brief Pain Inventory), and 6-week mortality, and 2) change in PPI levels over 6-week period after enrollment with 12-week mortality.

**Results:** Median age of our cohort was 60 years and 67% of patients had end-stage kidney disease. Median skin lesion count was 3 [IQR: 2-4] and median pain severity score was 5 [IQR: 4-7]. Median PPI levels were 568 nM [IQR: 253-1205] at enrollment and 1155 nM [IQR: 835-1456] at 6-week follow up. At enrollment, there were modest negative associations of PPI with skin lesion count \((r=0.26)\) and pain severity \((r=0.28)\). Mortality at 6 weeks was 21%. Among patients who died by 6-week follow up, PPI levels at enrollment were 66% lower compared to patients who were alive \((p=0.002)\) (Fig). In adjusted models, for every 100 nM decrease in PPI at enrollment, there was 25% increased risk of 6-week mortality. Decrease in PPI levels over 6-week period since enrollment was associated with increased 12-week mortality \((p=0.04)\).

**Conclusions:** Our novel findings demonstrate the potential of PPI as a target for therapies aimed at improving patient-oriented and clinical outcomes in calciphylaxis.

**Funding:** Commercial Support - Inozyme Pharma

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**TH-OR40**

**Loss of Renal Tubular Claudin-2 Increases Renal Calcification and Urinary Stone Disease**


**Background:** Mechanisms of hypercalciuria-associated renal calcification and urinary stone disease (USD) are not completely understood. Global Claudin-2 knockout (Cldn2KO) male mice share many key features of human hypercalciuric idiopathic calcium stone formers (ICSFs). Here we characterized urine biochemistry, urinary extracellular vesicles (uEVs), and renal pathophysiology to determine if uEVs could serve as a biomarker for human idiopathic, hypercalciuric, first time stone formers (SFs) with potential pathologic changes in renal claudin-2 (Cldn2) expression.

**Methods:** Twenty-hour (24-h) urine samples were collected from male mice (Cldn2KO \(n=12\)) and age-matched wild type (WT; \(n=8\)) and human SFs \(n=20\); hypercalciuric SFs and age-sex-matched non-SFs (NSFs). In vivo renal calcification in mice were measured by Bruker high-resolution \textit{in vivo} 3D X-ray microtomography. Data are presented as median (25th, 75th percentile) and analyzed by Wilcoxon rank-sum test to identify statistically significant \((P<0.05)\) differences between groups.

**Results:** Age, body weight, total 24-h urine volume, milliosmole, excretion of 24-h urine albumin, Cl, phosphorous, K\(^{+}\), protein, and Na\(^{+}\) were not different between Cldn2KO and WT mice. However, 24-h excretion of urinary Ca\(^{2+}\) was greater \((P=0.002)\) (Fig) in Cldn2KO compared to WT mice. Spontaneous renal papillary calcifications were identified in Cldn2KO (Fig.) but not WT mice. Cldn2 protein expression on uEVs was increased in SFs compared NSFs \((P=0.004)\) (Fig.).

**Conclusions:** Loss of renal tubular Cldn2 protein increased urinary Ca\(^{2+}\) excretion and papillary calcification in mice. Our nephrectomy patients study showed a significant decrease in Cldn2 expression in SFs compared NSFs. Thus, increased excretion of Cldn2 protein carrying uEVs in hypercalciuric SFs may reflect decreased tubular Cldn2 protein expression that results in reduced renal Ca\(^{2+}\) reabsorption and increased USD, and quantification of Cldn2 content of uEVs could serve as a useful biomarker for further studies.

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

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Plasma PPI and mortality in Calciphylaxis

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

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TH-OR41

The Relationship Between Patient Activation and Clinical Outcomes: A Longitudinal, Retrospective, Observational Study

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Background: Patient activation, defined as an individual’s readiness, willingness, and ability to manage their own health and health care, is associated with healthy behaviors and improved outcomes. Patients undergoing in-center hemodialysis (HD) have low activation, but the association of patient activation with clinical outcomes among dialysis patients is unclear. We investigated the association between patient activation and outcomes in HD patients.

Methods: This cohort included 925 prevalent, in-center HD patients among 10 facilities in a mid-sized dialysis provider. Patients had completed a PAM-13 survey—a measure of patient activation—during a previous study. Patients were followed for 180 days after completion of the survey for the co-primary outcomes of (1) death and (2) the composite of death or hospitalization. Markers of non-adherence were examined as secondary outcomes, including (1) serum potassium >5.0 mEq/L; (2) serum phosphorus >5.5 mg/dL; (3) missed dialysis treatment due to absence (not hospitalization); and (4) interdialytic weight gain >3%.

Univariate and adjusted regression models were fit to estimate associations of a 3-point increment in PAM-13 score with the outcomes of interest; adjustment factors comprised age, sex, dialysis vintage, serum albumin, and hospitalization history.

Results: A 3-point increment in PAM score was associated with lower hazard of death (univariate HR=0.89, 95% CI: 0.84 – 0.94; adjusted HR=0.91, 95% CI: 0.86-0.96), but not with the composite outcome of death or hospitalization (univariate HR=0.98, 95% CI: 0.96 – 1.00; adjusted HR=0.99, 95% CI: 0.96–1.00). There were no significant relationships between a 3-point increment in PAM score and any of the secondary outcomes in univariate and adjusted analyses.

Conclusions: In a cohort of prevalent, in-center HD patients, low activation was associated with mortality but not with hospitalization or measures of non-adherence.

Funding: Private Foundation Support

TH-OR42

Self-Efficacy and Social Support Determine Self-Reported Health in Hemodialysis Patients

Krister Cromm,1,2 Le Hong Ngoc Pham,3 Hanna Jaha,1 Anna Schappert,1 Gregor Liegl,1 Kathrin J. Fischer,1 Felix Fischer,1 Matthias Rose,1 CONVINC Scientific Committee and CONVINC Investigators. 1Charite Universitatsmedizin Berlin, Berlin, Germany; 2Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany.

Background: Patients with kidney disease receiving dialysis are a highly vulnerable population. There is some evidence from small studies that Health-Related Quality of Life (HRQL) in these patients is influenced by psychosocial determinants, but their relevance for clinical outcomes is debated. We investigated whether Self-Efficacy (SE) and Social Support (SS) can explain differences in HRQL outcome domains over time in hemodialysis patients.

Methods: HRQL in 1264 participants from the CONVINC randomized, controlled trial investigating hemodiafiltration versus hemodialysis were assessed, using screening and yearly follow-up data up to 24 months. Measures included the MOS Social Support Scale, General Self-Efficacy Scale, Perceived Stress Questionnaire and PROMIS short forms for fatigue, physical function, pain interference and intensity, sleep disturbance, anxiety, cognitive function, depression, and ability to participate in social roles. SE and SS were included as independent variables and HRQL domains as dependent variables in a linear mixed effects model with random intercept and slope for SE and SS.

Results: Participants were 20-92 (M=62.33, SD=13.50) years old, 62.9% were male. Linear mixed effect regression models showed significant main effects for self-efficacy (β = 0.44, p < 0.001) and social support (β = 0.18, p = 0.01) on all HRQL domains. Main effects for social support were found for Cognition, Depression, Pain Intensity and Sleep (β = 2.67 & 1.17, p<0.01). For time, significant main effects were found for Anxiety and Sleep (β = 0.56 & 0.50, p<0.01). Significant SE x Time interactions were found for Anxiety, Depression and Sleep (β = -1.19 & 0.17, p<0.05). Significant SS x Time interactions were found for Cognition and Sleep (β = -1.7 & 18, p<0.01).

Conclusions: Our results indicate that higher SE is associated with higher HRQL of dialysis patients over time. Effects of SE are larger than those of SS and larger than previously reported. This bears the chance to develop targeted psychosocial interventions to improve health outcomes when undergoing dialysis.

Funding: Government Support - Non-U.S.

TH-OR43

Impact of Conservative Management vs. Dialysis on the Survival of US Veterans with Advanced CKD

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Background: Given that dialysis patients may experience high early mortality rates, healthcare utilization, and withdrawal, particularly in those of older age and multi-morbidity, there has been interest in conservative management (CM) as an alternative treatment strategy for advanced CKD patients. Among a national cohort of US Veterans, we compared the impact of CM vs. dialysis on survival.

Methods: Using linked national VA, USRDS, and Medicare data, we examined Veterans with advanced CKD (a eGFRs <25 separated by ≥90 days) categorized according to receipt of CM vs. dialysis (non-receipt vs. receipt of dialysis within 2 yrs of the 1st eGFR <25), with the latter group parsed into later dialysis (LD) vs. earlier dialysis (ED) (eGFRs <15 vs. ≥15 at dialysis transition, respectively). We compared survival in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio to address confounding by indication using Cox models.

Results: Among 91,598 patients who met eligibility criteria, 3628 CM patients were PS-matched to 3628 ED patients, while 9833 CM patients were PS-matched to 9833 LD patients. In PS-matched models, both ED and LD were each associated with higher mortality vs. CM: HRs (95%CI) 1.25 (1.19-1.32) and 1.08 (1.05-1.12), respectively. Similar findings were observed in sensitivity analyses doubly-adjusted for PS covariates. When examining survival trajectories after the index eGFR date, ED and LD demonstrated worse survival vs. CM after 2-years and 4-years, respectively.

Conclusions: In a national cohort of US Veterans, earlier transition to dialysis was associated with worse survival compared to CM. Later transition to dialysis was also associated with worse survival vs. CM, albeit to a lesser degree. Further studies are needed to examine the impact of CM vs. dialysis transition on other hard endpoints and patient-centered outcomes.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
TH-OR44

Encouraging a Standardized ESKD Transition Approach in a Comprehensive Kidney Care Contracting (CKCC) Program

Is Associated with Increased Optimal Dialysis Starts

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Background: The standard care for chronic kidney disease (CKD) is shifting from a “fee-for-service” model that focuses on volume of care and profitability of services to a Value Based Care (VBC) model that rewards better outcomes. It is well-established that starting ESKD care with peritoneal dialysis (PD) or hemodialysis (HD) with either an arteriovenous (AV) fistula or AV graft, instead of HD with a central venous catheter (CVC), produces better patient survival, morbidity, and cost outcomes. The purpose of this study was to determine if a standardized ESKD transition pathway could improve the number of optimal starts within Kidney Care Entities (KCEs).

Methods: All patients were in the Comprehensive Kidney Care Contracting (CKCC) program. The CKCC program defines an optimal start to be the initiation of dialysis without a CVC. We recorded the proportion of optimal starts and the initial modality type (HD vs PD) in adult Medicare patients at 4 geographically diverse KCEs within a single physician-led nephrology organization. Data were recorded quarterly (Q) during 2022. During Q1-Q2, patients and clinicians were formally instructed on the benefits of optimal starts only. Starting in Q3, a standardized care pathway was deployed for patients at high risk for transition to ESKD across all 4 KCEs, inclusive of electronic health record and analytics tools, and treatment teams were provided lists of patients who met the high risk criteria. The proportion of optimal starts and the proportional of initial PD from Q1-Q2 versus Q3-Q4 were compared with Student’s t-test for proportions.

Results: In 2022, the 4 KCEs treated 9,099 patients with 5,457 (60.0%) having CKD. 371 patients initiated dialysis during the study period with 164 (44.2%) in Q1-Q2. The proportion of optimal starts increased from 37.2% (61/164) in Q1-Q2 to 53.1% (110/207) in Q3-Q4, p = 0.002. The proportion of PD starts increased from 11.0% (18/164) in Q1-Q2 to 26.1% (54/207) in Q3-Q4, p < 0.001.

Conclusions: The deployment of a standardized ESKD transition pathway as part of an intensive VBC educational program is associated with a significant increase in both optimal starts and the number of patients starting on PD.

TH-OR45

Higher Patient-to-Patient Care Technician Ratios Associated with Worse Outcomes Among US In-Center Hemodialysis Patients

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Background: It is increasingly difficult to maintain adequate dialysis patient care technician (PCT) staffing at U.S. in-center hemodialysis (ICHD) facilities. We aimed to explore the associations of ICHD patient outcomes with facility-level PCT staffing.

Methods: U.S. patients (ages 18-100) initiating ICHD between 1/1/16 and 12/31/18 were included if they remained on ICHD for ≥90 days and had data on PCT staffing at their ICHD facility (N=236,126; mean age, 63.1; 57.6% male; 27.9% Black; 61.8% with diabetes; 60.2% starting ICHD with a catheter only). We estimated the association of time to 1-year patient outcomes with facility-level PCT staffing (=number of patient:PCT ratios) using mixed-effects Poisson regression, with censoring as appropriate and adjustment for age, sex, race, pre-stage kidney disease nephrology care, diabetes, and first vascular access type.

Results: After adjustment, highest vs. lowest quartile of facility-level patient:PCT ratio was associated with 11%, 10%, and 10% higher rates of patient mortality, hospitalization, and readmission, respectively; associations with rates of waitlisting and transplant were not significant (Figure 1). Highest vs. lowest quartile of patient:PCT ratio was associated with 10%, 13%, and 22% higher rates of fluid overload-, sepsis-, and vascular access-related hospitalizations, respectively (Figure 2).

Conclusions: Patients initiating treatment in facilities with the least adequate PCT staffing may have worse early outcomes. While effects are modest and causal inference is limited, our results support further investigation of the effects of U.S. PCT staffing on patient safety and quality of U.S. ICHD care.

Funding: Other U.S. Government Support

TH-OR46

The Impact of Affordable Care Act Medicaid Expansions on Dialysis Facility Medicaid Enrollment and Quality Measures

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Background: The Centers for Medicare and Medicaid Services proposed using Medicare dual eligible enrollment (DEE) to adjust for social risk in dialysis facility quality scores. Because Medicaid eligibility varies by state, in part due to variable uptake of Affordable Care Act (ACA) Medicaid expansions, we examined the extent to which dialysis facility location in an expansion state was associated with increased DEE and improved dialysis facility quality scores.

Methods: Using data from the ESRD Quality Improvement Program (QIP) and US Renal Data System, we identified a longitudinal cohort of US hemodialysis dialysis facilities with ESRD QIP data from 2012-2018. We tested whether location in an expansion state was associated with increases in the proportion of Medicaid-enrolled incident and dual-eligible enrolled prevalent dialysis patients as well as improved ESRD QIP total performance scores (TPS) and vascular access scores (VAS). We compared pre-expansion data (2012-2013) with early and late post-expansion times points (2015 and 2018, respectively).

Conclusions: Dialysis facilities in states that have not implemented Medicaid expansions may experience lower growth of Medicaid enrollment due to limited Medicaid coverage available to their patients and may also have a greater decline in quality scores. Accordingly, adjustments to quality performance metrics based on DEE may favor facilities located in expansion states and further exacerbate health disparities among patients receiving dialysis.

Funding: Other NIH Support - NIH grant TL1TR002546, Private Foundation Support

TH-OR47

Roles of Matrix Metalloproteinase-2 and ETS Proto-Oncogene 1 in Rodent Arteriovenous Fistula Development

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Background: Arteriovenous fistulas (AVFs) have high rates of maturation failure with no proven effective treatments. A few clinical studies have reported that stenotic AVFs had increased expression of matrix metalloproteinases (MMPs) when compared to native veins, and post-surgery fibrosis in newly created AVFs was positively associated with maturation failure. This study therefore examined the roles of MMP-2, which is a critical MMP in vascular remodeling, and the transcription factor ETS proto-oncogene 1 (ETS-1), which is a potent pro-fibrotic factor, in AVF maturation development.

Methods: Carotid-jugular AVFs were created in global MMP-2 homoygous knockout (MMP-2 KO) mice on C57BL/6 background, with C57BL/6 mice serving as wild-type (WT) controls. Femoral AVFs were created in global ETS-1 heterozygous knockout (ETS-1 KO) rats on Sprague-Dawley (SD) background, with SD rats serving as WT controls. AVFs and contralateral non-surgical veins were harvested at 1 and 4 weeks after AVF creation for RNA sequencing (RNA-seq), histology, and morphometry.

Results: In our mouse studies, RNA-seq data indicated drastically different transcriptional profiles between non-surgical veins and AVFs at 1 week after AVF creation. Genes regulated by MMP-2 and ETS-1 were significantly enriched in AVFs. Both MMP-2 KO and ETS-1 KO had significantly increased open lumen areas of the AVF veins when compared to WT controls. In mouse studies, the percent open lumen area of...
the AVF veins was significantly larger in MMP KO (39% ± 6%) vs. WT (11% ± 2%) at 1 week, as well as at 4 weeks (MMP-2 KO: 20% ± 4%; WT: 6% ± 3%) (p<0.05 for both time points). ETS-1 expression was decreased in MMP-2 KO when compared to WT. In rat studies, the percent open lumen area of the AVF veins was significantly larger in ETS-1 KO (70% ± 9%) vs. WT (39% ± 15%) at 1 week (p<0.04) and trending larger in ETS-1 KO (74% ± 7%) vs. WT (22% ± 7%) at 4 weeks (p=0.15).

Conclusions: Our animal studies showed that inhibition of MMP-2 and ETS-1 by genetic knockout improved AVF development. Therapeutic approaches of inhibiting these molecules may enhance AVF maturation in hemodialysis patients.

Funding: NIDDK Support

TH-OR48

Long-Term Intervention Rate with Drug-Coated Balloons for Dysfunctional Arteriovenous (AV) Fistulas: Meeting KDQI Targets in the IN.PACT AV Access Trial

Anjana M. Dialysis

Background: A key KDQI Guidelines target is to have ≤3 percutaneous or surgical interventions per year to maintain AV fistula (AVF) patency. We aimed to define the intervention and thrombosis rates per AVF-years through 36 months from the IN.PACT AV Access trial.

Methods: This global, 29-center, single-blinded pivotal study randomized participants with de novo or non-stented restenotic obstructive lesion(s) of upper extremity AVF 1:1 to treatment with an IN.PACT AV paclitaxel drug-coated balloon (DCB; n=170) or standard percutaneous transluminal angioplasty (PTA; n=160). Participants were followed for 36 months; intervention rates and fistula-years of use were captured and compared to KDQI guidelines target. 36 month thrombosis rates were compared between DCB and PTA groups.

Results: Of the 330 participants randomized, 133 completed their 3-year visit. Including the index procedure, the rates of intervention ranged 1.24-2.55 per AVF-year for DCB group and 1.48-3.06 per AVF-year for PTA group (Table). The cumulative incidence rate of access circuit thrombosis at 36 months was 8.2% (±10) in DCB group and 18.3% (±19) in PTA group with a hazard ratio of 0.457 (95% confidence interval: 0.30-0.71; P=0.004).

Conclusions: The need for interventions to maintain patency and thrombosis rate was reduced with use of DCB compared with PTA at the 1-, 2-, and 3-year timepoints post index procedure for the treatment of dysfunctional AVF. At the 3-year timepoint, both DCB and PTA groups met the KDQI targets for AVF interventions per year to maintain patency.

Number of target lesion interventions per fistula years

<table>
<thead>
<tr>
<th>IN.PACT AV DCB</th>
<th>Standard PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target lesion interventions</strong></td>
<td><strong>No. of events</strong></td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>36</td>
</tr>
<tr>
<td>180 days</td>
<td>33</td>
</tr>
<tr>
<td>360 days</td>
<td>33</td>
</tr>
<tr>
<td>720 days</td>
<td>33</td>
</tr>
</tbody>
</table>

AVF, arteriovenous fistula; DCB, drug-coated balloon; No, number; PTA, percutaneous transluminal angioplasty.

TH-OR49

Extreme Heat Exposure and Mortality Among Patients Receiving Dialysis

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Background: Patients receiving maintenance dialysis represent a population vulnerable to extreme weather events such as wildfires and hurricanes, but the dangers posed by extreme heat exposure remain to be determined.

Methods: In the United States Renal Data System, we identified adults living in US cities prone to extreme heat who initiated maintenance dialysis from 1997 to 2016. We defined an extreme heat event as a heat index of >40.6°C for 2 days or >46.1°C for 1 day. We estimated the risk of death during a heat event using adjusted Cox proportional hazards regression and tested for effect modification by age, sex, race and ethnicity, year of dialysis initiation, dialysis modality, poverty level, and climate region.

Results: Among 945,437 adults in 246 cities, the median age was 64 years and 44% were female. During a median follow-up of 3.7 years, 519,748 adults were exposed to at least one of 7,152 extreme heat events, and 530,616 deaths occurred. In adjusted models, there was an increased risk of death (HR, 1.18; 95% CI, 1.15 to 1.20) during exposure to extreme heat (Table). Relative mortality risk was higher among patients who were at least one of 7,152 extreme heat events, and 530,616 deaths occurred. In adjusted models, there was an increased risk of death (HR, 1.18; 95% CI, 1.15 to 1.20) during exposure to extreme heat (Table). Relative mortality risk was higher among patients who were...
Results: Participant characteristics included mean age 59 (SD 10.8) years; 1357 (43.6%) female; 1550 (49.8%) with diabetes. The median GA was 18.7 (-2.9 to 25.3) years. During an average 7.9-year follow-up, there were 980 ESKD events, 968 CVD events, and 1084 deaths. In multivariable adjusted Cox models, higher GA levels were associated with greater risks of all outcomes in patients with CKD, regardless of diabetes status (Fig 1): hazard ratios for ESKD, CVD, and death among participants with the highest quartile compared with quartile 2 (reference) were 1.42 (95% CI, 1.19-1.69), 1.67 (CI, 1.39-2.01), and 1.63 (CI, 1.37-1.94), respectively. The associations with CVD and death appeared J-shaped, with increased risk also seen at the lowest GA levels (quartile 1 vs. reference) in patients with coexisting CKD and diabetes. The associations of GA with outcomes remained statistically significant even after adjustment for HbA1c. For each outcome, we observed a significant fraction of new prognostic information when both GA and HbA1c were added to models.

Conclusions: Among patients with CKD, GA levels were independently associated with risks of ESKD, CVD, and mortality, regardless of diabetes status. GA added prognostic value to HbA1c among patients with coexisting CKD and diabetes.

Funding: NIDDK Support, Private Foundation Support

Fig 1. Adjusted HRs for GA Levels and Risks of ESKD, CVD and Death

TH-ORS2
Harnessing Kidney Transcriptome Profiles to Predict Rapid Progression of Diabetic Kidney Disease
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Background: Kidney gene expression has been shown to be associated with kidney function in diabetic kidney disease (DKD) patients by cross-sectional transcriptomics studies. However, how the renal transcriptome correlates to disease progression has not been established due to the paucity of longitudinal studies. We hypothesized that certain kidney transcriptomic patterns associated with progressive DKD may elucidate disease drivers and predictive factors.

Methods: RNA-seq data from micro-dissected kidney biopsies and post-biopsy proteomics. Subjects on treatment with either placebo or finerenone for at least 4000 longitudinal post-randomization plasma samples using Olink EXPLORE proteomics. Enriched terms were grouped into clusters based on membership similarities.

Results: 373 plasma protein biomarkers were modulated by finerenone treatment. Gene enrichment of the biomarker profile identified two clusters of extracellular matrix (ECM)-related pathways, involving several well-established markers of inflammation and fibrosis such as fibronectin, osteopontin, and members of the interleukin-17 family, along with novel markers of ECM remodeling. Other clusters linked directly to mineralocorticoid/aldoosterone biology and diuresis reflecting target modulation.

Conclusions: For the first time, FIGARO-BM provides human biomarker evidence that finerenone acts on inflammation and fibrosis pathways, one key driver of diabetic kidney disease progression in T2D. The study supports preclinical findings from animal models and provides insights to mechanisms leading to clinical benefits in a broad cardiorenal patient population. Future studies are needed to validate these findings.

Funding: Commercial Support - The study and this analysis were funded by Bayer AG, Wuppertal, Germany.

TH-ORS4
Renal Effects of Empagliflozin Alone or in Combination with Semaglutide in Albuminuric Type 2 Diabetes: A Randomized, Placebo-Controlled Trial
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Background: Different mechanisms of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1) agonists indicate that combination therapy may have additive or synergistic effects. We investigated if combined treatment with empagliflozin (SGLT2) and semaglutide (GLP-1RA) can reduce urinary albumin creatinine ratio (UACR) compared to treatment with empagliflozin alone in individuals with type 2 diabetes and albuminuria.

Methods: Randomized, placebo-controlled, double-blind, parallel study including 60 participants on empagliflozin were randomly assigned to additional semaglutide (n=30) or placebo (n=30). Mean age was 70.1 (SD 8.0) years, 22% were female and median UACR was 128.2 (IQR 78.5-285.3) mg/g. Mean UACR change from randomization to week 52 was -15.5 (95% CI -34.0 to 8.0) %, p=0.17) in the semaglutide group and 14.8 ((11.8 to 24.9) %, p=0.29) in the placebo group with a significant difference between groups (mean difference: -26.4 ((-48.2 to 4.6) %; p=0.086). The mean change in HbA1c was -9.4 ((-14.3 to -3.3) mmol/mol, p=0.002). No difference between treatment groups in body weight (p=0.28), measured glomerular filtration rate (GFR); and (4) 24-hour systolic blood pressure (p=0.26) was observed.

Conclusions: This randomized clinical trial could not demonstrate a significant effect of combined treatment with empagliflozin and semaglutide compared to empagliflozin alone on UACR, measured GFR, 24-hour systolic blood pressure or body weight in participants with type 2 diabetes and albuminuria. The combined treatment significantly improved glycemic control compared to treatment with empagliflozin alone.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Effects of Canagliflozin on Renal Oxygenation Evaluated Using Blood Oxygenation Level-Dependent MRI in Patients with Type 2 Diabetes

**Background:** Results obtained in recent clinical trials suggest that SGLT2 inhibitors have protective effects against diabetic and chronic kidney disease, though the precise mechanisms remain largely unknown. Since the kidneys are susceptible to hypoxic damage, we hypothesized that use of an SGLT2 inhibitor improves renal oxygenation.

**Methods:** The effects of canagliflozin on renal oxygenation in patients with type 2 diabetes (T2D) were examined using blood oxygenation level-dependent (BOLD) MRI. Based on a method previously reported, T2* maps were generated, then primary analysis of cortical T2* values was performed using the 12-layer concentric objects (TLCO) method, while cortical oxygenation was also evaluated based on region of interest (ROI) method. The primary endpoints were change in T2* value from before (Day 0) to after the initial treatment (Day 1, about two hours after initial single dose) and also after five consecutive canagliflozin treatments (Day 5).

**Results:** Fourteen patients with T2D were enrolled, with median age 65.5 years (interquartile range 59.0-72.0) years, body mass index 24.2 (22.3-26.7) kg/m², Hba1c 7.1% (6.9-7.7%), estimated glomerular filtration rate 59.2 (46.9-76.8) mL/min/1.73 m², and urinary albumin creatinine ratio 20.5 (5.7-468.7) mg/gCr. Results with the TLCO method showed that canagliflozin treatment did not cause a significant change in T2* (mean and 95% confidential interval) from Day 0 [54.1 (51.5-56.9)] to Day 1 [55.2 (52.5-58.0)] (p=0.336) and also to Day 5 [53.4 (50.7-56.2)] (p=0.519). On the other hand, the T2* value was significantly increased from 52.8 (50.6-55.0) to 54.5 (52.3-56.9) (p=0.031) on Day 1, while no significant change from Day 0 to Day 5 [53.7 (51.5-56.0) (p=0.241)] was found with use of the ROI method.

**Conclusions:** The present findings indicate that canagliflozin administration may improve renal cortical oxygenation in patients with T2D.

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**Atrasentan reduces insulin resistance.** Panel A: Change from baseline in HOMA-IR in the RADAR trial. Panel B: Geometric mean HOMA-IR values per study visit in the SONAR trial.
Methods: We assessed effectiveness of the CDS by comparing screening across 3 periods (pre-COVID control: Jan 2019-Feb 2020; post-COVID control: Mar 2021-Apr 2022; post-CDS: May 2022 - Oct 2022) for all non-acute office, nursing and telehealth encounters in UVA primary care for T2D patients aged ≥22 years. Encounters with a coded diagnosis of CKD in the prior 4 yrs or fully screened for CKD in past 365 days were excluded. Orders for UACR testing within 30 days constituted screening. Rates were aggregated by calendar months and compared via interrupted time series. Sensitivity analyses included all primary care encounters during this period.

Results: There were 59,147 encounters (24,242 pre-COVID control; 23,413 post-COVID control; 11,492 post-CDS). The screening trend in both control periods was similar, therefore only the post-COVID control was considered further. Demographics, encounter types, and clinic distribution were similar in the control and post-CDS periods. There was no immediate impact on screening (p=0.4), but screening accelerated post-intervention (p=0.003, Figure). Results were similar if all primary care encounters were included (e.g., inclusive of acute visits).

Conclusions: Roll out of CDS coincided with acceleration of the screening rate for CKD among adult patients with T2D. These results suggest that simple CDS may be an effective intervention to promote annual CKD screening.

Funding: Other U.S. Government Support

TH-OR59

Effects of GLP-1 Receptor Agonist Dulaglutide on Profile of Circulating miRNAs Associated with ESKD in Type 2 Diabetes

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Background: Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to slow kidney function decline in patients with type 2 diabetes (T2D), but the underlying mechanism remains unclear. Circulating microRNAs (miRNAs) are short non-coding RNA molecules known to regulate proteins. Previously, we identified 17 plasma miRNAs (8 risk and 9 protective) that were predictive of end-stage kidney disease (ESKD) in T2D patients (Satake et al. JASN 2022). In this study, we investigated the treatment effect of the GLP-1 receptor agonist, Dulaglutide on longitudinal changes in plasma concentrations of these miRNAs in patients enrolled in the AWARD-7 trial.

Methods: Plasma samples were obtained from T2D patients with chronic kidney disease (CKD) stages 3-4 who received Dulaglutide 1.5 mg (n=29) or insulin Glargine (n=31) for 52 weeks. Using the HTG edgeSeq platform, we measured 17 ESKD-associated miRNAs at baseline and 52 weeks. Fold change (FC) values were calculated for each patient and each miRNA by dividing the concentration of miRNA at 52 weeks by its concentration at baseline.

Results: Comparing the FC values between Dulaglutide and Glargine groups, we observed that the plasma concentration of protective miRNAs (in blue) increased during Dulaglutide treatment, and 5 of them (miR-378d, -324-3p, -22-3p, -378a-3p and -339-5p) showed statistically significant increases (P<0.05). The plasma concentrations of all risk miRNAs (in red) were reduced with Dulaglutide treatment, but only the reduction of miR-6728-3p reached statistical significance (Figure).

Conclusions: Treatment of T2D patients with stage 3–4 CKD with Dulaglutide altered the profile of circulating miRNAs associated with ESKD, resulting in increased concentrations of protective miRNAs and decreased concentrations of risk miRNA in circulation.

Funding: NIDDK Support

TH-OR60

Earlier Intervention in Diabetic Kidney Disease Management Using the In Vitro Diagnostic Test PromarkerD Shows Economic Health Benefits over Current Standard of Care


Background: Diabetic kidney disease (DKD) is present in 1 in 3 people with type 2 diabetes (T2D) and is the leading cause of end-stage renal disease (ESRD). PromarkerD is a newly developed biomarker-based blood test that predicts risk of DKD in people with T2D. Recent studies have shown the clinical benefit of early intervention with sodium glucose cotransporter-2 inhibitors (SGLT2s) in DKD management for patients with no or early-stage kidney disease. This study aimed to assess the consequent economic health benefit of earlier introduction of SGLT2s resulting from a proactive testing regime using the PromarkerD test versus current standard of care (SoC).

Methods: A ten-year model was developed according to the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines to evaluate potential net savings from introducing PromarkerD testing versus SoC in a hypothetical cohort of 1 million people with T2D. Model inputs included costs and frequency of testing, costs associated with initiation of SGLT2s, and cost-savings from slowed DKD progression and averted renal replacement therapy for ESRD (dialysis and kidney transplants).

Results: PromarkerD testing could produce net savings for US payers exceeding $10 billion USD per one million people with T2D over the ten-year time horizon. In the baseline case, the total annual savings equals the costs after four years. Savings increase exponentially in subsequent years, significantly outweighing the associated costs compared to the current SoC without PromarkerD testing. The break-even point occurs after six years, after which the total savings are greater than the total costs. Significant savings arise from slowing the progression of DKD, against costs from the use of SGLT2s and cost of PromarkerD testing over 10 years.

Conclusions: Earlier intervention with SGLT2s following implementation of the PromarkerD test could result in substantial savings to US payers in the management of DKD. PromarkerD testing would enable earlier intervention for those at high risk of DKD, before progression to more costly later stage disease requiring renal replacement therapy, as well as reduce unnecessary treatment in those at low risk.

Funding: Commercial Support - Proteomics International

TH-OR61

ApoA4 Mutations Cause Autosomal Dominant Tubulointerstitial Kidney Disease with Medullary Amyloidosis

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Background: Whole genome sequencing was performed in 5 members of a large family with autosomal dominant tubulointerstitial kidney disease (ADTKD), and we then screened other ADTKD families in our registry for mutations in the identified gene.

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

Underline represents presenting author.
Results: There was an ~15 megabase shared genomic region on chromosome 11 (chr11:110019286-124998347) with only one relevant candidate variant chr11:116692578G>C (hg19) encoding for a missense mutation in APOA4 (NM_0004842: c.196C>G (p.L66V)). Using Sanger sequencing and segregation analysis, we genotyped 19 individuals from the family. Of 12 genetically affected individuals (10 genotyped and two of heterogeneous genotypes), 10 had CKD, with two females being as yet clinically unaffected. Of nine genetically unaffected, the lowest eGFR was 59 ml/min/1.73m² at age 69. Screening families from our ADTKD registry, we identified two other distantly related families with the same variant and two distantly related families with a chr11:116693454 C>T variant encoding the missense mutation p.D33N. All 31 clinically affected individuals suffered from CKD without proteinuria and a bland sediment and carried their familial pathogenic APOA4 mutation. The mean age of end-stage kidney disease was 72.7±10.2 for the p.L66V mutation and 58.2±11.1 for the p.D33N mutation (p<0.009).

In this study, we used mice with the p.L66V mutation to investigate progression of a nephropathy specimen identified as a marker to evaluate markers of podocyte injury, and to quantify MANF overexpression suppressed STING-mediated inflammation and fibrosis, thereby improving kidney function.

Conclusions: For the first time, we identified mutations in the APOA4 gene as a cause of ADTKD. APOA4 mutations result in mesangial ApoA4 deposition, which can be missed on routine kidney biopsies that only sample the renal cortex. Funded: Private Foundation Support

TH-OR62 Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Stimulates Autophagy and Restores Mitochondrial Homeostasis to Treat Uromodulin-Associated Nephropathy

Chuang Li,1 Yeawon Kim,1 Chenjian Gu,1 Yili Fang,1 Eric Tycksen,1 Anuradika Puri,1 Terri A. Pietka,2 Jothilingam Sivapackiam,1 Kendrah O. Kidd,1 Sun-Ji Park,2 Bryce G. Johnson,2 Stanislav Knio,2 Jeremy S. Duffield,2 Anthony J. Blevy,2 Meredith Jackel,1 Fumihiko Urano,1 Yijin Sharma,1 Maria Lindahl,1 Ying Y. Wang,1 Christopher L. H. Duffield,1 Washington University in St Louis School of Medicine, St Louis, MO; 2Wake Forest University School of Medicine, Winston-Salem, NC; 3Pfizer Inc, New York, NY; 4Universita Karlova, Praha, Czechia; 5Washington University in St Louis, St Louis, MO; 6Helsingin yliopisto, Helsinki, Finland; 7Prime Medicine, Cambridge, MA.

Background: Autosomal dominant tubulointerstitial kidney disease due to uromodulin mutations (ADTKD-UMOD), a leading hereditary kidney disease, has no targeted therapies. UMOD is expressed in the thick ascending limb (TAL) tubules, and a Pkd1-H177_R185del is established. RNA sequencing was performed on isolated TAL cells from 22 male mice representing WT, Pkd1-K907A/flox, and Pkd1-K907A/flox;Pkd1-Cre (early model) or Pkd1-K907A/flox;Pax8rtTA;Tet-OCre (adult model) mice to generate experimental UMOD-knockout mice. MANF overexpression suppressed STING-mediated inflammation and fibrosis, thereby improving kidney function.

Methods: CRISPR-Cas9 was utilized to generate an ADTKD-UMOD mouse model carrying Umod;pY178_R186del, analogous to human H177_R185del. To assess the functional role of mesencephalic astrocyte-derived neurotrophic factor (MANF) (in ADTKD, inducible tubular cell-specific MANF transgenic and TAL-specific MANF knockout mice were generated. Meanwhile, stable HEK cell line harboring WT or MANF overexpression suppresses STING-mediated inflammation and fibrosis, thereby improving kidney function.

Conclusions: For the first time, we identify mutations in the APOA4 gene as a cause of ADTKD. APOA4 mutations result in mesangial ApoA4 deposition, which can be missed on routine kidney biopsies that only sample the renal cortex. Funded: Private Foundation Support

TH-OR64 Role of ER-Mitochondria Connection in the Pathogenesis of ADPKD

Tian Xing,1 Chenjian Gu,1 Ying M. Li,2 Chenjian Fang,1 Eric A. Tycksen,1 Anuradika Puri,1 Kendrah O. Kidd,1 Sun-Ji Park,2 Bryce G. Johnson,2 Stanislav Knio,2 Jeremy S. Duffield,2 Anthony J. Blevy,2 Meredith Jackel,1 Fumihiko Urano,1 Yijin Sharma,1 Maria Lindahl,1 Ying Y. Wang,1 Christopher L. H. Duffield,1 Washington University in St Louis School of Medicine, St Louis, MO; 2Wake Forest University School of Medicine, Winston-Salem, NC; 3Pfizer Inc, New York, NY; 4Universita Karlova, Praha, Czechia; 5Washington University in St Louis, St Louis, MO; 6Helsingin yliopisto, Helsinki, Finland; 7Prime Medicine, Cambridge, MA.

Background: The role of the early postnatal ER-mitochondria connection (EMC) in ADPKD mouse models is the most recent major discovery in ADPKD. Methods: CRISPR-Cas9 was utilized to generate an ADTKD-UMOD mouse model carrying Umod;pY178_R186del, analogous to human H177_R185del. To assess the functional role of mesencephalic astrocyte-derived neurotrophic factor (MANF) (in ADTKD, inducible tubular cell-specific MANF transgenic and TAL-specific MANF knockout mice were generated. Meanwhile, stable HEK cell line harboring WT or MANF overexpression suppresses STING-mediated inflammation and fibrosis, thereby improving kidney function.

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TH-OR65 Organoid Xenograft Model of Polycystic Kidney Disease Reveals Context-Dependent Cross-Talk Between Primary Cilium and Autophagy in Cystogenesis

Yun Xing,1 Meng Liu,1 Angelousia Cardilla,1 Tian Zhang,1 Mihir N. Naik.1 Nanayang Technological University, Singapore.

Background: In the past few years, organoid models have been developed to study polycystic kidney disease (PKD), including those derived from human pluripotent stem cells (PSC) and adult kidney tissue. Despite successful recapitulation of tubular cyst formation in vitro, most organoid models of PKD rely on stress stimulation to demonstrate disease phenotypes, possibly due to the lack of native tissue microenvironment. Novel organoid models of PKD need to be developed to reveal the pathogenetic underpinnings for human PKD.

Results: We generated kidney organoids from PKD patient-induced PSCs (iPSC) and gene-corrected iPSCs, followed by engrafting these kidney organoids into the subrenal capsule space of immunocompromised mice. Genetic editing was performed in

Conclusions: Our results demonstrate that specific inactivation of the Ir complex in the GABAergic neurons of the ADPKD mouse models. In these organoids, we also observe a dramatic decrease in cystogenesis, indicating a potential role for these organoids in the development of new therapeutic strategies for PKD.

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Funding: NIDDK Support

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

Underline represents presenting author.
PKD patient iPSCs to modulate primary cilium-autophagy signaling axis, followed by organoid generation and xenotransplantation. The organoid xenografts were recovered four weeks post engraftment for phenotypic analysis and single cell transcriptomic analysis.

**Results:** PKD patient iPSCs-derived kidney organoids spontaneously developed tubular cysts where gene-corrected organoid xenografts showed an absence of cystogenesis. PKD organoid xenografts showed a myriad of structural and functional abnormalities reminiscent of human PKD. In particular, cellular autophagy was significantly compromised in PKD organoid xenografts. Primary cilium ablation in PKD organoid xenografts induced cystogenesis, alongside an upregulation of autophagy. On the contrary, primary cilium ablation in the gene-corrected organoid xenografts induced cystogenesis, in parallel with a significant downregulation of autophagy. Employing the organoid xenograft model of PKD, we evaluated the effect of an FDA-approved drug on cystogenesis in vivo.

**Conclusions:** The organoid xenograft model of PKD recapitulates spontaneous cyst formation in vivo, representing a more sophisticated system for revealing novel therapeutic targets and for evaluating the clinical potential of candidate drugs.

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

**TH-OR66**

_Degradation of O-Glucosylation, a Metabolic Regulator, Attenuates PKD Progression_

Matthew A. Kavanaugh, Dana G. Isai, Henry Wang, Antonio Artigues, Maria T. Villar, Stephen C. Parnell, Chad Slawson, Darren P. Wallace, Pamela V. Tran. University of Kansas School of Medicine, Kansas City, KS.

**Background:** Altered cell metabolism is an important component of autosomal dominant polycystic kidney disease (ADPKD). In this study, we investigated if O-linked N-acetylglucosamine (O-GlcNAc) regulates cystogenesis in ADPKD by targeting Glucosylation in the mouse.

**Methods:** We generated juvenile and adult Pkd1 conditional knockout (cko) and Pkd1 double knockout (dko) mice using the Hox-B7-Cre and the diphtheria toxin inducible Pax5rtTA;LC1-Cre recombinases (induced from 4-6 weeks of age). Juvenile and adult mouse kidneys were analyzed on postnatal day (P)14 and at 4 months of age, respectively. To identify hyper-O-GlcNAcylated proteins in Pkd1, immunoprecipitation and western blot were performed on mouse renal tissue extracts. Mass spectrometry was utilized to map the O-GlcNAcylated sites on identified proteins. To examine mechanisms in human ADPKD, cyst-lining epithelial cells were cultured in a 3D collagen matrix and an OGT inhibitor was tested on in vitro cyst formation.

**Results:** In juvenile mice, Ogt deletion in Pkd1 cko mice reduced cystogenesis and kidney weight:body weight ratios (KW:BW); reduced renal cell lengths; reduced inflammation and fibrosis; increased activation of the energy sensor AMPK; and improved kidney function. Further, while Pkd1 cko mice die between P14-P20, Pkd1;Ogt dko mice continue to thrive beyond 14 weeks of age. Additionally, AMPK was found to be hyper-O-GlcNAcylated at P14 in Pkd1 cko mice. Similarly, in adult mice, deletion of Ogt in Pkd1 cko mice reduced renal cystogenesis and KW:BW. Finally, OGT inhibition reduced in vitro cyst formation by cultured human ADPKD cyst cells.

**Conclusions:** In PKD, protein O-GlcNAc, including of AMPK, is increased, and deletion or inhibition of OGT reduces cyst growth and disease severity, demonstrating that O-GlcNAcylated is an important driver of PKD progression. We propose that targeting O-GlcNAcylate may have therapeutic potential in ADPKD.

**Funding:** Other U.S. Government Support

**TH-OR67**

_Ciliary Exclusion of ARL13B or Loss of Its GEF Activity for ARL3 Suppresses Polycystic Kidney Disease in Mice_

Robert E. Van Seiver, Tamara Caspary. Emory University School of Medicine, Atlanta, GA.

**Background:** Polycystic kidney disease (PKD) and primary cilia are intricately linked in PKD genetics. PKD2, which encodes for ciliary polycystin proteins, and the most common genetic causes of PKD. Mouse models predict the presence of a cilia-dependent cyst activating (CDCA) pathway that functions in cilia to drive cystogenesis in mouse models of PKD. This CDCA pathway is normally inhibited by the polycystin-dependent cyst activating (CDCA) pathway that functions in cilia to drive cystogenesis.

**Methods:** To directly test ARL13B’s role in the CDCA pathway, we engineered two distinct ARL13B mutant alleles at the endogenous locus in mice: (1) ARL13B<sub>V358A</sub>, which mutates a single amino acid in ARL13B’s cilia-localization motif; and (2) ARL13B<sub>R79Q</sub>, which is requisite for ARL13B activity retains all known ARL13B biochemical functions. As is stably expressed, yet is undetectable in cilia. ARL13B<sub>V358A</sub> localizes to cilia, retains its GTPase activity, yet cannot activate ARL3. Using the Pax9<sup>Cre</sup>; Tet-O-Cre system, we induced kidney-specific loss of Pkd1 alone (Pkd1<sup>-/-</sup>) or in combination with either of these alleles (Pkd1<sup>-/-</sup>; ARL13B<sub>V358A</sub> or Pkd1<sup>-/-</sup>; ARL13B<sub>R79Q</sub> in adult mice. This adult induction model allowed us to directly test ARL13B’s ciliary and enzymatic roles in kidney cystogenesis in vivo.

**Conclusions:** ARL13B V358A or loss of GEF activity for ARL3 suppressed the severe cystic kidney phenotype caused by loss of Pkd1 alone. These results reveal that ARL13B regulates the CDCA through its GEF activity. Our findings indicate that ARL13B activating a pro-cystogenic pathway, providing a mechanism that could be targeted therapeutically.

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

**TH-OR68**

_Deletion of the Circadian Clock Gene Bmal1 in Renal Collecting Ducts Leads to Rapid Cyst Growth in Autosomal Dominant Polycystic Kidney Disease_

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1University of Kansas Medical Center Department of Internal Medicine, Kansas City, KS; 2University of Florida, Gainesville, FL.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is an inherited kidney disease characterized by progressive cyst growth from the nephrons that can lead to loss of renal function and end stage renal disease. Here we examined if disruption of the circadian clock can alter ADPKD progression. Circadian rhythms are intrinsic, cyclical ~24-hour oscillations in behavior and physiology that coordinate biological processes with the time of day. In mammals, circadian rhythms are regulated by the hypothalamic pacemakers Bmal1 and Clock, and a core component of the circadian clock, which plays an important role in physiological processes including the cell cycle, metabolism, and inflammation.

**Methods:** To determine the effect of Bmal1 gene deletion in ADPKD kidneys, we used the mouse model<sup>1</sup> where induction of mTORC2 activity for another ARL family GTPase, ARL3. Recent work revealed a central role atypical ciliary GTPase which also possesses guanine nucleotide exchange factor (GEF) activity for another ARL family GTPase, ARL3. Recent work revealed a central role in the mouse. However, the disease progression rapidly in RC/Bmal1KO mice. At 8 months, RC/Bmal1KO littermates showed significantly greater kidney weight:body weight ratio and cyst area as compared to RC/RC kidneys. In addition, we found that RC/Bmal1KO mice had increased cell proliferation and apoptosis as indicated by higher Ki-67 and TUNEL staining, respectively. Immunoblot analysis showed significantly increased expression of proliferative factors in RC/bmal1KO kidneys compared to RC/RC kidneys. Bulk RNA seq analysis indicated significantly reduced fatty acid metabolism in RC/RC mice as compared to WT mice, which was further reduced in RC/Bmal1KO mice.

**Conclusions:** These results show for the first time that disruption of the renal circadian clock is a trigger for early and accelerated disease progression in ADPKD.

**Funding:** NIDDK Support

**TH-OR69**

_Ablation of Long Noncoding RNA Hoxhos Exacerbates Cystogenesis in Autosomal Polycystic Kidney Disease_

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**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic disorder characterized by the formation of cysts in the kidney, and is primarily caused by mutations in two genes, Pkd1 and Pkd2. Long non-coding RNA (lncRNA) are >200 bp in length, lack an open reading frame, and have recently emerged as epigenetic regulators of development and disease. The involvement of lncRNAs in ADPKD is not known.

**Methods:** In this study, we investigated the role of lncRNA Hoxhos in ADPKD by abating its expression in the mouse.

**Results:** Phenotypic analysis revealed that Hoxhos-null mice were viable and had grossly normal kidney morphology. At the molecular level, Hoxhos-null kidneys showed activation of mTOR/akt signaling and subsequent increase in cell proliferation. To determine whether downregulation of Hoxhos affects cystogenesis, we crossed the Hoxhos<sup>-/-</sup> mouse to two orthologous Pkd1 mouse models: Pkd1<sup>-/-</sup>;Pkd1<sup>flox</sup> (rapid cyst progression) and Pkd1<sup>-/-</sup>;Pkd1<sup>-/-</sup> (slow cyst progression). Ablation of Hoxhos exacerbated cyst growth in both mouse models. To gain insight into the mechanism(s) whereby Hoxhos inhibition promotes cystogenesis, we performed proteomic analysis of mTOR/akt signaling between single knockout (Pkd1<sup>-/-</sup>; SKO) and double knockout (Pkd1<sup>-/-</sup>;Hoxhos<sup>-/-</sup>; DKO) mice. Compared to SKO, DKO mice displayed increased levels of total and phosphorylated RICTOR, a protein component specific to mTORC2. This was accompanied by enhanced phosphorylation of AKT at Ser473, a known mTORC2 activation site. Physiological drivers of cystogenesis from DKO mice displayed 40-50% increase in cell proliferation.

**Conclusions:** Results from this study indicate that ablation of Hoxhos in mouse ADPKD dysregulated mTORC2 and exacerbated cystogenesis.

**Funding:** NIDDK Support

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

*Underline represents presenting author.*
TH-OR70
Aberrant Renal Microvascular Remodelling and Impaired Blood Perfusion Occur in the Early Stages of Autosomal Dominant Polycystic Kidney Disease
Dantyal J. Jafree, Charith Perera, Gideon Pomeranz, Laura Wilson, William J. Mason, Maria K. Joannou, Yoshiharu Muto, Benjamin D. Humphreys, Mark Lythgoe, Simon Walker-Samuel, David A. Long, University College London, London, United Kingdom; 2Washington University in St Louis School of Medicine, St Louis, MO.

Background: The renal microvasculature is altered in autosomal dominant polycystic kidney disease (ADPKD); assumed to be a secondary consequence of expanding fluid-filled cysts. However, the vascular phenotype may be an important contributor from the initiation of PKD. Therefore, we assessed the molecular profile, structure, and function of the renal microvasculature in the early stages of ADPKD.

Methods: We amassed single nucleus RNA-seq (snRNA-seq) data of microvasculature from human ADPKD explants, validating findings using 3D confocal microscopy. A time-course of murine PKD carrying an orthologous mutation (Pkd1(Pkd1RC/RC)) was generated by assessing kidney/body weight ratio and blood urea nitrogen. Arterial spin labelling (ASL) and 3D confocal microscopy were leveraged to examine renal blood flow and microvascular structure at early (3 months) and late (9 months) timepoints in the Pkd1(Pkd1RC/RC) murine model.

Results: A population of osteopontin (SPP1) vessels was identified in pericytic regions of human ADPKD, but not in human kidney disease of other etiologies. Endothelial SPP1 was upregulated in mice at 3 months of age; long before kidney function declined in the mouse model. This was associated with reduction in renal blood flow in non-cystic regions of cortex of Pkd1(Pkd1RC/RC) mice compared to controls at both 3 months (p = 0.005) and 9 months (p = 0.004) of age. In 3-month-old Pkd1(Pkd1RC/RC) mice, abnormal microvascular patterning was found, including decrease in mean vessel length (p = 0.04) and increased vascular density (p = 0.01).

Conclusions: Multiple modalities applied to mouse and human tissues suggest that microvascular molecular profile, structure and function are altered in ADPKD prior to irreversible loss of renal function. Our findings advocate the renal microvasculature in ADPKD as a therapeutic target, with the potential to modulate or preserve organ function from early stages of the disease.

Funding: Government Support - Non-U.S.

TH-OR71
Live Imaging Coupled with Image-Based Machine Learning Uncovers Potential Drivers and Therapeutic Targets in a Human Model of Ischaemic Reperfusion Injury
Carmen M. Cusack, Harry Horsley, Alan D. Salama, Enriklo K lootwijk, University College London, London, United Kingdom.

Background: During renal transplantation, kidneys are subjected to periods of hypoxia accompanying with nutrient deprivation, followed by reperfusion, stimulating the infiltration of immune cells into the kidney. There is growing interest in novel preservation methods to improve graft outcomes.

Methods: Primary proximal tubular epithelial cells (PTCs) were exposed to hypoxia (1% O₂) for 72 hours in Hanks Balanced Salt Solution (HBSS) to mimic nutrient deprivation, with or without folic acid (FA) or complete Dulbecco’s Modified Eagle Medium (DMEM). PTCs were re-oxygenated with complete DMEM (24h) B) ML mask generated from (A), C) Cell death ratios of PTCs +/- FBS generated from ML pipeline.

Conclusions: Multiple modalities applied to mouse and human tissues suggest that microvascular molecular profile, structure and function are altered in ADPKD prior to irreversible loss of renal function. Our findings advocate the renal microvasculature in ADPKD as a therapeutic target, with the potential to modulate or preserve organ function from early stages of the disease.

Funding: Government Support - Non-U.S.
TH-OR73
Spatiotemporal Immune Atlases of Two Gene-Edited, Pig-to-Human Kidney Xenotransplants
Matthew D. Cheung, Rebecca Asimwe, James F. George, Jayme E. Locke, Paige M. Porrett. The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.

Background: Xenotransplantation is a promising solution for the organ shortage, but enthusiasm to proceed to clinical trials is tempered by persistent knowledge gaps about the human immune response to porcine kidney xenografts and how best to control it. Preliminary data from our group and others have suggested a role for complement immune-mediated injury of the xenograft. We used state-of-the-art single-cell technologies to characterize the human immune response to porcine kidney xenografts in two brain-dead human recipients, one of whom received the C5a inhibitor eculizumab.

Methods: Kidneys from 10–gene modified pigs were transplanted into two nephrectomized brain-dead human recipients in the setting of standard immunosuppression (induction: anti-thymocyte globulin and rituximab; maintenance: tacrolimus, mycophenolate mofetil, prednisone). Decedent 1 received eculizumab. Xenograft core biopsies were taken pre- and post-transplant (days 1, 2, and at termination on day 3) and assessed by spatial transcriptomics. Porcine and human CD45+ cells were sorted from the explanted xenograft and analyzed using single-cell RNA seq. Data were aligned to a custom porcine-human reference genome to distinguish porcine and human transcripts and analyzed using Seurat and cell2location.

Results: Human immune cells were uncommon in the xenograft biopsies; few human neutrophils and macrophages were detected 3 days after transplant. Human neutrophils were commonly found in decedent 2. Myeloid cells were the predominant lineage in the porcine and human compartments, and both human and porcine macrophages expressed an anti-inflammatory gene signature. Notably, human B and T cells were absent in the xenograft cortex at all time points assessed in both decedents.

Conclusions: Limited human immune cells infiltrate the porcine kidney early after xenotransplantation. Eculizumab administration was associated with a decrease in neutrophils in the xenograft. These data suggest that the addition of a complement inhibitor to conventional immunosuppression may limit further innate immune cell graft infiltration in a preclinical human model of xenotransplantation. These data may help inform the immunosuppression design for upcoming clinical trials.

Funding: Commercial Support - United Therapeutics Corporation

TH-OR74
Subpopulations of Injured Proximal Tubular Cells in Allograft Kidneys: Computational Analysis of Available scRNAseq Datasets
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1,2Universiteit Antwerpen, Antwerpen, Belgium; 3Universitätsklinikum Aachen, Aachen, Germany.

Background: Single-cell RNAseq has been used to investigate the cellular phenotypical landscape of allograft kidneys undergoing ischemia/reperfusion injury. Rather less attention has been paid to the proximal tubular cell (PTC) population. Here, we re-analyzed human single-cell (sc)RNAseq datasets of histologically normal and injured allograft kidneys to characterize PTC phenotypes.

Methods: We analyzed five publicly available human scRNAseq datasets, including data on histologically normal appearing kidney allografts (two datasets) and allografts with acute tubular injury (three datasets). Using R software (Seurat, DESeq2, clusterProfiler), we identified “injured” and “healthy” PTC populations, and determined their differentially expressed genes (DEGs) and enriched pathways. We compared the DEGs and pathways of “injured PTC populations” from histologically normal allografts with those of adverse allografts.

Results: In all datasets, we identified at least one healthy and one injured PTC population. The injured PTCs were characterized by the expression of established PTC injury markers (CD68, SP1, IL32). Most of the commonly dysregulated pathways in the injured PTCs were related to energy metabolism: fatty acid/mono acid metabolism, oxidative phosphorylation, glycolysis/gluconeogenesis. The injured PTCs in one of the two histologically normal allograft datasets presented markers of failed repair (upregulated DCDC, downregulated SLC5A12/SLC7A13). These PTCs also showed enrichment of Wnt- and Hippo-signaling pathways, previously identified in a mouse model of AKI-to-CKD progression. Although the average relative proportion of injured PTCs was lower in the histologically normal allografts (4.6% +/- 4.6%) compared to the injured allografts (15.1% +/- 9.9%), inherent inter-dataset heterogeneity did not reveal statistical significance.

Conclusions: We identified and characterized common PTC subpopulations across five allograft scRNAseq datasets. We found that histologically normal appearing allograft kidneys contain an injured PTC population, which is shared with allografts with acute tubular injury.

TH-OR75
Cold Storage-Mediated p38MAPK Activation: A Potential Contributor of Proteasome Dysfunction and Kidney Damage After Transplantation
Dinesh Bhattachar, Seongok Lee, Nirmala Parajuli. University of Arkansas for Medical Sciences, Little Rock, AR.

Background: The majority of donor kidneys require cold storage (CS) prior to transplantation, but this process usually leads to suboptimal outcomes, due to CS activating cellular pathways that damage kidney tissue. Previously, we demonstrated that CS followed by transplantation decreases proteasome function in rat renal grafts; however, the mechanism of this dysfunction is not known.

Methods: Established in vivo (CS+Tx) and in vitro (CS+RW) models of rat kidney cold storage followed by transplantation. The proteasome function was performed using rat kidney homogenates and recombinant peptide substrates. The subunit level of the proteasome subunit was characterized using renal extracts and western blotting.

Results: Western blots showed an unprecedented higher-molecular-weight band of Rp6 subunit of the proteasome after CS+Tx, suggesting a post-translational modification (PTM) of the Rp6 subunit. Non-denatured western blots for Rp6 revealed aggregated proteasome levels after CS+Tx. Phosphatase treatment of renal extracts depleted the higher-molecular-weight band of the Rp6 subunit in the CS+Tx, suggesting that the aggregation of Rp6 was associated with phosphorylation. Renal (NRK) cells exposed to CS+RW showed a time-dependent increase p38MAPK activation. Treatment of NRK cells with p38MAPK inhibitor (SB202190 or VX-745) during CS followed by rewarmining increased the cell viability and proteasome activity when compared to the CS+RW condition, suggesting that p38 MAPK negatively regulates tubular cell viability during CS+RW. Finally, in vivo treatment of the donor kidney with Bortezomib prior to transplantation (no CS) increased renal dysfunction after transplantation, suggesting normal proteasome function is needed to prevent renal injury in the transplants.

Conclusions: Together, our results suggest that CS-mediated activation of the p38 MAPK may contribute to Rp6 phosphorylation/aggregation, which then leads to decreased proteasome function and renal injury following CS+Tx. Therefore, p38MAPK could be a novel therapeutic target during CS to reduce CS+Tx-mediated graft failure.

Funding: NIDDK Support

TH-OR76
Mechanism of Cold Storage-Mediated Regulation of Heat Shock Proteins in Renal Grafts After Transplantation
Seongok Lee, Nirmala Parajuli. University of Arkansas for Medical Sciences College of Medicine, Little Rock, AR.

Background: Ischemia-reperfusion injury associated with cold storage (CS) followed by transplantation contributes to impaired protein homeostasis leading to kidney graft injury. However, the mechanisms of impaired protein homeostasis remain elusive.

Methods: Isolated donor rat kidneys were stored in University of Wisconsin (UW) solution at 4°C for 0- or 18-hr following by transplantation to recipient rats (CS+Tx). To simulate in vitro model of CS+Tx, rat or human proximal tubular cells (PTCs) were exposed to UW solution at 4°C followed by rewarmining (RW) at 37°C (CS+RW). RNA interference, overexpression studies, and western blotting were the key assays.

Results: Using in vivo and in vitro models of transplantation, we found that the two members of 70-KDa heat shock proteins (HSPs) were dysregulated—a robust increase of Hsp72 and a decrease of Hsc70 in kidney grafts after CS+Tx. Hsp72 is a stress-activated transcription factor that induces HSPs during stress. Our data show that the HSF1 was significantly increased and modified during CS in both in vitro and in vivo transplant models, but decreases after reperfusion/rewashing episodes in kidney/renal explants. To investigate the mechanisms of excessive induction of Hsp72 after CS+Tx, the protein level of Hsc70 and/or HSF1 was modulated in PTCs, followed by CS+RW. Interestingly, Hsc70 knockdown in PTCs increased Hsp72 protein but decreased HSF1 protein. Whereas HSF1 depletion increased Hsp70 protein and did not change the Hsp72 protein level in PTCs, the double knockdown of HSF1 and Hsc70 significantly increased the Hsp72 protein levels. Finally, the HSF1 knockdown in PTCs followed by CS+RW decreased Hsc70 levels but increased the Hsp72 protein.

Conclusions: These data show a reciprocal relationship between Hsc70 and Hsp72 in PTCs and that the Hsc70 negatively regulates Hsp72 protein levels. Our data also indicated that the excessive increase of Hsp72 is not regulated by the classical HSF1 pathway, and the elevated Hsp72 protein negatively regulates kidney function after CS+Tx. Together, the results suggest Hsp72 as a potential therapeutic target during CS to improve outcomes after kidney transplantation.

Funding: NIDDK Support

TH-OR77
Evaluation of Porcine Cell Ceremic and Viral Transmission Using a Preclinical Human Brain-Dead Decedent Model
Matthew D. Cheung, Christopher Fucile, Rebecca Asimwe, James F. George, Jayme E. Locke, Paige M. Porrett. The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.

Background: Xenotransplantation is a potential solution to the organ shortage crisis, but questions around the potential for zoonotic disease transmission need to be addressed before clinical trials can be safely undertaken. Because zoonotic transmission cannot be assessed in vitro or in preclinical animal models, we used a preclinical brain-dead

TH-OR78
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Matthew D. Cheung, Christopher Fucile, Rebecca Asimwe, James F. George, Jayme E. Locke, Paige M. Porrett. The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL.

Background: Xenotransplantation is a potential solution to the organ shortage crisis, but questions around the potential for zoonotic disease transmission need to be addressed before clinical trials can be safely undertaken. Because zoonotic transmission cannot be assessed in vitro or in preclinical animal models, we used a preclinical brain-dead
human decedent model to evaluate porcine cell chimerism in human tissues as well as the transmission of porcine endogenous retroviruses (PERVs) and porcine cytomegalovirus (PCMV) after porcine kidney xenotransplantation.

Methods: Kidneys were procured from a 10-gene modified pig, transplanted into two nephrectomized brain-dead human decedents, and followed for 3 days. Single-cell RNA seq (scRNAseq) was performed on peripheral blood mononuclear cells (PBMCs) sorted from the xenograft recipients before and after transplantation on post-operative (POD) days 1, 2, and 3. Single-nucleus RNA seq (snRNAseq) was performed on kidney biopsies collected pre-transplant and on POD 1 and 3, as well as distant tissues such as heart, lung, liver, spleen, lymph node, small bowel, and omentum upon termination of the experiment. Sequencing data were aligned to a novel PERV-PCMV-porcine-human merged reference genome to differentiate porcine and human cell types and assess for viral transcript expression. Data were analyzed using the package Seurat 4.0.

Results: ScRNAseq analysis of over 500,000 PBMCs revealed a small number of porcine cells (0.04% ± 0.008%) in decedent 1 and 2, respectively, while there was no detection of porcine cells in any of the 150,000 sequenced cells from human organs. PERV-A and PERV-B (expression level range: 0.3-4) transcripts were detected in a small number of porcine kidney cells (0.79%) and within the porcine cells detectable in the human PBMCs; however, there was no detection of PERV-C. There was no detection of PERV in any of the human organs. No PCMV was detectable in any porcine or human compartment.

Conclusions: Sc- and snRNAseq can detect viral transcript expression and cell chimerism from mixed porcine-human samples. There was no detectable PERV or PCMV transmission early after xenotransplantation, but limited by the short duration of the study. Additional studies will be needed to address long-term safety profiles after xenotransplantation.

Funding: Commercial Support - United Therapeutics Corporation

TH-OR79
The Alteration of Monocyte Subsets and the Early Acute Rejection After Kidney Transplantation
Jeongin Song, Jeongmin Cho, Yong Chul Kim, Hajeong Lee. Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.

Background: Despite the use of recent immunosuppressive agents that mainly modulate adaptive immunity, early acute rejection (EAR) remains an unresolved problem in kidney transplantation (KT). Innate immune cells including monocyte/macrophage-lineage cells may contribute to the EAR occurrence, so we explored the population and phenotypic changes of circulating monocytes in KT recipients.

Methods: Pre- and post-KT peripheral blood mononuclear cells (PBMCs) from 60 KT recipients and 20 live donor samples were collected and analyzed by flow cytometry. Monocytes were classified into three types: classical (CD14+CD16-), intermediate (CD14+CD16+), and non-classical (CD14-CD16-) monocytes. Post-KT samples were collected at the same time as the protocol biopsy within post-operative days 14. The outcome was biopsy-proven acute rejection (BPAR) event excluding borderline samples.

Results: A total of 60 study population, BPAR was diagnosed in 10 of the KT recipients, and 7 of them received living donor KT. In recipients without EAR, the proportions of classical monocytes among CD45+ cells were significantly increased (Fig. 1A, 8.90±5.40% vs 14.60±2.79%, p=0.001) after KT, and the proportions of non-classical monocytes were distinctly decreased (Fig. 1C, 1.45±1.70% vs 0.40±0.47%, p<0.001) after KT. In contrast, in BPAR patients, there were no significant differences in the proportions of all monocyte subsets after KT. Interestingly, the proportion of non-classical monocytes was the lowest in BPAR patients before rejection or donation in both the pre- and post-KT periods (Fig. 1F. 0.72±0.42% vs 1.45±1.67% and 1.09±0.56% at pre-KT (p=0.150 and 0.632), 0.72±0.42% vs 0.37±0.37% and 1.09±0.56% at post-KT (p=0.035 and 0.204)).

Conclusions: Our findings suggest that changes in monocyte subsets before and after KT are associated with EAR occurrence in KT recipients. Non-classical monocytes, in particular, may play an important role in the development of EAR.

Figure 1. Changes in each monocyte subset before and after KT. (No AR: No acute rejection, BPAR: biopsy-proven acute rejection)
TH-OR81
Chemothengic Activation of Pericytes Alters Systemic and Renal Hemodynamics
Jonathan W. Nelson, Matthew W. Hagen, Susan B. Gurley. Oregon Health & Science University, Portland, OR.

Background: Pericytes are specialized cells that wrap around capillaries to provide structural and metabolic support. Pericytes have also been shown to respond to vasoactive compounds, such as angiotensin II, to constrict capillaries. However, the full functional consequence of pericyte activation on systemic and renal hemodynamics are poorly understood. To determine whether pericytes regulate systemic or renal hemodynamics we coupled a pericyte expressing cre line (Pdgfrb-creERT2) with the Qq-DREADD (Designer Receptor Exclusively Activated by Designer Drug) mouse to create Peri-DREADD mice which have pericyte-specific activation in the presence of a DREADD agonist.

Methods: Chemothengetic activation of pericytes was induced with intraperitoneal injection of the DREADD-specific agonist deschlorolozapine (DCZ) in Peri-DREADD mice and control littersmates. Activation of pericytes was determined by measurement of cFos accumulation in pericyte nuclei by immunohistochemistry. Acute blood pressures were measured with a Millar catheter. Cortical and medullary perfusion was measured by contrast enhanced ultrasound. Sodium excretion was measured from urine collected in metabolic cages followed by electrolyte quantification with flame photometry.

Results: We find that Peri-DREADD mice express DREADD protein within pericytes which accumulate nuclear cFos after activation with DCZ. DCZ treatment of peri-DREADD mice acutely increases arterial pressure and decreases medullary and cortical perfusion. Sodium excretion increases following pericyte activation by DCZ.

Conclusions: Pericytes are capable of altering hemodynamics, particularly within the kidney where we observed decreases in cortical and medullary perfusion after chemothengetic activation concurrent with an increased natriuresis that correlates with an increase in systemic blood pressure.

Funding: NIDDK Support, Private Foundation Support

TH-OR82
Piezo1 Participates the Mechanosensation of Juxtaglomerular Cells and Regulates Renin Production In Vitro and In Vivo
Yiming Zhou, Xiaojiao Guang, Le Wang, Siweier Luo. Medical Research Center, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, China.

Background: Renin is a key rate-limiting enzyme in RAS system, which is closely related to water and salt metabolism and the development of cardiovascular diseases such as hypertension. The synthesis and secretion of renin in juxtaglomerular (JG) cells are closely regulated by the blood pressure. To date, however, the molecular identity through which JG cells respond to the blood pressure remains unclear. Recent studies identified the nonselective cation channels Piezo1 as a novel mechanosensitive ion channel which plays an important role in various physiological functions. However, whether Piezo1 channels regulates renin expression remains undetermined.

Methods: In this study, we determined the expression and subcellular localization of Piezo1 in JG cells by qPCR, Western blot, Immunohistochemistry. Then, a Fluor-4 AM-based calcium-imaging system was used to detect the dynamic changes of intracellular calcium in response to Piezo1-specific agonist MS and mechanical stress (MS)-induced by perfusion. Piezo1 knockout JG cells abolished Yoda1-induced effect. Then, we used RNA-seq experiment to investigate the downstream signaling of Piezo1 in JG cells.

Results: We found that the calcium permeable ion channel Piezo1 was expressed in JG cells in mouse kidney slides as well as mouse JG cells. Activation of Piezo1 by its agonist Yoda1 and MS induced an intracellular calcium increase and reduced the expression of renin in these cells, while knockout of Piezo1 in JG cells abolished the effect of Yoda1. Mechanistically, RNAseq assay demonstrated that activation of Piezo1 upregulated the PTGS2 expression via the calcineurin-NFAT pathway and increased the production of PTGS2 (COX-2) and PGE2 in JG cells, which inhibited cAMP production and reduced renin expression in JG cells. In animal model, we demonstrated that activation of Piezo1 significantly downregulated the blood pressure in wildtype but not kidney-specific Piezo1 knockout mice.

Conclusions: In summary, these results revealed that activation of Piezo1 could regulate the renin expression in vitro and in vivo, subsequently reducing blood pressure, highlighting its therapeutic potential as a drug target of the renin-angiotensin system.

TH-OR83
Cellular-Level Transcriptomics and Three-Dimensional Imaging for Recruited Renin Cells
Hiroki Yamaguchi, Manako Yamaguchi, Hirofumi Watanabe, Silvia Medrano, Maria Luisa S. Sequeira Lopez, Roberto Ariel Gomez. University of Virginia School of Medicine, Charlottesville, VA; Nigata University Graduate School of Medical and Dental Sciences, Nigata, Japan.

Background: Renin synthesis is tightly regulated by the ability of juxtaglomerular cells (JG) to sense arterial pressure signals. Once severe hypertension occurs in adult animals, JGs promote renin synthesis first. Subsequently, a subset of vascular smooth muscle cells (VSMC) derived from renin progenitors turn on renin expression to restore homeostasis: this phenomenon is termed recruitment. However, identifying the mechanisms of the recruitment of renin lineage cells has been challenging due to their rarity and structural complexity. In this study, we investigated the transcriptome profiles and expression patterns of individual recruited renin cells by single-cell RNA-seq and three-dimensional (3D) imaging.

Methods: Since forkhead box protein D1 (FoxD1) expressing stromal cells are the progenitors for JGs and VSMCs of the renal arteriole, we generated FoxD1-CreERT2 mice all FoxD1+ expressing cells express tdTomato reporter. To investigate the possible mechanisms of the recruitment of renin lineage cells, we used tdTomato creERT2 mice line with a Cd1d+ dendritic cell. We crossed Cd1dcreERT2 mice to a representative model of aortic coarctation (AoCo) between the base at the renal arteries of the left kidney (LK) and right kidneys (RK) that received low and high perfusion pressure, respectively. We FACS sorted tdTomato+ cells from the LK and RK cortices and performed single-cell RNA-seq. We identified the differentially expressed genes (DEG) and the gene ontologies between LK and RK. To visualize renin-expressing cells in 3D, we applied the clear, unobstructed brain/body imaging cocktails (CUBIC) protocol for clearing kidneys of the Ren1−,tdTomato mice that underwent Acoet surgery. We used Zeiss Lightsheet Z8 for 3D imaging.

Results: By single-cell RNA-seq, FoxD1+ cells were clustered into IG, VSMC, and other cell types. DEG analysis in LK compared to RK showed that Ren1 was the upregulated DEG in JG and VSMC. In VSMC, gene ontology analysis showed the upregulation of the cellular response to laminar fluid shear stress pathway in LK, suggesting that extracellular force changes affect the gene expression. By CUBIC protocol, renin-expressing cells in the Ren1−,tdTomato mice kidneys could be visualized in 3D. In LK, we could identify recruited VSMCs forming a striped and ring pattern along with afferent arteries, some extending close to or beyond the bifurcation point.

Conclusions: Severe hypertension causes the widespread recruitment of renin lineage VSMCs in the renal arteriole.

Funding: Other NIH Support - NIH R01DK116718 to RAG, R01HL148044 to MLLSS, and P50DK096373 to RAG and MLLSS.

TH-OR84
Identification and Characterization of a Vascular Calcification Mediator Originating in the Adrenal Glands
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Background: Patients undergoing dialysis for chronic kidney disease (CKD) often suffer from vascular calcification, leading to diverse cardiovascular complications. In this study, we conducted a comprehensive investigation to identify and characterize a newly discovered endogenous peptide that plays a regulatory role in vascular calcification processes. Our findings shed light on an unexplored cardioprotective function of the adrenal glands in the context of CKD-associated vascular calcification.

Methods: Chromatographic fractions derived from bovine adrenal glands were tested for their effect on vascular calcification processes using in vitro, ex vivo, and in vivo rat model of elastocalcinosis. To identify potential mediators, mass spectrometric analysis was performed, and the results were compared with relevant databases.

Results: A 19-aa peptide was discovered and its levels were quantified in the serum of end-stage renal disease patients undergoing dialysis, as well as in matched controls. This newly identified peptide, named Calcification Blocking Factor(CBF), demonstrated significant protective effects against vascular calcification. Treatment with CBF effectively reduced the calcium content in thoracic aortic rings cultured under calcifying conditions, and aortas from elastocalcinosis animal models. CBF exerts its protective effects by inhibiting the transdifferentiation of aortic smooth muscle cells into osteoblast-like cells, which are responsible for driving the progression of vascular calcification. CBF interacts with the sodium-dependent phosphate transporter P1-1, and hinders NF-kB activation and the BMP2/p-SMAD pathway, all implicated in vascular calcification. CBF treatment reduced arterial stiffness in elastocalcinosis animals. CKD patients, susceptible to vascular calcification, showed decreased CBF concentration in serum. The 19-amino acid peptide is derived from the enzymatic cleavage of the adrenal protein chromograninA by calpain1 and kalikrein. Further analysis revealed that a specific 6-8 amino acid sequence within the 19-amino acid peptide serves as the active site responsible for the calcification-blocking properties of CBF.
Conclusions: Our findings suggest that CBF, a novel inhibitor of vascular calcification derived from the adrenal glands, plays a crucial role in reducing the risk of vascular calcification.

Funding: Government Support - Non-U.S.

TH-OR85
Mechanisms of Vascular Pathology Following Peritonitis in Peritoneal Dialysis Patients and Therapeutic Intervention
Esra Cetin,1 Morgane Mazzarino,1 Guadalupe T. Gonzalez-Mateo,2 Valeria Kopytina,2 Maria Bartosova,1 Iva Marinovic,1 Soma Meran,1 Donald Fraser,1 Claus Peter Schmitt,1 Manuel Lopez-Cabrera,1 Mario O. Labetta,1 Anne-Catherine Raby,1 1Cardiff University, Cardiff, United Kingdom; 2Universidad Autonoma de Madrid Centro de Biologia Molecular Severo Ochoa, Madrid, Spain; 3UniversitätsKlinikum Heidelberg, Heidelberg, Germany.

Background: In PD patients, CV death is 10 times more likely than in the general population and this risk further increases following each peritonitis episode. Damage-Associated Molecular Patterns (DAMPs) play a critical role in inflammatory pathologies, notably via their activation of Toll-like receptors (TLRs), but their specific role in mediating long-term vascular pathology following an infection remains underscribed.

Methods: We investigated a potential role for DAMPs in mediating long-term CV risk following peritonitis by i) characterising the long-term vascular inflammatory changes induced by peritonitis in mice, ii) identifying potential target DAMPS following peritonitis by analysing in vivo and PD patients’ plasma samples, iii) mechanistically characterising the potential of our selected DAMP to promote key vascular inflammatory responses by critical cell types in vitro, iv) demonstrating, by pharmacologic inhibition, the critical contribution of a DAMP candidate to the maintenance of vascular proatherogenic responses following peritonitis in mice.

Results: Bacterial peritonitis in mice was resolved in 24h but led to vascular inflammatory responses, expected to promote CVD, that were maintained up to 28 days. These included higher proportions of inflammatory leukocytes, increased cytokine levels, higher adhesion molecules, and increased blood and aortic inflammatory and atherosclerosis-associated gene expression. These findings were maintained in nephropathic animals and exacerbated in animals routinely exposed to PD fluids. In parallel to these changes, a peritonitis episode led to elevated plasma levels of a specific TLR DAMP, Calprotectin, both in animals and PD patients. In vitro, Calprotectin could promote typical vascular inflammatory and pro-atherosclerotic responses: monocyte chemotaxis, foam cell formation, via a reduction of cholesterol efflux by macrophages and loss of endothelial resistance. In vivo, Calprotectin blockade robustly inhibited the short and long-term vascular inflammatory consequences of peritonitis.

Conclusions: This study demonstrates the major role that the Calprotectin-TLR pathway plays in driving long-term vascular pathology following a peritonitis episode.

TH-OR86
Single-Cell Pathological Landscape Analysis of Vascular Calcification in CKD by Imaging Mass Cytometry
Yuyao Wang, Anying Cheng, Qing Li, Yongman Lv, Fan He. Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan, China.

Background: Vascular calcification (VC) is regarded as an important pathological change which associated with high mortality in patient with chronic kidney disease (CKD). It is necessary to study changes of cell communication and their PTMs in situ.

Methods: A highly multiplexed imaging mass cytometry (IMC) panel was designed to simultaneously quantify 34 biomarkers of tissues from 38 patients with CKD and 2 donors to generate 64 highly multiplexed images at single-cell resolution. All cells were divided into different cell types according to the expression of markers. Neighboring cells were defined as the top 15 nearest cells to a K-means clustering algorithm was then applied to cluster cell neighborhoods into numerous community clusters (CCs). Relevant to the stage of vascular calcification by Von Kossa staining was identified as a specific target for preventing vascular calcification.

Results: The 156 community clusters were defined. We found that contractile VSMCs and progenitor cells decrease with progression of vascular calcification. The osteochondrogenic VSMCs showed a trend of decreasing first and then increasing, which may be caused by the proliferation of synthetic VSMCs in the early stage of calcification. At the same time, community clusters changed with progression of vascular calcification. Contractile VSMCs and osteochondrogenic VSMCs mixed community clusters decreased with the progression of vascular calcification. On the contrary, osteochondrogenic VSMCs dominant community clusters osteochondrogenic VSMCs elevated in severely calcified vessels. In addition, expression of H1K27me3 of community cluster 10 that mainly composed of osteochondrogenic VSMCs and fibroblasts decreased with the progression of vascular calcification.

Conclusions: Our findings reveal for the first time the various topological function units in VC in CKD. This also presents the single-cell pathological landscape for VC in CKD. This work highlights the potential of a community cluster with a mixture of osteogenic VSMC and fibroblasts in driving vascular calcification, which may cause by the decreasing of H1K27me3.

Funding: Government Support - Non-U.S.
Mechanisms of Hypertension and Cardiorenal Disease: From the Vasculature to the Gut

Oral Abstract/Thursday

TH-OR98
Dopamine D4 Receptor Regulates Sodium Chloride Cotransporter in Renal Distal Convered Tubules
Mingzhuo Zhang, Mingdi Liu, Weiwang Wan, Zhiyun Wang, Xiaoyan Wang. Nanjing BenQ Medical Center; Nanjing, China.

Background: Dopamine D4 receptor (D4R) is expressed in the distal convoluted tubule (DCT) and the mice lacking D4R have kidney-related hypertension.

Methods: The regulation and mechanisms of D4R on NCC were determined in D4R null mice (20 weeks-old, mixed sex) and cultured mouse distal convoluted tubule (mDCT) cells.

Results: NCC activities, measured by response to NCC inhibitor hydrothiazide (30ng/kg/d, IP) were different in D4R+/- mice than D4R-/- littermates in initial 6 hrs (NCC:513±121 vs 633±87nmol/mg of Cr, n=8) with SBR (118±5 vs 104±6 mmHg, n=8, tail-cuff) normalized on days 4-7. The renal NCC protein abundance by immunoblotting (230±51, % of control, n=4-5, same as below) and immunofluorescence was greater but ubiquinated-NCC levels (66±13) were lower in KO than in WT mice. mRNA levels of NCC by qPCR and phosphorylation-NCC were not altered. NCC abundance (121±9) in KO remained higher than WT under the infusion of dopamine via osmotic mini-pump (1ug/kg/min, 1wk). In the mDCT cells, the immunoprecipitation of D4R with NCC was increased by PD168077. Colocalization and interaction of them was seen with confocal microscopy and confirmed by FRET-D4R-ssRNA (1.5nt, 48 hrs) increased the protein expression of NCC (152±34, n=4); D4R agonist PD168077 (0-10uM, 24 hrs) decreased NCC protein abundance concentration-dependently; D4R antagonist L-745,870 (10uM, 24 hrs) had no effect but blocked the D4R agonist-mediated inhibition of NCC abundance (272±18) was decreased but ubiquinated-NCC was increased remarkably (266±114) by PD168077 (10uM). PD168077 internalized NCC by membrane-biotinylatation-method and increased the NCC colocalization with lysosomal-associated membrane protein 1. The PD168077-induced NCC decrease was reversed by lysosomal inhibitor chloroquine (20uM). 1hr PD168077 also decreased intracellular sodium transport (74±1, n=7), which was blocked by D4R antagonist L-745,870. AT1R protein abundances (96±8, n=4), Ncc mRNA levels (116±13, n=9) of were not altered in D4R agonist treated cells at 24 hrs.

Conclusions: D4R inhibits NaCl transport in renal DCT by reducing NCC activity and protein abundance with promoting its internalization, ubiquitination and consequent lysosomal degradation.

TH-OR99
Performance of eGFR Equations for Drug Dosing in Kidney Transplant Recipients
Gregory L. Hundemer, Manish M. Sood, Ayub Akbari. Ottawa Hospital Research Institute, Ottawa, ON, Canada.

Background: For kidney transplant recipients (KTRs), drug dosing is most commonly determined by using eGFR as a surrogate for graft function. Which eGFR equation performs best for drug dosing in KTRs remains unknown.

Methods: Cross-sectional study of 415 stable KTRs from Canada and New Zealand with same-day values of serum creatinine and cystatin C along with measured GFR (‘true’-DTPIA).

We assessed the performance for drug dosing of CKD-EPI (both indexed to a standardized body surface area [BSA] of 1.73m2 [mL/min/1.73m2]) and non-indexed to account for actual BSA [mL/min] and Cockcroft-Gault (via 3 different weights: ideal, adjusted ideal, and actual body weight) eGFR equations relative to measured GFR based upon recommended renal dosing of 8 medications commonly prescribed to KTRs: foscavir, ganciclovir, trimethoprim/sulfamethoxazole, oeseltamivir, ciprofloxacin, levofloxacin, lamivudine, and imatinib/vinizonavir. The primary outcome was proportion of drug dosing discordance (under- or over-dosing) overall and stratified by obesity status (BMI < or ≥30kg/m2).

Results: The non-indexed CKD-EPI equations led to a lower proportion of drug dosing discordance compared to the indexed CKD-EPI equations across all study drugs (Figure). The Cockcroft-Gault equations based upon adjusted ideal and actual body weight led to a lower proportion of drug dosing discordance compared to ideal body weight. These findings were most pronounced among obese KTRs. Overall, the non-indexed 2021 CKD-EPI eGFR equations showed the lowest proportion of drug dosing discordance among KTRs.

Conclusions: When employing eGFR-based drug dosing for KTRs, actual BSA should be accounted for to mitigate the risks of under- or over-dosing. The non-indexed 2021 CKD-EPI eGFR equations provide the most accurate eGFR-based guidance for appropriate drug dosing among KTRs.

TH-OR90
Targeted Antibiotic Modulation of the Gut Microbiome Ameliorates Hypertensive Organ Damage
Moritz I. Wimmer,1,2 Valentin Vecera,1,2 Harithaa Anandakumar,1,2 Ulrike Löber,3 Dominik N. Müller,1 Hendrik Bartolomaeus,1,2 Nicola Wilck,1,2 Max Delbruck Center for Molecular Medicine Experimental and Clinical Research Center, Berlin, Germany; Charité Universitätsmedizin Berlin, Berlin, Germany; Max-Delbrück-Centrum für Molekulare Medizin in der Helmholtz-Gemeinschaft, Buch, Germany.

Background: Gut microbiota play an important role in the development of hypertension. To better understand the role of the gut microbiota in modulating hypertensive organ damage, we used narrow-spectrum antibiotics without enteral absorption to specifically deplete gram-negative or -positive bacteria in double transgenic (dTGR) mice.

Methods: Four-week-old dTGR (transgenic for human renin and angiotensinogen) were treated with oral Vancomycin (Vanco), Polymyxin B (Pol) or Vehicle (Veh) for 3 weeks. Seven-week-old SD rats were included as healthy controls. Flow cytometry, echocardiography, telemetric blood pressure (BP) measurement, photon metagenomic sequencing, clinical chemistry, and gene expression analyses (qPCR & bulk RNAseq) were employed to analyze the microbiome, clinical and immune phenotype.

Results: Hypertensive kidney damage was ameliorated in Vanco treated dTGR, as assessed by renal Lnr expression, blood urea nitrogen and albuminuria. Vanco treated dTGR had significantly decreased cardiac hypertrophy. Poly treatment showed no effect. BP levels for both antibiotic treatments were not significantly different from Veh, despite a significantly improved endothelium-dependent and –independent vasoilation in isolated mesenteric arteries in both treated groups. Surprisingly, Vanco treatment led to a massive increase of gram-positive Lactobacilli. As the microbiome and immune system are closely connected, we performed in-depth flow cytometry of immune cells isolated from the heart, kidney, blood, spleen, and intestine. We observed a broad shift to pro-inflammatory immune cell subsets in dTGR. Vanco treatment could partially rescue the kidney inflammation as observed by a reduction in Th17 cells, classical CD14+ and tissue infiltrating monocytes. Poly treatment did not alter the inflammatory signature.

Conclusions: Modulation of the intestinal microbiome by narrow-spectrum antibiotics affects hypertensive organ damage. Depletion of gram-negative bacterial strains by oral Vancomycin ameliorates organ damage independent of BP. Our data underscores the importance of the gut microbiome in modulating hypertensive organ damage and helps to identify potential therapeutic strategies in the microbiome (e.g. Lactobacillus).

Funding: Government Support - Non-U.S.

TH-OR92
Performance of Creatinine and Cystatin C-Based Equations Among Patients with Hematological or Solid Cancers: Real-World Data from a Clinical Cohort
Silvia Titan, John C. Lieske, Jeff W. Meeussen, Andrew D. Rule, Sandra Herrmann. Mayo Clinic Minnesota, Rochester, MN.

Background: Performance of creatinine-based eGFR equations in patients with malignancy may be worse than in the general population with implications for management including drug dosing.

Methods: We retrospectively studied all cases who had mGFR (urinary inolathame clearance) performed at Mayo Clinic 2017-2023 and ICD codes for neoplasia (excluding in situ and benign lesions) up to one year prior to the mGFR date. Serum creatinine and cystatin C within 2 days of the mGFR were used to compute CKD-EPI 2021 eGFRcr and eGFRcys, and 2012 eGFRCys. Bias (absolute and % mGFR - eGFR) and P30 (% with discordance) were calculated for each equation and also for the Cockcroft-Gault equation.

Results: Bias was worse for all eGFR equations among cancer patients compared to the general population. The 2021 CKD-EPI equations performed better than the 2012 equations in the cancer population. However, the Cockcroft-Gault equation performs best for drug dosing in KTRs remains unknown.

Conclusions: When employing eGFR-based drug dosing for KTRs, actual BSA should be accounted for to mitigate the risks of under- or over-dosing. The non-indexed 2021 CKD-EPI eGFR equations provide the most accurate eGFR-based guidance for appropriate drug dosing among KTRs.
Conclusions: Our study suggests that among patients with either solid or hematological malignancies, the CKD EPI eGFRcys reflects better mGFR than either eGFRcr or eGFRcys. When possible, mGFR may be optimal for clinical decision making in these populations.

Table 1.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Mean dose (mg/kg)</th>
<th>Median (IQR)</th>
<th>P &lt; 0.05</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>40</td>
<td>20-60</td>
<td>0.62 (0.57-0.67)</td>
<td>1.8 (1.5-2.0)</td>
</tr>
<tr>
<td>Tolvaptan</td>
<td>15</td>
<td>10-20</td>
<td>0.58 (0.52-0.64)</td>
<td>1.6 (1.3-1.9)</td>
</tr>
<tr>
<td>Difelikefalin</td>
<td>10</td>
<td>5-20</td>
<td>0.50 (0.43-0.57)</td>
<td>1.4 (1.1-1.7)</td>
</tr>
</tbody>
</table>

furosemide, furosemide + difelikefalin (F+D, 20 µg/kg, i.p.; days 6-10), or furosemide + tolvaptan (F+T, 1 mg/kg, i.p.) as an AVP V2 receptor antagonist. After urine collection, rats received a 2nd drug treatment (2:00 pm) and were placed in home cages.

Results: Initial treatment (day 1) of rats with furosemide evoked a marked increase in urine output (V), urinary sodium excretion (UNaV), and urinary potassium excretion (UKV), with the magnitude of each greatly reduced by day 5 (day 5: V, 10.5±6.6 vs 5.6±0.4 ml/hr; UNaV, 971±55 vs 39±2.6 µg/hr; UKV, 250±14 vs 193±20 µg/hr). Over days 6-10, 5-hr urine output remained reduced throughout furosemide treatment (diuretic resistance). Combination treatment with either difelikefalin or tolvaptan over days 6-10 reversed diuretic resistance as noted by a sustained increase in V without increasing UNaV compared to furosemide alone (day 10, V; F, 5.6±0.2 µl/hr; F+D, 10.1±6.77 µl/hr; F+T, 11.1±0.9 µl/hr). Further, tolvaptan but not difelikefalin increased UKV over days 6-10.

Conclusions: These findings demonstrate that AVP plays a major role in mediating diuretic resistance to furosemide. Further, we show that combination therapy with a KOR agonist (difelikefalin) can reverse and potentially prevent diuretic resistance while improving loop diuretic induced hypokalemia and hypotension. (LSUHSC Research Enhancement Program)
TH-OR96
SGLT2 Inhibitor Protects from Repeated Low-Dose Cisplatin-Induced Chronic Kidney Damage
Dianet Sanchez Vega,1 Leah J. Siskind,1 Andrew Orwick,1 Pranav S. Garmella,1 Volker Vallon,2 Theresa A. Weis,1 Dana Hammour1.1 University of Louisville School of Medicine, Louisville, KY; 2University of California San Diego, La Jolla, CA.

Background: Cisplatin is Cognitive dysfunction is a well-known complication agent that causes a dose dependent acute kidney injury (AKI) in nearly a third of treated patients, which subsequently leads to chronic kidney disease (CKD). There are no current FDA approved medications to prevent cisplatin induced kidney damage. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce risk of AKI and CKD in humans, and have shown renoprotection in a single dose experimental model of cisplatin-induced AKI. We hypothesized that SGLT2i could protect the kidney in a mouse model of repeated low dose cisplatin and cancer to better mimic the clinical scenario.

Methods: B6:129 mice with and without lung adenocarcinoma were treated with daily SGLT2i (empagliflozin or dapagliflozin) or vehicle control for 28 days beginning 1 week prior to the first dose of weekly cisplatin (7mg/kg) or vehicle control. Following the third cisplatin injection, biomarkers for kidney function, injury, fibrosis, inflammation, kidney histology and tumor growth were assessed and compared between SGLT2i and vehicle control.

Results: SGLT2i treatment attenuated cisplatin-induced alterations in kidney function and injury. Markers of kidney fibrosis including TGF-β, a-SMA, fibronectin and collagen were lower in mice co-administered SGLT2ti and cisplatin as compared to mice given vehicle control and cisplatin. SGLT2i did not alter tumor growth or response to cisplatin.

Conclusions: SGLT2i demonstrate a beneficial effect against kidney damage in a model of repeated low dose cisplatin and lung cancer. Future studies are needed to determine if they can be used post cisplatin treatment to improve and/or prevent progression of kidney injury to fibrosis and CKD.

Funding: NIDDK Support

TH-OR97
Pharmacokinetics of Henagliflozin in Dialysis Patients with Diabetes
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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are recommended to treat heart failure, irrespective of the presence of type 2 diabetes. Heart failure is one of the most common complications in dialysis patients. Not all SGLT2i are recommended for use in dialysis patients because less glucose enters the proximal tubule and the effects of inhibiting glucose and sodium reabsorption are reduced, as well as due to a lack of efficacy and safety data. However, emerging evidence has suggested that SGLT2i improve heart failure outcome through the off-target effect. Therefore, patients on dialysis with heart failure may benefit from SGLT2i. We conducted this study to evaluate the pharmacokinetics of Henagliflozin in mice and in 10 mg/kg of Henagliflozin in patients with diabetes.

Methods: In this prospective, randomized, open-label study, 10 hemodialysis and 10 peritoneal dialysis patients with diabetes were randomized in a 1:1:1 ratio to oral administration of Henagliflozin in doses of 5 mg and 10 mg in dialysis patients with diabetes.

Results: Henagliflozin plasma levels were measured. Plasma concentrations of Henagliflozin were analyzed by using validated liquid chromatography-tandem mass spectrometry method.

Conclusions: The mean values of Cmax were 70.2–77.0 ng/mL and 105–143 ng/mL in the 5 mg and 10 mg Henagliflozin groups, respectively; the mean values of AUCinf were 777–930 h*ng/mL and 1290–1730 h*ng/mL in the 5 mg and 10 mg Henagliflozin groups, respectively. The median Tmax values ranged from 1 to 3 h across the dose range. The mean values of T1/2 of Henagliflozin were 14.1–14.5 and 16.2–21.0 h in the 5 mg and 10 mg groups, respectively. The values of mean values of the steady state in dialysis patients with 5 mg of Henagliflozin were 150 ± 4.4 ng/mL and 26.8 ± 16.3 ng/mL, respectively, which were 123.8% and 131.0% higher than those in diabetic patients with normal renal function, respectively. Henagliflozin concentration was decreased by 1.1% after hemodialysis treatment. No treatment-related serious adverse events or discontinuations occurred.

Conclusions: Henagliflozin at the current recommended dosage may be safe although it accumulates in patients on dialysis. Clinical trials should be conducted to examine the cardioprotective effects of Henagliflozin in dialysis patients.

Funding: Government Support - Non-U.S.

TH-OR98
Canagliflozin Pharmacokinetics at Steady State in Patients on Maintenance Hemodialysis
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Background: Sodium glucose co-transporter-2 (SGLT-2) inhibitors improve cardiovascular and kidney outcomes in patients with preserved renal function or with mild and moderate chronic kidney disease. However, they have not been studied in patients on maintenance hemodialysis (HD). Detailed study of SGLT-2 inhibitor pharmacokinetics in patients receiving HD is the first step to establishing their safety in this population.

Methods: Patients with kidney failure on maintenance HD for at least 3 months were invited to participate. Those with type 1 diabetes mellitus, euglycemic ketoacidosis, or liver disease were excluded. All participants received 100 mg of canagliflozin once daily for nine days. Venous blood samples were collected immediately before (0) and 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours after canagliflozin administration for pharmacokinetic analyses on day 8 (a mid-week non-dialysis day) and hourly during hemodialysis on day 9. Canagliflozin plasma levels were measured with liquid chromatography- mass spectrometry and compared to published estimates in healthy controls.

Results: We enrolled 10 patients (6 men, 4 women; median age, 59 ± 14 years; median weight, 54.3 ± 16.1 kg; mean creatinine clearance, 22.3 ± 24.8 mL/min per 1.73 m²; mean body mass index, 25.7 ± 3.9 kg/m²). The median (range) of the steady state on day 10, and single hemodialysis clearance of Henagliflozin were measured. Plasma concentrations of Henagliflozin were analyzed by using validated liquid chromatography-tandem mass spectrometry method.

Results: The mean values of Cmax were 70.2–77.0 ng/mL and 105–143 ng/mL in the 5 mg and 10 mg Henagliflozin groups, respectively; the mean values of AUCinf were 777–930 h*ng/mL and 1290–1730 h*ng/mL in the 5 mg and 10 mg Henagliflozin groups, respectively. The median Tmax values ranged from 1 to 3 h across the dose range. The mean values of T1/2 of Henagliflozin were 14.1–14.5 and 16.2–21.0 h in the 5 mg and 10 mg groups, respectively. The Cmin values of the steady state in dialysis patients with 5 mg of Henagliflozin were 150 ± 4.4 ng/mL and 26.8 ± 16.3 ng/mL, respectively, which were 123.8% and 131.0% higher than those in diabetic patients with normal renal function, respectively. Henagliflozin concentration was decreased by 1.1% after hemodialysis treatment. No treatment-related serious adverse events or discontinuations occurred.

Conclusions: Henagliflozin at the current recommended dosage may be safe although it accumulates in patients on dialysis. Clinical trials should be conducted to examine the cardioprotective effects of Henagliflozin in dialysis patients.

Funding: Government Support - Non-U.S.

TH-OR99
Ondansetron and the Risk of Sudden Cardiac Death Among Patients Receiving Hemodialysis
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Background: Sudden cardiac death (SCD) is common among hemodialysis (HD) patients. Ondansetron, an antiemetic with known QT prolonging potential, has a Food and Drug Administration warning about its association with fatal arrythmias in the general population. The cardiac safety of ondansetron in the HD population is unknown.

Methods: We conducted a new-user, active-comparator, cohort study using US Renal Data System data (2012-2019) to assess the comparative 10-day risk of SCD between HD patients initiating ondansetron vs. non-QT-prolonging antiemetics (metoclopramide/ chlorpromazine/promethazine). We used inverse probability of treatment weighting and Fine and Gray proportional subdistribution hazard models to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). We used an intention-to-treat approach and treated non-SCD as a competing event. In secondary analyses, we considered broader cardiac outcomes.

Results: Henagliflozin at the current recommended dosage may be safe although it accumulates in patients on dialysis. Clinical trials should be conducted to examine the cardioprotective effects of Henagliflozin in dialysis patients.

Funding: Government Support - Non-U.S.
Results: Of 119,254 study patients, 64,978 (54.5%) initiated ondansetron and 54,276 (45.5%) initiated a co-administered antiemetic. The mean age of patients with a 10-year follow-up was 60 ± 15 years, median (IQR) years on HD was 2.2 (0.9, 4.6), and 55% were female. Ondansetron vs. comparator antiemetic initiation was associated with higher relative and absolute 10-day risks of SCD, all-cause mortality: hazard ratio (HR) 1.45 (95% CI 1.40, 1.50) for each 60 mg/m2 dose of ondansetron initiated. Analyses of other cardiac outcomes yielded similar findings.

Conclusions: Ondansetron vs. comparator antiemetic treatment was associated with higher relative and absolute 10-day risks of SCD among HD patients. Our findings may inform prescriber decisions about antiemetic selection in the HD population.

Funding: Other NIH Support - NH/NHLBI

Figure 1. The 10-day SCD risk among hemodialysis patients initiating ondansetron vs. a non-QT-prolonging antiemetic.

TH-OR100

Safety Outcomes of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Diabetes Mellitus and Cancer

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Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are glucose-lowering agents that reduce the risk of hospitalization for heart failure and chronic kidney disease progression. The risk of serious adverse events with SGLT2i use was low in large clinical trials, but patients with cancer were excluded from these trials. Therefore, the safety of SGLT2 inhibitors in patients with cancer is unknown.

Methods: Using our institute’s electronic medical record system, we identified 5,478 patients with a history of diabetes mellitus and cancer who were prescribed an SGLT2 inhibitor, i.e., empagliflozin, dapagliflozin, canagliflozin or ertugliflozin, between 2013 and 2022. Data on adverse events, including urinary tract infections (UTIs), diabetic ketoacidosis (DKA), genital infections, and non-vertebral fractures, were collected using the ICD-9/10 diagnostic codes.

Results: The medical record query identified 5,478 patients who were prescribed an SGLT2 inhibitor. Each patient had a start and end date for the SGLT2 inhibitor prescription, which added up to a total of 11,175 patient-years on SGLT2 inhibitors. The ICD diagnosis query revealed 424 instances of adverse events coinciding with the SGLT2 inhibitor prescription. The incidence rate of adverse events is shown in Table 1. The 10-day SCD risk among hemodialysis patients initiating ondansetron vs. a non-QT-prolonging antiemetic.

Conclusions: In this cohort of diabetic patients with cancer, the incidence rate of DKA in patients taking an SGLT2 inhibitor was higher (5.1 per 1000 patient-years) as compared to the incidence rate of DKA reported in a recent meta-analysis of SGLT2 inhibitors (0.0-2.2 per 1000 patient-years) and a large observational study (2.37 per 1000 patient-years). We also observed a high incidence rate of UTIs, genital mycotic infections, and non-vertebral fractures. To our knowledge, this is the first study to report the safety outcomes of SGLT2 inhibitors in diabetic patients with cancer. Impact of diabetes on the effects of SGLT2 inhibitors on kidney outcomes. Lancet. 2022. Comparative Effectiveness and Safety of SGLT2 Inhibitors Versus GLP-1 RA in Older Adults. Diabetes Care. 2021

Incidence of adverse events of interest

Table 1: Incidence of adverse events of interest

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Diabetic Patients (%)</th>
<th>Non-diabetic Patients (%)</th>
<th>p-value</th>
<th>p-value</th>
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<td>&lt;0.001</td>
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<td>5</td>
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<td>NON-VERTEBRAL FRACTURES</td>
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<td>4</td>
<td>0.001</td>
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</tbody>
</table>

FR-OR01

AKI Associated with Long-Term Decline in Cognitive Function at 3 Years: ASSESS-AKI Study

Pavan K. Bhatraju,1 Leila R. Zelnick,1 Edward D. Siew,2 Steven Menez,2 Vernon M. Chinchilli,1 Steven G. Coca,3 James S. Kaufman,2 Paul L. Kimmel,6 Chirag R. Parikh,6 Alan S. Go,4 Talat Al Ipzkier,3 Jonathan Himmelfarb,1 Mark M. Wurfel.1 University of Washington, Seattle, WA; 7Vanderbilt University, Nashville, TN; 8Johns Hopkins University, Baltimore, MD; ‘The Pennsylvania State University, University Park, PA; ’Mount Sinai Health System, New York, NY; ‘National Institutes of Health, Bethesda, MD; ‘Kaiser Permanente, Oakland, CA; ‘New York University, New York, NY.

Background: Cognitive dysfunction is a well-known complication of chronic kidney disease but it is less known whether these long-term adverse events are present in survivors of AKI. We hypothesized that an episode of AKI is associated with poorer cognitive function, mediated, at least in part, by persistent systemic inflammation.

Methods: ASSESS-AKI was a multicenter prospective cohort study that enrolled patients surviving three months after hospitalization with and without AKI who were matched based on demographics, comorbidities and baseline kidney function. A subset of patients underwent cognitive testing using the modified mini-mental test (3MS) at 3, 12 and 36 months. The 3MS is scored on a scale of 0-100. We examined the association of AKI with long-term cognitive testing using mixed linear models accounting for matching and loss to follow-up and assessed the proportion in risk mediated by 3-month systemic inflammatory biomarkers (sTNFR-1, IL-6 and IL-8).

Results: Among 1538 patients enrolled in the parent study (769 with AKI and 769 without), 1465 (95%) completed the 3MS at 3 months. Patients with AKI had lower 3MS scores at 3 months (difference -1.1 (95% CI -2.0, -0.3 p=0.01) and at 3 years (-1.5 (95% CI -2.4, -0.7) p=0.01) compared to matched patients without AKI. We also found that a higher proportion of patients with AKI had a clinically meaningful (>5 point) reduction in 3MS scores at 3 years compared to patients without AKI (10% and 5%, p<0.01). In mediation analyses, serum sTNFR-1 mediated 34% (p=0.01) of the AKI related risk for 3MS scores at 3 years, while IL-6 and IL-8 had non-significant mediation.

Conclusions: We found that patients with AKI had significantly worse cognitive function at 3 years after hospitalization. We also found that sTNFR-1 levels appear to mediate a significant proportion of the risk of long-term cognitive impairment.

Funding: NIDDK Support

FR-OR02

AKI, Glomerulonephritis, and Tubulointerstitial Nephritis Following Vaccination: VigiBase Analysis

Soo-Young Yoon,1 Hyo Jin Lee,2 Jae Kyu Kim,2 Jin sug Kim,2 Yang Gyun Kim,2 Ju young Moon,2 Kyungwan Jeong,1 Hyeon Seok Hwang,1 Yong Hee University Hospital, Dongdaemun-gu, Seoul, Republic of Korea; 2Yong Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.

Background: Vaccination is the long-term established measure for disease prevention and worldwide outbreak of COVID-19 necessitates mass scale vaccination. However, there is a public concern on the risk of renal adverse reactions from several types of vaccination.

Methods: We analyzed VigiBase (n = 120,715,116 reports), the World Health Organization pharmacovigilance database from Dec 1967 to Jul 2022 using disproportionat Bayesian reporting. Information component (IC) compares observed and expected values to find the associations of vaccines with acute kidney injury (AKI), glomerulonephritis (GN) and tubulointerstitial nephritis (TIN).

Results: We found 5,484 AKI (13.8% fatal), 2,846 GN (29.4% fatal) and 289 TIN reports (23.2% fatal) as vaccine-associated adverse reactions. Almost reports indicated single drug as AKI, GN and TIN gradually increased and Americas was most prevalent regions of reporting. Examining the different types of vaccination.

Conclusions: AKI, GN and TIN substantially occurred following vaccination and it was most noticeable in patients exposed to COVID-19 mRNA vaccines. Clinicians should consider the increased risk of renal adverse reactions after vaccination.
FR-OR03

Use of a Recurrent Neural Network to Predict Development of Nephrotoxic AKI in Adults

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1University of Iowa Hospitals and Clinics, Iowa City, IA; 2The University of Iowa Stead Family Children’s Hospital, Iowa City, IA.

Background: The Nephrotoxic Injury Negated by Just-in Time Action (NINJA) program identifies children with high exposure to nephrotoxic medications and has been shown to reduce rates of acute kidney injury (AKI) by 25% through preemptive medication adjustments. However, attempts to translate NINJA to the adult population have been hampered by the much larger patient volume at adult hospitals combined with NINJA’s relatively low positive predictive value (PPV), which generates a high number of false alerts. We used a recurrent neural network (RNN) machine learning algorithm to improve nephrotoxic AKI prediction in patients with high nephrotoxic exposure.

Methods: We collected over 100 variables including demographics, laboratory data, vital signs, and medication usage on adult patients admitted to the University of Iowa Hospital from 2017-2022. Patients admitted for >48 hours who met the NINA definition for high nephrotoxic exposure (≥3 nephrotoxins on 1 day or intravenous aminoglycoside or vancomycin for ≥3 days) were included in the final dataset. A gated recurrent unit (GRU)-based RNN was trained on 85% of the data, and then tested on the remaining 15%, with the goal of predicting AKI development (defined as a creatinine increase of ≥0.3 mg/dL or ≥1.5x baseline) within 48 hours. We then used an artificial neural network (ANN) to determine feature importance.

Results: There were 37,300 patient-days meeting criteria for NINA high nephrotoxic exposure. In the testing cohort, 29% of exposures developed AKI within 48 hours (2.4 false alerts per true AKI). The RNN model predicted 48-hour AKI with a PPV of 0.58 (0.7 false alerts per true AKI) and a NPV of 0.87. Hospital day, lowest hemoglobin, lowest platelet count, lowest blood pressure, and highest white blood cell count were the 5 most important variables in the RNN model. Vancomycin, piperacillin-tazobactam, isampinolid, and lisinopril were the most important medication variables.

Conclusions: Our RNN machine learning model was able to dramatically reduce the number of false alerts for nephrotoxic AKI in adults, which may facilitate NINA translation to adult hospitals by providing more targeted intervention with less resource utilization.

FR-OR04

Genome-Wide Association Study of Hospitalized AKI

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Background: AKI commonly complicates hospitalization and has a potential genetic basis for susceptibility.

Methods: We conducted a genome-wide association study of AKI in the Million Veteran Program (MVP) and Vanderbilt University’s DNA biobank (BioVU). Among patients hospitalized during 2002-2019, AKI cases were defined as KDIGO Stage 2 or, Stage 3 AKI cases were defined among hospitalized patients without historical evidence of AKI. Single variant logistic regression analyses were performed on imputed genetic variants, adjusting for sex, age, and the top 10 principal components of ancestry. Results were meta-analyzed using fixed effects analyses. A meta-analysis was performed with summary statistics from UK Biobank, FinnGen, and BioBank Japan. Bioinformatic analyses were performed to provide functional information for significant variants.

Results: There were 58,891 patients with AKI (53,079 MVP, 5,812 BioVU) and 130,098 non-AKI controls (127,627 in MVP, 11,471 BioVU). Three novel loci reached genome-wide significance (FDR<5x10^-8; p<1x10^-8; EAF=0.2-0.3): MPPED2 (OR 1.05(95% CI 1.03-1.06), p=2.9x10^-8, EAF=0.2); INTS14 (OR 1.04(95% CI 1.02-1.06), p=3.1x10^-8, EAF=0.2); and FTO (OR 1.06(95% CI 1.04-1.08), p=3.9x10^-8, EAF=0.2). Effects were consistent across groups and replicated in diagnosis code-based datasets. Within MVP, FTO remained significant after adjusting for BMI. Genome-wide meta-analysis of BioBank Japan, FinnGen, and UK Biobank (N=67,051 cases, 788,014 controls) identified one additional significant locus: rs76704056 in NALCN [EAF = 1%; OR 0.82 (95%CI 0.77-0.88)]. FTO and MPPED2 remained significant (p ≤ 0.010-17 and 9.6x10-9, respectively), while INTS14 did not (p = 8.1x10-8).

Conclusions: Three loci were associated with AKI including one (MPPED2) previously associated with CKD. FTO may contribute to the risk of AKI independently of BMI. Further work to determine how these genes may contribute to AKI is ongoing.

Funding: Veterans Affairs Support

FR-OR05

Machine Learning-Guided Novel Subphenotypes of Sepsis-Associated Persistent AKI

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Background: Sepsis associated acute kidney injury (SA-AKI) is common and is associated with high mortality. AKI lasting 48 hours or longer, known as persistent AKI (pAKI), has much worse outcomes. SA-AKI is a heterogeneous disease, however, it is unknown whether such heterogeneity exists in SA-pAKI. We aimed to identify subphenotypes (SP) of SA-pAKI using routinely collected data in electronic medical records.

Methods: We conducted a retrospective study using MIMIC IV database. We defined AKI and pAKI using both creatinine and urine output based KDIGO criteria. We identified adult patients (≥18y) with sepsis who developed SA-AKI within 48th and SA-pAKI within 96th of ICU admission. We used available features for demographics, comorbidities, SOFA score, vital signs, labs, fluid balance & vasopressors to identify SPs. We used factor analysis of mixed data for dimensionality reduction followed by k-means clustering to identify SPs. Outcomes were 30-day in-hospital mortality and 30-day AKI recovery while adjusting for competing risk of mortality.

Results: Among 6,681 patients with SA-pAKI, we identified 4 distinct SPs. Each SP demonstrated distinct characteristics and outcomes (Fig 1a & b). SP1 (n=1,137) included patients with severe AKI, low systolic BP, high INR, and WBC counts. It had highest mortality(47%) and low AKI recovery(37%). SP 2 (n=1,231) had moderate to severe AKI but low vasopressor requirements. It had low mortality(19%) but also low rates of AKI recovery(32%). SP3 (n=1,315) included patients with high comorbidity burden but low disease acuity. Their mortality was between that of first two SPs and had high rates of AKI recovery(54%). SP 4 (n=1,353) included patients with mild to moderate AKI and low disease acuity. They had highest rates of AKI recovery(56%) and lowest mortality(13%).

Conclusions: We identified 4 distinct SPs of SA-pAKI with differing patient characteristics and outcomes. Early recognition of these SPs will allow for personalized management strategies.

Funding: NIDDK Support, Other NIH Support - WO: T32DK007757, TL1DK136048, AS: IK0SDK131286, GN: R01DK108803 U101HG007278 U101HG009610 U101DK116100

FR-OR06

Arterial Stiffness and AKI in the Atherosclerosis Risk in Communities (ARIC) Study

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Background: Acute kidney injury (AKI) is associated with prolonged hospitalization and increased in-hospital mortality risk. However, the prediction of incident AKI is inaccurate and additional predictors of AKI are strongly needed. Arterial stiffness, as measured by carotid-femoral pulse wave velocity (cPWV), is associated with}

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function decline and may serve as a plausible predictor of AKI. We hypothesized a higher cfPWV at baseline would be independently associated with AKI risk in community-dwelling older adults who participated in the Atherosclerosis Risk in Communities (ARIC) Study.

Methods: We included adults with available PWV measures (i.e., cfPWV [primary predictor], femoral PWV [fPWV], heart-ankle PWV [haPWV], heart-ankle PWV [haPWV], femoral-ankle PWV [faPWV]). Cox proportional hazard models were used to examine the association between PWV measures and time to AKI. Given its J-shaped relation with AKI, cfPWV was modeled as a categorical variable in quartiles (Q), with Q2 serving as the reference category.

Results: A total of 4,245 participants (44% male; 77% white; mean±SD age 75±5 years; cfPWV 11.9±3.9 m/s) were included. There appeared to be a J-shaped association between cfPWV and AKI risk (Q1, hazard ratio 1.35 [95% confidence interval 0.90-1.46]; Q4, 1.38 [1.08-1.77] vs. Q2) after fully adjusting for demographics, CV risk factors, and markers for kidney function and peripheral artery disease (Figure).

Conclusions: A higher arterial stiffness, measured by cfPWV, is an independent predictor of AKI in community-dwelling older adults.

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

FR-OR08

AKI Diagnostic Accuracy and Implications of AKI Baseline Creatinine (ABC) vs. Other Baseline Creatinine Estimating Equations

Erik C. Bjornstad,1 Mithun K. Acharjee,2 Akm F. Rahman,1 Michael Zappitelli,1 Rajit K. Basu,1 George J. Schwartz,2 Stuart Goldstein,3 Chloe G. Braun,4 David J. Askenazi,1 The University of Alabama at Birmingham Department of Pediatrics, Birmingham, AL;1 The University of Alabama at Birmingham Department of Biostatistics, Birmingham, AL;1 Toronto Hospital for Sick Children, Toronto, ON, Canada;2 Ann and Robert H Lurie Children’s Hospital of Chicago, Chicago, IL;1 University of Rochester, Rochester, NY;4 Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

Background: Acute kidney injury (AKI) definitions rely on a known baseline creatinine (Cr), which is missing in up to 75% of hospitalized children. A new method (ABC equation) for estimating Cr was derived from children without kidney disease. We aim to externally validate the ABC method in an international cohort and assess how different Cr estimating equations alter AKI epidemiology.

Methods: AWARE is a prospective international study of 4984 critically ill children (age 0-25 years) from 32 PICUs. The validation of the ABC equations uses a subset of this cohort (n=2451) with a known Cr, which serves as the gold standard, using statistical measures of accuracy and precision. The entire cohort is used for assessing changes in AKI epidemiology for different Cr estimating equations (3 ABC equations and 4 common cGFR equations). Univariate statistics determine how different Cr equations impact the incidence of AKI and its association with key clinical outcomes including 28-day mortality.

Results: The simplified ABC equation (requiring only age) performed similarly to existing Cr equations (e.g., new Schwartz). When an admission hospital creatinine value was available, the ABC equations outperformed all existing equations up to 19% in accuracy and 32% in precision. AKI incidence varied from 2-10% depending on Cr definition. Adverse clinical outcomes were rare: 28-day mortality (n=169) was 3.4% and ICU length of stay=14 days (n=147) was 2.9%. Compared to previous Cr equations, ABC equations consistently perform better (or similar) to predict poor clinical outcomes. For example, relative risk (RR) of AKI using the ABC equation for 28-day mortality was 4.5 (95% CI 2.8-7.2); this was 5-29% higher RR than AKI defined by other Cr equations.

Conclusions: ABC equations outperform existing Cr estimating equations. This international cohort confirms earlier findings that ABC equations are improved methods for estimating Cr values. The data suggest ABC equations performed similarly, or perhaps better, in predicting select poor clinical outcomes.

FR-OR09

Vancomycin-Tacrolimus Combination Increases AKI Risk in Post-Hematopoietic Stem Cell Transplantation (HSCT) Patients

Tusha Gupta,1 Yuan Liu,2 Kevin Hall,1 Minal J. Suratdi,1 Edmund K. Waller,1 Tulane State Medical University, Tulsi, Georgia;2 Emory University, Atlanta, GA.

Background: Acute kidney injury (AKI) is a common complication in hematopoietic stem cell transplant (HSCT) recipients, leading to prolonged hospital stays, increased healthcare costs and mortality rates. Drug-related effects are major contributors of AKI in this patient population. Immunosuppressive and antibacterial drugs, such as vancomycin and tacrolimus, have well-documented nephrotoxic effects. Combinations of tacrolimus and vancomycin with other drugs are known to induce AKI. However, the combined nephrotoxic effect of vancomycin and tacrolimus warrants further investigation. This study aims to evaluate their simultaneous nephrotoxic effects in HSCT patients.

Methods: Institutional Review Board approval was obtained for retrospective analysis of transplant outcomes. This retrospective cohort study includes 1444 HSCT patients (age-18) from 2018-2021 at Emory University Hospital. Patients with end-stage renal disease were excluded from the study. The KDIGO guidelines: increase in serum creatinine levels ≥0.3 mg/dl within 48 hours or ≥50% within 7 days, were used

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to define AKI in the study population. Data was collected from day 0 to day +30 post-HSCT by reviewing in and outpatient medical records. Univariate and multivariable logistic regression was used to estimate the interaction effect between vancomycin and tacrolimus.

**Results:** The median patient age was 61, with 55% males, 58% white/35% black. Of the total patients, 51% had hypertension, 14% diabetes mellitus, 15% CKD, 8% congestive heart failure (CHF). The overall AKI incidence was 9.94%, with 19.81% among allogeneic transplant recipients and 7.24% among autologous transplant recipients (OR 3.28 p<0.001). Other AKI associated covariates were male gender (OR 1.59 p = 0.049), history of hypertension (OR 2.12, p = 0.006), high BMI (OR 1.06, p = 0.001) and low creatinine clearance (OR 0.96 p<0.001). Using multivariable logistic regression, the primary outcome measure, the incidence of AKI was significantly higher in patients receiving a combination of vancomycin and tacrolimus (OR 5.50 p<0.001) than patients receiving tacrolimus alone without vancomycin (OR 4.04 p<0.001).

**Conclusions:** Concurrent administration of vancomycin and tacrolimus greatly increases the risk of AKI compared to the individual drugs alone. Thus, the simultaneous use of these medications should be avoided or minimized with close monitoring in allo-HSCT recipients.

**FR-OR10**

Heart Failure with Preserved Ejection Fraction (HFpEF) vs. Heart Failure with Reduced Ejection Fraction (HFrEF) After AKI

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**Background:** There is an increased risk of incident heart failure (HF) after acute kidney injury (AKI). Preclinical studies have shown AKI causes structural changes and diastolic dysfunction. The nature and phenotype of HF experienced by AKI survivors is unknown.

**Methods:** We conducted a case control study of adults at Vanderbilt University Medical Center. To ensure patients had established care at VUMC, we required at least one outpatient serum creatinine at least two years prior to the code for HF. Eligible patients were also required to have an echocardiogram within 30 days before or 1 year after HF diagnosis to determine HF subtype. Patients with a history of ESRD were excluded. The primary exposure was hospitalization defined using creatinine-based KDIGO definitions during the exposure ascertainment period. The primary outcome was determined as HF, defined by either 1 inpatient or 2 outpatient diagnosis codes and classified using the echocardiogram closest to the HF diagnosis date (HFpEF if EF ≤45%, HFrEF if EF >45%). Baseline vitals, conditions, and medications were ascertained prior to AKI. Multivariable logistic regression was used to estimate the odds of AKI prior to HFpEF versus HFrEF.

**Results:** We identified 7,509 adults with incident HF (5,544 HFpEF, 1,965 HFrEF). AKI (stages 1-3) was associated with a 20% higher odds of HFpEF which was not statistically significant (OR 0.80, 95% CI 0.62 – 1.03). Stage 1 AKI was associated with a 40% higher odds of HFpEF (OR for HFpEF 0.60, 95% CI 0.42 – 0.85) whereas Stage 2-3 AKI was associated with a 17% higher odds of HFpEF, though this finding was not statistically significant (OR 1.17, 95% CI 0.81 – 1.68).

**Conclusions:** Stage 1 AKI was preferential towards incident HFpEF compared to HFrEF, with an association on par with other HFpEF risk factors such as female sex, obesity, atrial fibrillation, and hypertension. More severe AKI trended towards favoring HFrEF, though the relationship between Wnt signaling and establishment of epithelial junctions and apical-basal polarity during renal MET is unclear, and in general, developmental MET processes in vivo are poorly understood.

**Methods:** To investigate transcriptional control of MET, we used human induced pluripotent stem cell-derived renal organoids, which recapitulate nephrogenesis and generate epithelial tubules that express molecular markers of nephron cell types. Organoids were harvested for single nucleus multi-omic (paired RNA-seq and ATAC-seq) profiling to investigate transcription factors driving MET. CRISPR-interference was used to perturb candidate transcription factors.

**Results:** Human renal organoids recapitulate MET with upregulation of epithelial genes including CDH1 (E-cadherin), establishment of apical-basal polarity and epithelial junctions. Organoids exhibit dynamic gene expression and chromatin accessibility signatures throughout MET driven by transcriptional activators and repressors. PAX8 is a critical upstream regulator of human renal MET. Previous studies found PAX8 was dispensable for mouse renal MET. We show using CRISPR-interference that PAX8 is essential for initiation of MET in human kidney organoids. Moreover, Wnt signalling must be deactivated for completion of MET; persistent Wnt activation prevented completion of epithelial polarisation.

**Conclusions:** These results reveal how the developing kidney balances fate-commitment and morphogenesis with implications for understanding both developmental kidney diseases and aberrant epithelial plasticity following adult renal tubular injury.

**Funding:** Commercial Support – AstraZeneca PLC

**FR-OR11**

Role of Biomechanics in the Regulation of Ureteric Bud Branching Morphogenesis


**Background:** Branching morphogenesis is a fundamental developmental process driving the formation of several organs. Branching pattern in the developing kidney is stereotyped and involves geometrically distinct modes: tip bifurcation and trilobation, and only very rarely lateral branching. The branching epithelium, known as ureteric bud (UB), undergoes a series of complex changes which first transform a single layered epithelial bud to an ampulla where then the terminal bifurcations take place. While the molecular mediators of tissue crosstalk during renal branching are rather well characterized, the mechanisms controlling exact branch-initiating cell identity in UB tips remain unknown. Moreover, roles of cellular extracellular matrix and biomechanics in branched point determination are poorly understood.

**Methods:** We utilize a combination of mouse genetics and a custom machine-learning based segmentation pipeline in MATLAB to quantify 3D UB epithelial cell shapes. We further study downstream signaling mechanisms involved in complex branching patterns. Live imaging of fluorescently labelled UB cells, traction force microscopy and primary UB cell cultures on matrices with varying stiffness are utilized to study how basic cellular features drive arborization of ureteric bud epithelium into complex and growth factor deficient kidneys.

**Results:** Cell shape characterization of 3D epithelium shows that individual cells in the bud stage are mostly elliptical but become significantly rounder as ureteric branching proceeds to the ampulla stage. In the next branch phase, the cells convert into a more flat shape suggesting that the ampulla remodeling to bifurcated tips involves spatial constraints squeezing bud epithelial cells into tube-like organization. Accordingly, our results demonstrate not only remarkable differences in cell shapes in the MAPK/ERK-deficient UB epithelium incapable of complex branch formation but also clear fluctuations in adhesive forces exerted between epithelial cells themselves and towards their niche composed of nephron progenitors.

**Conclusions:** Our work describes the basic characteristics of ureteric bud epithelial cells during different branch formation phases. Together with our biomechanical studies, this provides a new cellular mechanism through which novel branch points are determined and how growth is regulated in developing kidney.

**Funding:** Government Support – Non-U.S.
adapted from a cell vertex model and validating with laser ablation shows that tip domains express Fgf9 preferentially differentiate into posterior NTB cells and form eNTBs at the expense of tunica adventitia cells layer is significantly expanded compared to wild-type littermate controls. In conclusion, our findings revealed a crucial role of acetyl-CoA metabolism in the maintenance of renal progenitor populations increased Wnt-driven commitment to early nephron cell aggregates. The enhancer/deleterious role of mechanical stress within nephron progenitor populations could constitute a clock that synchronizes nephron formation and ureteric tubule duplication. Ongoing work to understand the spatial and temporal regulation of nephron induction will clarify variation in nephron endowment between kidneys and advanced engineered replacement kidney tissues for regenerative medicine.

Funding: NIDDK Support

FR-OR15

The Multimodal Role of TBX6 in Kidney and Urinary Tract Development and Disease
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Background: Abnormalities of the urinary tract and CAKUT phenotype in MWS patients. The study also shed new light on the pathological mechanism underlying the developmental abnormalities of the ureteric tract and CUKAT phenotype in MWS patients.

Methods: We performed ZEB2 protein expression analysis in the developing mouse ureteral mesenchyme using quantitative mass spectrometry and validated with in situ hybridization. Ureteral and renal structural and molecular changes were studied using cell-specific markers such as TAGLN, ACTA2, FOXD1, POSTN, CDH1, TBX18, and SOX9.

Results: We found ZEB2 is expressed in TBX18 ureteral mesenchymal cells at E14.5 and E15.5 during mouse fetal development. Deletion of Zeb2 in developing ureteral mesenchymal cells causes hydronephrosis and hydroureteric phenotypes, leading to obstructive uropathy, kidney failure, and early mortality. Cellular and molecular changes were correlated with the TAGLN+ and ACTA2+ ureteral smooth muscle cells (SMCs) layer is not formed in Zeb2 KO mice at E15.5, but the FOXD1+ and POSTN+ tuica adventitia cells layer is significantly expanded compared to wild-type littermate controls. CDH1+ urothelial cells are reduced considerably in the Zeb2 KO ureters at E15.5. Moreover, we found that Zeb2 KO mice have significantly decreased TBX6 expression but an increased SOX9 expression in the developing ureter at E14.5 and E15.5 compared to wild-type littermate controls.

Conclusions: Our results show that ZEB2 is essential for mouse ureter development by maintaining ureteral mesenchymal cell differentiation into normal ureteral SMCs. Our study also shed new light on the pathological mechanism underlying the developmental abnormalities of the urinary tract and CUKAT phenotype in MWS patients.

Funding: NIDDK Support

FR-OR16

TGFβ Signaling Regulates Renal Patterning via Cadm1 During Nephrogenesis
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Background: Impaired nephrogenesis affects kidney health, causing childhood CKD and increasing CKD risk in adults. Foxd1+ kidney stromal cells regulate nephron development by interacting with Six2+ nephrogenic precursors. Previously, we (Rowan CJ et al, Development, 2018) demonstrated that Hedgehog-GLI signaling in Foxd1+ stromal cells is required to promote murine nephrogenesis through TGFβ signaling, specifically via promoting the transformation of mesenchymal cells into epithelial cells (MET) in the Six2+ nephrogenic zone. However, the underlying molecular mechanisms that guide MET are incompletely defined. Here we aim to define molecular mechanisms by which TGFβ signaling regulates nephrogenesis.

Methods: Whole-kidney RNA seq and single-cell RNA seq to examine Tgfβ2 deficiency in Foxd1+ stromal and Six2+ nephrogenic kidneys. We validated the bioinformatics data through immuno-staining and Western blot. Compound mutant mice were generated to investigate the deficiency of Cadm1 alone or both Tgfβ2 and Cadm1, followed by histological analysis, immunostaining, and nephron quantitation.

Results: Whole-kidney RNA seq and scRNA seq (n=169 cell, P<0.001) in Foxd1+ stromal and Six2+ nephrogenic deficient kidneys identified Cadm1 (P<0.00003,P<0.0013) in Foxd1+ stromal cells as a TGFβ signaling downstream target. Western blot analysis in HEK-T293 cells (n=2) demonstrated that treatment with TGFβ1 induced CAMD1 expression in a dose-dependent manner. Kidney tissue with Stromal and/or nephrogenic cell deficiency of Cadm1 exhibited normal nephrogenesis (n≈2-3,P<0.01). Kidney tissue with deficiency of both Tgfβ2 and Cadm1 in Foxd1+ stromal exhibited renal hypoplasia characterized by 32% reduction in kidney/body weight (n=6,P<0.0001), a 35% reduction in nephron number (n=3,P<0.05), expansion of Sox9+ cells/UB tip (n=2,P<0.05), and loosely packed cortex and irregular stromal pattern (n=3). Similarly, kidney tissue with deficiency of both Tgfβ2 and Cadm1 in Six2+ nephrogenic cells exhibited renal hypoplasia characterized by a 27% reduction in kidney/body weight (n=3,P<0.01), a 48% reduction in nephron number (n=2,P<0.05) and expansion of Sox9+ cells/UB tip (n=3, P<0.01).

Conclusions: We conclude that Cadm1 is required for normal nephrogenesis in mice. Further, our data suggest that CAMD1 may play a role in regulating the epithelialization of nephrogenic precursors under the influence of TGFβ signaling.

Funding: Government Support - Non-U.S.

FR-OR17

ATP-Citrate Lyase (ACLY) Is a Key Modulator of Nephron Progenitor Cell Fate Decisions in Vivo
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Background: Nephron endowment at birth impacts long-term renal and cardiovascular health and is contingent on the nephron progenitor cells (NPC) pool. NPC fate decisions are influenced by the cell’s metabolism. Acetyl-CoA is a key molecule involved in cellular metabolism. Acetyl-CoA provides energy and serves as a metabolic intermediate necessary for cellular growth and differentiation. However, in vivo requirement of Acetyl-CoA for kidney development is still unknown.

Methods: Six2GFP;Acly−/− males were bred to floxed Acly homoygous female mice to generate embryos lacking Acly expression in the NPC and nephrogenic lineage. Immunofluorescence (E14.5, E16.5, and P0) and organ culture (E12.5+24h) were used to examine renal and ureteric cell proliferation. Six2Cre-mediated removal of Acly led to the upregulation of Acyl-CoA Synthetase Short Chain Family Member 2 (Acsc2) in nascent proximal tubules (PT) exclusively. Uregulation of Acsc2 suggested a compensatory route for acetyl-CoA production during PT nephrogenesis. The regulation of Acsc2 was accompanied by an increased abundance of Hfy4a, a key regulator of proximal tubule maturation.

Results: Removal of Acly (a gene that regulates cytosolic availability of acetyl-CoA) from the NPC pool during embryonic development led to a reduction in glomeruli counts (≈30%), depletion of cap-mesenchyme (WT ≈44 vs MUT ≈32 NPC/niche), and increased Wnt4 expression at birth. Cap depletion and UB abnormalities were evident at E14.5 and E16.5. Sodium-acetate supplementation to cultured E13.5 mutant kidneys rescued cap and mesenchyme depletion without hindering differentiation. Furthermore, Six2Cre-mediated removal of Acly led to the upregulation of Acyl-CoA Synthetase Short Chain Family Member 2 (Acsc2) in nascent proximal tubules (PT) exclusively. Uregulation of Acsc2 suggested a compensatory route for acetyl-CoA production during PT nephrogenesis. The regulation of Acsc2 was accompanied by an increased abundance of Hfy4a, a key regulator of proximal tubule maturation.

Conclusions: In conclusion, our findings revealed a crucial role of acetyl-CoA metabolism during kidney development and provided insights into the molecular mechanisms underlying early nephrogenesis. In addition, we identified a new molecular target with therapeutic potential to offset the programming process during early life to prevent the development of adult kidney disease.

Funding: NIDDK Support
FR-OR18
A Single-Cell Atlas of Human Fetal Kidneys Identifies Cell States Associated with Rare and Common Human Disease
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Background: Abnormal kidney development can present as congenital anomalies which can severely impact renal function. It is further thought that development may also influence more subtle phenotypes that can present later in life. Low birth weight is a risk factor for hypertension and prematurity is a risk factor for CKD.

Methods: We performed single cell RNA sequencing of 5 human fetal kidneys. We mapped developmental trajectories using RNA velocity and CellRank, creating a probabilistic model for cell differentiation in nephron development.

Results: We created an atlas of cells of human fetal kidney with a total of 65,348 cells, the largest, most comprehensive atlas of this tissue to date. This atlas demonstrates contiguous trajectories of cell states starting from a putative progenitor population to mature cell types. By examining diffusive properties within this map, we were able to identify and map previously hypothesized transitions between PTs, PECs and podocytes. We also applied this model to identify the cell states and transitions during fetal development to both common and rare human genetic disease, finding cell states that appear to be important in C-KUT, as well as cell states that influence adult eGFR.

Conclusions: We present the most complete atlas of the human fetal kidney to date. Using this atlas, we identify cell states are associated with human genetic disease and that these states are correlated by phenotype, leading to novel insights into developmental mechanisms of human disease.

Funding: NIDDK Support

FR-OR19
Identification of Genes and Regulatory Elements Affecting Human Kidney Function
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Background: The molecular mechanisms underlying human kidney disease remain largely unknown. Genome-wide association studies (GWAS) have identified hundreds of genomic loci associated with kidney function and disease. However, the genetic variants and genes mediating the effect of most of these loci remain unclear.

Methods: We performed a genome-wide association study (GWAS) of kidney function estimated using both creatinine in the UK Biobank and eGFR, and used functionally informed fine-mapping to identify putative causal kidney function variants. To determine the effect of genetic variants implicated in kidney function, we used scATAC-seq in human kidneys, genome-wide measurements of H3K27 acetylation (CUT&RUN), and measured the effect of CRISPR-mediated perturbation of regulatory elements on gene expression.

Results: We found that 58% of kidney function SNP heritability localized to candidate regulatory elements of kidney tubule epithelial cells, an additional 6.5% localized to podocyte candidate regulatory elements, and <1% localized within endothelial, stromal, or immune cell-specific regulatory elements. We identified putative causal kidney function variants using functionally-informed fine-mapping and used these variants to identify regulatory elements and genes involved in kidney function. In human kidneys and primary tubule epithelial cells, we assessed how kidney function variants affect chromatin accessibility and enhancer function. We found that kidney function variants alter chromatin accessibility and enhancer function within tubule epithelial regulatory elements. A pooled screen targeting kidney function noncoding regulatory elements with CRISPR interference (CRISPRi) identified novel genes involved in human kidney function.

Conclusions: By integrating human genetics and studies of enhancer function, this work provides a framework for identifying variants, regulatory elements, and genes involved in human kidney disease. The combination of fine-mapping of GWAS-nominated variants, regulatory element identification, and mapping enhancers to regulated genes provides a framework for moving from GWAS to molecular mechanisms of disease.

Funding: NIDDK Support, Other NIH Support - NIAMS

FR-OR20
Genome-Wide Association Study Across Biobanks Identifies New Susceptibility Loci for Urinary Tract Infections
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Background: Urinary tract infections (UTIs) represent the most common bacterial infections worldwide and if untreated, can lead to pyelonephritis, urosepsis, and severe complications. Urologic abnormalities, immunosuppression, sexual activity, and other known risk factors do not completely explain why some individuals are more susceptible to severe or recurrent UTIs. Genetic predisposition to UTIs has not been well studied.

Methods: We designed an electronic phenotype for UTIs and defined 75,485 cases and 634,538 controls across several biobanks, including eMERGE, UKBB, BioVU, and All of Us. Cases were defined by ICD9/10 codes by a2 events ±a week apart in the absence of known clinical risk factors. We performed a GWAS for UTI across diverse ancestries using REGENE, controlling for age, sex, and ancestry, followed by a fixed effects meta-analysis across individual biobanks. We also performed single cell RNA-seq (scRNAseq) and bacteria binding assays identified key site of regulated Mg2+ transport.

Results: Our UTI GWAS meta-analysis defined several genome-wide significant loci including PSCA locus (P = 9.9E-11). This gene can be specifically expressed in urothelium and kidney papilla. Based on the latest kidney eQTL datasets, the risk allele at this locus was associated with lower PSCA expression in the tubulointerstitial compartment (P = 8.9E-39). Our scRNAseq data demonstrated its expression in the kidney pelvic epithelial cells in both infected and noninfected mice, and we localized kidney PSCA exclusively to the ascending thin limbs. In binding assays, we found E. coli bound to human PSCA, a heavily N-glycosylated protein (initial calculations show >1000 PSCA molecules/bacterium). Co-incubation with PSCA in vitro limited bacterial growth in a dose-dependent manner (0.35±0.02, p=0.004).

Conclusions: Our large-scale multi-biobank-based GWAS combined with kidney scRNAseq data and bacteria binding assays identified PSCA as a candidate causal gene in human UTIs. PSCA is expressed in various urinary tract epithelia and inhibits bacterial growth in vitro. Our findings suggest that PSCA plays an important role in human innate immunity against bacterial UTIs.

Funding: NIDDK Support

FR-OR21
Empagliflozin Blunts Renal Mg2+ Wasting and Restores Distal Tubule Sodium Chloride Cotransporter Expression in Rats with Cisplatin-Induced Hyponagemesia
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Background: The chemotherapeutic agent cisplatin is known to cause hyponagemesia and renal Mg2+ wasting. Damage to the distal convoluted tubule (DCT), a key site of regulated Mg2+ reabsorption, may contribute. Recent clinical studies suggest that SGLT2 inhibitors increase serum Mg2+ concentration in patients with diabetes. However, the potential therapeutic use of SGLT2 inhibitors in a scenario of cisplatin-induced hyponagemesia has not been investigated. This study tested the hypothesis that the SGLT2 inhibitor empagliflozin (EMPA) attenuates cisplatin-induced hyponagemesia in rats through effects on the DCT.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Male Wistar rats (10 weeks of age) were treated weekly with cisplatin (2.5 mg/kg body weight, i.p.) for 6 weeks. All rats were then randomized to control (Cis) and vehicle-treated (Ctrl) rats were randomized and orally treated or not with EMPA (10 mg/kg/day) for two weeks.

Results: cis-Treated rats developed significant hypomagnesemia (1.42 ± 0.05 vs. 2.19 ± 0.12 mmol/L, p < 0.05) and decreased serum Mg concentration in cis-platin-treated rats. The effects of the SGLT2 inhibitor were associated with reversal of DCT injury, rescue of expression of TRPM6, NCC, and phosphorylated NCC, and normalization of NCC activity.

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

FR-OR22
Critical Role of mTORC2 in Maintaining Sodium and Potassium Balance: Implications of Aldosterone-Independent Regulation of Epithelial Sodium Channel (ENaC) in the Distal Nephron


Background: mTORC2 complex-2 (mTORC2) is crucial for maintaining sodium and potassium balance in the kidneys and responding to high K intake. Recent evidence supports the idea that, in contrast to the late connecting tubule (CNT) and cortical collecting duct (CCD), ENaC activity in the distal convoluted tubule (DCT) and early CCD is mTORC2-dependent. Here, we examined the role of mTORC2 in distal nephron K secretion by disrupting mTORC2 expression in various distal segments and examining its effects on potassium secretion during high dietary potassium conditions.

Methods: Rictor, a core component of mTORC2, was selectively knock-out (KO) in specific segments of the distal nephron or throughout the entire nephron using a segment-specific Cre-Lox-KO techniques. Both WT and KO mice were fed a high K diet for short-term (4 h) or medium-term (48 h). Various parameters, including urinary and blood electrolytes, renal transporter expression and activity, and phosphorylation status of mTORC2 targets were assessed.

Results: Mice lacking mTORC2 in the DCT and CNT (when called by Cre-driver) responded to high K intake in a manner resembling mice in which Rictor was KO’d throughout the nephron (using Pax5/LC1): they developed hyperkalemia, increased urinary output, elevated BUN levels, lower serum sodium, and elevated plasma aldosterone levels under both short (4 h) and medium (48 h) high K intake conditions. After 48 h under HK diet, these mice showed severe pathophysiological changes including weight loss, reduced food intake, markedly reduced GFR and listlessness. Phosphorylation of mTORC2 activity is crucial for maintaining sodium and potassium balance in the kidneys and responding to high K intake. Recent evidence supports the idea that, in contrast to the late connecting tubule (CNT) and cortical collecting duct (CCD), ENaC activity in the distal convoluted tubule (DCT) and early CCD is mTORC2-dependent. Here, we examined the role of mTORC2 in distal nephron K secretion by disrupting mTORC2 expression in various distal segments and examining its effects on potassium secretion during high dietary potassium conditions.

Background: The kidneys and their surrounding tissues, in the context of high dietary potassium, control potassium balance in the kidney. The current study supports the original hypothesis that the SGLT2 inhibitor reversed Cis-induced DCT injury.

Conclusions: mTORC2 is critical for the maintenance of sodium and potassium homeostasis during high dietary potassium intake. The combination of mTORC2 inhibition and SGLT2 inhibition reversed Cis-induced DCT injury.

Funding: NIDDK Support, Private Foundation Support

FR-OR23
Role of KHL3-S433 Phosphorylation in Potassium Homeostasis in Mice

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Background: KHL3 is a component of an E3 ubiquitin ligase complex that binds and degrades with a chaperone, Ikaputa, to promote its degradation. Previous studies have reported that depletion of potassium (K) causes a significant increase in protein expression and activity of the ENaC, which is a key ion channel involved in aldosterone regulation. However, the role of KHL3 in potassium homeostasis is currently unknown. Therefore, we hypothesized that KHL3 plays a role in potassium homeostasis.

Methods: We used in vitro and in vivo models to study the role of KHL3 in potassium homeostasis.

Results: KHL3 KO mice had lower plasma K levels than WT mice, indicating a role for KHL3 in potassium homeostasis. Additionally, we observed a significant decrease in plasma aldosterone levels in KHL3 KO mice. These findings suggest that KHL3 may be involved in the regulation of aldosterone levels in response to changes in potassium intake.

Conclusions: KHL3 plays a role in potassium homeostasis through its interaction with ENaC. The reduction in aldosterone levels observed in KHL3 KO mice suggests that KHL3 may regulate aldosterone levels in response to changes in potassium intake. Further studies are needed to elucidate the molecular mechanisms by which KHL3 regulates aldosterone levels.

Funding: NIDDK Support, Private Foundation Support

FR-OR24
PIEZ01 Channels Are Necessary for BK Channel-Mediated Flow-Induced K+ Secretion (FKS) in the Cortical Collecting Duct (CCD)

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Background: BK channel-mediated FKS in intercalated cells (IC) of the CCD requires an increase in intracellular calcium concentration ([Ca2+]i), triggered by hydrodynamic forces associated with tubular flow rate (TFR). This increase in [Ca2+]i is proposed to be due to influx of extracellular Ca2+ through apical and basolateral mechanosensitive Ca2+ channels and release of Ca2+ from internal stores. We previously identified functional expression of the mechanosensitive Ca2+ channel PIEZO1 at the basolateral membranes of CCD principal (PC) and ICs (ASN Kidney Week, 2021). We hypothesize that PIEZO1 contributes to the flow-induced increase in [Ca2+]i necessary for BK channel-mediated FKS.

Methods: To test this hypothesis, control and conditional IC-cell Piezo1 KO mice were fed a high K diet (HK, 5% KCl) for 10 days. Isolated CCDs were micropipetted in vitro to measure flow-induced increases in [Ca2+]i, and net transcapillary transport (Jp) of Na+ and K+ at slow and fast tubular fluid flow rates (0.9 and 5.5 nL/min).

Results: All experiments were performed in HK conditions. Basolateral PIEZO1 channels are necessary for BK channel-mediated FKS.

Conclusions: We conclude that mechanosensitive PIEZO1 channels mediate basolateral influx of Ca2+ in CCD ICs, and are indispensable for BK channel-mediated FKS. We further speculate that basalolateral PIEZO1 channels are activated by increases in mechanical tension associated with an increase in TFRR.

Funding: NIDDK Support

FR-OR25
The Role of Renal Mechanotransduction in Blood Volume Sensing

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Background: The kidneys tightly control the composition of our internal environment to maintain homeostasis in the face of external variability. For example, the regulation of blood volume begins in the kidneys and is essential for vertebrate life in terrestrial environments where water availability is unpredictable. Mechanosensitive renal mechanotransduction by glomerular cells to modulate vascular tone and glomerular filtration is integral to blood volume and blood pressure regulation. The kidneys have been associated with the expression of a variety of mechanosensitive currents that are thought to modulate blood volume sensing.

Methods: To study the role of renal mechanotransduction in blood volume sensing, we used in vitro and in vivo approaches to assess the role of mechanotransduction in blood volume sensing.

Results: We used in vitro and in vivo models to study the role of renal mechanotransduction in blood volume sensing. We observed that the expression of mechanosensitive currents in renal glomerular cells is necessary for blood volume sensing.

Conclusions: Our findings support the hypothesis that renal mechanotransduction plays a critical role in blood volume sensing.

Funding: NIDDK Support

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

Underline represents presenting author.
enhances renin release and RAAS function and promotes glomerular hyperfiltration. Furthermore, we find that primary cultured renin-expressing and mesangial cells are mechanosensitive and express functional force-gated ion channels.

Conclusions: Our findings highlight the importance of mechanotransduction within the JGA to renal blood volume sensing and represent the first molecular and cellular characterization of JGA mechanosensitivity and the consequences of its loss in vivo.

Funding: Private Foundation Support

FR-OR26

Kidney Tubular YAP Controls the Expression of Collecting Duct Aquaporins and Water Homeostasis

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Background: Final urine volume and concentration are defined by water reabsorption through the water channel proteins aquaporin (AQP)2-4, and -3 and -4 in the collecting duct. However, the transcriptional regulation of these AQPs is not well understood. The Hippo/YAP pathway plays an important role in organ size control and tissue homeostasis. When the Hippo pathway including the Mst1/Mst2 kinases is inhibited, YAP is activated and functions as a transcription co-activator. Our previous work revealed a pathological role of tubular YAP activation in chronic kidney disease, but the physiological role of YAP in the kidney remains to be established.

Methods: Tubule-specific Yap knockout (Yap cKO) mice were generated by crossing Yap+/– mice with Ksp-Cre mice. Double-specific Mst1/Mst2 double (dKO) mice and Mst1/Mst2/Yap triple (tKO) mice were generated by crossing Mst1f/f;Mst2f/f and Mst1f/f;Mst2f/f;Yapf/f mice with Ksp-Cre mice respectively. Primary mouse medullary collecting duct cells were isolated from control and Yap cKO mice. RNA sequencing was performed on the medullae of control and Yap cKO mice at 6 weeks of age. CHIP-qPCR was performed using an YAP antibody to determine whether YAP binds to the promoters of the Aqp2 and Aqp4 genes. Immunoprecipitation experiments were carried out to examine the interactions of YAP and GATA2, GATA3 or NFAT1.

Results: Tubule-specific Yap knockout mice showed increased urine output and decreased urinary osmolality. Decreases in Aqp2, -3 and -4 mRNA and protein abundance in the kidney were evident in Yap knockout mice. Analysis of Mst1/Mst2 double knockout and Mst1/Mst2/Yap triple knockout mice showed that expression of Aqp2 and Aqp4 but not Aqp3 was dependent on YAP. Furthermore, YAP was recruited to the promoters of the Aqp2 and Aqp4 genes and stimulated their transcription. Interestingly, YAP was found to interact with transcription factors GATA2, GATA3 and NFAT1. These three factors promoted Aqp2 transcription in a YAP dependent manner in collecting duct cells. These three factors also promoted Aqp4 transcription whereas only GATA2 and GATA3 enhanced Aqp3 transcription.

Conclusions: Our results suggest that YAP promotes Aqp2 and Aqp4 transcription, interacts with GATA2, GATA3 and NFATc1 to control Aqp2 expression, while Aqp2, -3 and -4 are controlled by different mechanisms for their baseline transcriptional regulation.

Funding: Government Support - Non-U.S.

FR-OR27

Calcium-Binding Protein 39 (Cab39) Is Required for Na+/Cl– Cotransporter (NCC) Phosphorylation in Mice

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Background: The Na+-Cl– cotransporter (NCC), expressed along the distal convoluted tubule (DCT) in the kidney, is essential for sodium and potassium homeostasis and blood pressure (BP) regulation. We showed previously that WNK4 (with-no-lysine kinase 4) phosphorylates NCC and selectively activates SPAK (STE20/SPK1-related proline alanine-rich kinase), which in turn phosphorylates and activates NCC. According to in vitro studies, calcium-binding protein 39 (Cab39) is a scaffold that facilitates SPAK activation by stabilizing a fully active kinase conformation. Cab39 and its homolog, Cab39-like (Cab39L), are both expressed in the DCT. A previous study published in abstract form showed that Cab39L-knockout (Cab39L-KO) mice did not exhibit differences in electrolyte homeostasis or BP compared with wild-type mice. Here we created a Cab39/39L double knockout mouse to test if the adaptor proteins are necessary for WNK-SPA-KCC signaling in the DCT.

Methods: Inducible NCC-Cre was used to remove Cab39L along the DCT, creating DCT-specific double knockout (DKO) mice against the background of global Cab39L-KO mice. With blood electrolyte analysis, protein quantification and localization analyses were carried out using Western blotting and immunofluorescence, respectively in wild-type or single Cab39L-KO and Cab39L/Cab39L double knockout (DKO) mice.

Results: We showed that phosphorylated NCC abundance, a proxy for NCC function, and total NCC abundance were significantly lower in DKO mice. Despite having lower levels of WNK4 and expression of total and phosphorylated (active) SPAK, DKO mice on a low K+ diet, a known activator of NCC function, had lower blood K+ and significantly less phosphorylated and total NCC abundance. Importantly SPAK was distributed in puncta in the DKO mice, compared to the apical membrane of wild-type mice.

Conclusions: Our study demonstrates that Cab39 is critical for SPAK phosphorylation and localization and NCC function. Deletion of Cab39/Cab39L along the DCT prevents SPAK activation and causes SPAK to be confined to cytosolic puncta. Mice lacking Cab39 have compromised NCC function, reminiscent of Gitelman syndrome.

Funding: NIDDK Support, Private Foundation Support

FR-OR28

Extracellular Calcium-Sensing Receptor (CaSRR) and Vasopressin Type 2 Receptor (V2R) Interaction: An Emerging Mechanism to Fine-Tune Water Permeability in Renal Cells

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Background: We have previously shown that Extracellular Calcium-Sensing Receptor (CaSRR) signaling counteracts Vasopressin type 2 receptor (V2R) signaling in renal collecting duct cells. In collecting duct principal cells, the V2R is expressed in both the basolateral and apical membranes.

Methods: Biochemical, computational, and functional methods were used to provide evidence that CaSRR and V2R interact as a multiomic complex. AQP2-mediated osmotic water permeability measurements were performed to evaluate the functional CaSRR/V2R interaction.

Results: In collecting duct MDC4 cells and mouse kidney, immunolocalization and confocal xz reconstruction confirmed that both the CaSRR and V2R are co-expressed in the apical membrane with a significant degree of co-localization. Moreover, the CaSRR co-immunoprecipitated with the V2R, and stimulation with vasopressin increased the amount of immunoprecipitated CaSRR. Proximity ligation experiments confirmed CaSRR/V2R interaction and their sensitivity to vasopressin stimulation. In silico comparative modeling analysis allowed us to predict a possible structure of the CaSRR/V2R protein complex. Functional data obtained in isolated perfused rat inner medullary collecting duct indicated that luminal vasopressin acts as a negative feedback system to the basolateral action of vasopressin on osmotic water permeability (Pi), and luminal CaSRR activation further inhibited the Pi providing a functional significance to the described receptor-receptor interaction.

Conclusions: This study opens new perspectives on the regulation of AQP2 trafficking and function not considered when the two GPCRs are viewed individually.

Funding: Government Support - Non-U.S.

FR-OR29

Inhibition of Urate Transporters and Insulin-Activated Urate Transport by SGLT2 Inhibitors

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have well-established uricosuric and urate-lowering effects, with protective effects on gout. The mechanisms of these uricosuric effects are not clear, however, and direct effects on urate transporters have not been fully investigated. We report the effects of empagliflozin, canagliflozin, and dapagliflozin on urate transport in a human proximal tubular cell line and in Xenopus oocytes expressing individual urate transporters.

Methods: Western blotting, in vitro transcription of cRNA from cloned cDNA and urate transport assays in human renal proximal tubule epithelial cells (PTC-05) and Xenopus oocytes expressing individual urate transporters.

Results: SGLT2 inhibitors significantly inhibited net urate uptake in a dose-dependent manner in human PTC-05 cells, which express endogenous SGLT2 and the urate transporters GLUT9a, GLUT9b, OAT1, OAT3, NPT1, ABCG2 and ABCC4. In the Xenopus laevis oocyte expression system, these inhibitors inhibited the basal urate transport activities of URAT1, OAT1, OAT3 and ABC4 but not GLUT9, OAT1, and ABCG2. OAT10 was only modestly sensitive to empagliflozin and canagliflozin (~38% and 28% inhibition with 500 µM empagliflozin and canagliflozin respectively). For URAT1, the IC50s for empagliflozin, canagliflozin, and dapagliflozin were 460, 230, and 487 µM, respectively; for OAT3 the IC50s were 42, 29, and 21 µM, respectively. In addition, SGLT2i inhibited insulin-induced stimulation of urate transport in PTC-05 cells, with dose-dependent inhibitory effects on insulin-induced phosphorylation of the downstream Akt and ERK kinases.

Conclusions: These results indicate that the uricosuric action of SGLT2 inhibitors is at least partially due to direct inhibition of the apical urate reabsorptive transporters URAT1 and OAT10. Additionally, SGLT2 inhibitors inhibited insulin-activated transport of uric acid in a proximal tubular cell line, with attenuated phosphorylation of Akt and ERK, given the key role for insulin-activated urate transport in the genesis of hyperuricemia this indicates another potential mechanism for SGLT2-associated uricosuria.

Funding: Other NIH Support - NIAIMS

FR-OR30

EnAc Inhibition with Trimethoprim Occurs Without Changing Urinary H+ Excretion

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Background: There is growing consensus that collecting duct H+ secretion occurs independent of changes in the transepithelial voltage (Vte). We recently identified a new mechanism how benzamid stimulates acute urinary alkalization. In addition to its
direct inhibition of the epithelial sodium channel (ENaC), benzamil acutely impairs H+ excretion by blocking the H+/K+ ATPase. The latter effect explains benzamil’s acute and marked effect on urine alkalization. However, the question remained whether inhibition of ENaC activity causes alterations in renal H+ excretion. To revisit this question, we studied the effect of a direct ENaC inhibitor which is structurally different from benzamil. Here, we chose the inorganic molecule trimethoprim, well-known to cause K+ retention by direct ENaC inhibition.

Methods: In vitro experiments were performed in bladder-catheterized C57BL/6J mice, allowing real-time measurement of urinary pH, electrolyte, and acid excretion. Trimethoprim was used as an infusion of bolus injection (5 mg/kg bw). Additionally, the effect of trimethoprim on H+/K+ ATPase activity was assessed in vitro in pig gastric H/K+ ATPase enriched membrane vesicles under different pH and extracellular K+ concentrations.

Results: We found that trimethoprim inhibits ENaC, acutely increasing natriuresis and decreasing kaliuresis, thus confirming earlier studies. However, trimethoprim had no effect on urinary pH or net acid excretion, contrasting the effects of benzamil that acutely alkalizes the urine and reduces net acid excretion. Moreover, in vitro experiments on isolated pig gastric H+/K+ ATPase proteins showed near to no effect of trimethoprim on the pump’s activity, again contrasting the action of benzamil.

Conclusions: In comparison to benzamil, that inhibits both ENaC and the H+/K+ ATPase proteins, the renal action of trimethoprim appears to be confined to ENaC inhibition. These findings further support the hypothesis that inhibition of ENaC is the cause of inhibition of H+ secretion in the collecting duct. Thus, these results add an additional argument refuting the hypothesis of voltage-dependent H+ secretion in collecting duct.

Funding: Government Support - Non-U.S.

FR-OR31
Decoding the Spatial Transcriptomic Landscape of Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) is a major cause of chronic kidney disease globally. However, the lack of targeted treatments for renal fibrosis in DN is due to an incomplete understanding of disease progression. We generated a detailed map of human diabetic nephropathy by employing single-cell gene expression and spatial transcriptomic proling of DN patients and controls.

Methods: We characterized the signature of diabetic nephropathy through spatial transcriptomics, analyzing eight patient biopsies using the 10x VISION-FPPE platform. Integrating spatially resolved transcriptomics with single-cell gene expression, we manipulate transcriptome types in space, revealing the global organization and way of DN tissue. Our analysis included trajectory analysis for cell direction transitions, spatial dependencies between signaling pathways and cell types, and gene-regulatory networks distinguishing DN from normal kidney tissue. Furthermore, subcellular characterization of 100 genes of interest was performed using Molecular Cartography on frozen tissues from the same patients.

Results: Deconvoluting spatial transcriptomic spots into cell-type abundances unveiled the spatial organization of kidney tissue, identifying major cell-type niches as structural building blocks. Within the glomerulus niche, we inferred a pseudotime unfolds distinguished from normal kidney tissue. Furthermore, subcellular characterization of 100 genes of interest was performed using Molecular Cartography on frozen tissues from the same patients.

Conclusions: Our study provides an integrative molecular map of diabetic nephropathy, serving as a vital reference for the field and facilitating advanced mechanistic and therapeutic investigations of diabetic kidney disease.

FR-OR32
Spatially Localized Mesangial Cell Communication in Diabetic Kidney Disease
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Background: Substantial knowledge has been gained regarding podocyte injury in diabetic kidney disease (DKD) but less is known about the mechanisms of mesangial expansion, nodulation, and its relationship with neovascularization. Changes in communication between injured cells serve as both a marker of disease progression and a mediator, promoting injury responses through positive feedback in surrounding cells. In this study, we aim to spatially localize changes in intra-glomerular communication between mesangial, endothelial, and epithelial cells.

Methods: We subdivided the KMPF / HuBMAP snRNAseq atlas into reference (N=11) and diabetic (N=7) samples. Using the CellChat database, we modeled cell-cell communication in glomerular cell types. The snRNAseq atlas was used as reference to discover other 23 kidney spatial transcriptomics, including reference (N=6) and diabetic (N=10). The modelled cell-cell communication and associated pathway vectors were then localized on glomeruli with COMMAT.

Results: The cellular communication decreases in diabetic glomeruli (44%) when compared to mesangial cells (54%), podocytes (40%), and endothelial cells (65%). The latter effect explains benzamil’s acute and marked effect on urine alkalization. However, the question remained whether inhibition of ENaC activity causes alterations in renal H+ excretion. To revisit this question, we studied the effect of a direct ENaC inhibitor which is structurally different from benzamil. Here, we chose the inorganic molecule trimethoprim, well-known to cause K+ retention by direct ENaC inhibition.

Methods: In vitro experiments were performed in bladder-catheterized C57BL/6J mice, allowing real-time measurement of urinary pH, electrolyte, and acid excretion. Trimethoprim was used as an infusion of bolus injection (5 mg/kg bw). Additionally, the effect of trimethoprim on H+/K+ ATPase activity was assessed in vitro in pig gastric H/K+ ATPase enriched membrane vesicles under different pH and extracellular K+ concentrations.

Results: We found that trimethoprim inhibits ENaC, acutely increasing natriuresis and decreasing kaliuresis, thus confirming earlier studies. However, trimethoprim had no effect on urinary pH or net acid excretion, contrasting the effects of benzamil that acutely alkalizes the urine and reduces net acid excretion. Moreover, in vitro experiments on isolated pig gastric H+/K+ ATPase proteins showed near to no effect of trimethoprim on the pump’s activity, again contrasting the action of benzamil.

Conclusions: In comparison to benzamil, that inhibits both ENaC and the H+/K+ ATPase proteins, the renal action of trimethoprim appears to be confined to ENaC inhibition. These findings further support the hypothesis that inhibition of ENaC is the cause of inhibition of H+ secretion in the collecting duct. Thus, these results add an additional argument refuting the hypothesis of voltage-dependent H+ secretion in collecting duct.

Funding: Government Support - Non-U.S.

FR-OR33
Interferon-γ (IFN-γ) Signaling in Diabetic Kidney Disease (DKD) Associated with ESKD
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Background: The mechanisms by which circulating pro-inflammatory factors modulate kidney signaling and disease progression in DKD remain poorly defined.

Methods: SOMASCAN plasma proteomics (n=162) and urine profilings (n=74) from kidney biopsies of Southwest Native Americans with type 2 diabetes were used to identify differentially expressed genes (DEGs) and proteins and upstream regulators (URs) associated with progression to ESKD. Based on quantitative transcriptomic analysis, activation scores for IFN-γ signaling were calculated and associated with structural lesions and outcomes in DKD patients. These findings were validated in cultured human kidney cell lines, kidney tissue from 2 DKD mouse models (DBA/2 podocyte-JAK2 transgenic and uninephrectomized BKS ReninAV db/db mice) and human kidney organoid cultures.

Results: Plasma IFN-γ was upregulated in ESKD patients and identified as the top predicted UR for ESKD-associated kidney DEGs. Higher IFN-γ activation scores, in both glomeruli and tubulo-interstitium correlated (r=0.40 and 0.35, respectively, p=0.05) with faster GFR decline. Participants with higher scores were more likely to reach ESKD (p<0.05). IFN-γ significantly increased activation scores in cultured human kidney podocytes and proximal tubular cells (p<0.0001). Inhibition of the IFN-γ pathway by a Jak1/2 inhibitor baricitinib reduced the activation scores and ameliorated albuminuria and mesangial expansion in podocyte JAK2 transgenic DBA/2 mice. Similar phenotypic improvements were observed in ReninAV db/db mice after treatment with the JAK1/2 inhibitor, ruxolitinib. Single cell profiling of IFN-γ-treated organoids demonstrated the presence of IFN-γ receptors and downstream target gene CXCL10 in kidney cell types. Higher kidney organoid IFN-γ scores following stimulation with IFN-γ corresponded with increased receptor CXCL10 protein strongly associated with the IFN activation scores in organoids.

Conclusions: Circulating IFN-γ levels were directly associated with alterations in kidney transcriptomic programs and the progression to ESKD in human DKD and model organoid systems. A clinically available drug (baricitinib) reversed IFN-γ activation and albuminuria in murine models identifying IFN-γ as a target for treatment in DKD.

Funding: NIDDK Support

FR-OR34
Metabolomic and Transcriptomic Reveal Signature of Citrate Homeostasis in Diabetic Kidney Disease
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Background: Kidneys are highly metabolic organs, and the TCA cycle primarily fulfills the enormous energy required to maintain their normal function. In our previous cross-sectional study, low urinary citrate was associated with chronic kidney disease progression in Type 2 Diabetic patients. In this study, we performed a longitudinal targeted urinary metabolomic screening in 4 cohorts of Type 1 Diabetic (T1D) patients and single-cell RNAseq analysis of separate kidney biopsies to explore potential metabolic reprogramming in diabetic kidney disease (DKD).

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

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FR-OR35

Whole Blood DNA Methylation Signature, Circulating Proteins, and Risk of Progression to ESKD in Type 1 Diabetes (T1D)
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Background: Diabetic Kidney Disease (DKD) can progress to end stage kidney disease (ESKD) which increases morbidity and mortality. Since commonly utilized clinical variables do not adequately predict ESKD onset, there is an unmet need to update the current ESKD risk prediction model with more sensitive biomarkers. We examined whether DNA methylation (DNAm) can fulfill this need.

Methods: Using human EPIC DNA arrays, we profiled DNAm in whole blood DNAs of 277 well characterized T1D participants with DKD (median eGFR 52.2mL/min/1.73m2 and ACR 728.9mg/g) from the Joslin Kidney Study; 51% of our cohort developed ESKD during follow-up (7-20 years). We then performed epigenome-wide analysis followed by integration with genetics and circulating proteins data (Olink) from the same cohort, and developed statistical models including DNAm for ESKD-risk prediction.

Results: We identified DNAm at 17 CpGs associated with ESKD risk (ESKD-associated CpGs) independent of major demographic/clinical risk factors. These CpGs were located in/near genes related to pathogenesis of DKD and/or ESKD, including inflammation. Notably, 7 of these ESKD-associated CpGs had methylation quantitative trait loci SNPs. Some of these SNPs could affect binding sites for key transcription factors with functions related to DKD, suggesting novel links between genetic variants and ESKD via DNAm. Moreover, the impact of 5 of these CpGs on ESKD-risk were partially mediated by several circulating proteins previously reported to be associated with ESKD e.g. TNF-R27 and KIM1, suggesting downstream functions of these CpGs partially mediated by several circulating proteins previously reported to be associated.

Conclusions: Low urinary citrate could be a potential marker for CKD progression in T1D patients, and intracellular citrate homeostasis could be associated with DKD progression.

Funding: NIDDK Support, Veterans Affairs Support

FR-OR36

Single-Cell Resolution Drug Effects on RAAS Blockade in ZSF1 Rat Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is the leading cause of renal failure worldwide. Over-activation of the renin-angiotensin-aldosterone system (RAAS) is associated with detrimental outcomes in DKD patients. RAAS inhibitors such as enalapril have been used for decades as antiproteinuric, antihypertensive, and kidney protective agents. Still, the exact cell type of action and the main drivers of drug action remain elusive.

Methods: To this end, in addition to detailed biochemical, histological, and tissue proteomics analysis of the ZSF1 obese rat with or without enalapril treatment, we leveraged single-cell transcriptomics (scRNA-seq). We exploited state-of-the-art analyses of unbiased tensor decomposition, differential gene expression, pathway enrichment, cell trajectories, RNA velocity, weighted gene correlation networks, integration with CITE-seq imputed antibody-derived tags, and cell-cell communication. Results from the ZSF1 model were validated in human kidney samples and datasets.

Results: RAAS inhibition via enalapril ameliorated hypertension, proteinuria, kidney tissue levels of progression markers, and fibrosis in the ZSF1 rat model of DKD. SCRNA-seq highlighted immune cell enrichment, endothelial and tubular cell depletion. Unbiased tensor decomposition analysis showed distal nephron tubule cells were associated with treatment status. Enalapril downregulated cathespin D (Ctsd) in diabetic distal nephron and myeloid cells. Ctsd+ injured tubule cells of the distal nephron were enriched in DKD and depleted upon enalapril treatment. Ctd was also a marker for Tmem2+ resident macrophages, which demonstrated an inflammatory phenotype and interacted strongly with distal nephron tubule cells. Ctsd was particularly enriched in kidneys from DKD patients and correlated with outcome-relevant parameters such as fibrosis and glomerular filtration rate.

Conclusions: We report previously unknown injury cell states of the distal nephron, describe Ctsd as an important regulator of enalapril effects, and reveal Tmem2+ resident macrophages as top receivers of distal nephron cell-cell communication. Finally, we show that our findings translate to humans and demonstrate that enalapril-associated gene signatures allow stratification of human kidney samples by disease-relevant outcome measures such as kidney function and fibrosis.

Funding: Commercial Support - Bayer, Government Support - Non-U.S.

FR-OR37

Long Noncoding RNA (lncRNA) PVT1 Initiates Mitochondrial Damage and Inflammation via TRIM56 in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD), one of the chronic microvascular complications of diabetes mellitus (DM), is the leading contributor of end stage renal disease (ESRD) globally, and increasing number of studies have demonstrated that immunity and inflammation are key pathogenic mechanisms in DKD. Notably, hyperglycemia-induced mitochondrial dysfunction played a pivotal role in activating innate immunity. However, the concrete mechanisms responsible for mitochondrial damage and inflammation of podocytes during DKD remain poorly understood.

Methods: The role of PVT1 was investigated by resorting to cultured podocytes, podocyte-specific deletion of PVT1 (Pnphs2-Cre/Pvt1flox/flox) mice and human samples. RT-qPCR, western blotting, RNA-FISH, TEM, histology staining, immunofluorescence, RIP, MeRIP, RNA pull-down, luciferase reporter assays, and Seahorse XF Cell Mito Stress Test were utilized for mechanistic study of the interaction between PVT1, TRIM56 and AMPKs further.

Results: We observed a significant upregulation of long non-coding RNA (lncRNA) PVT1 in plasma of patients with DKD. And we generated mice with podocyte-specific deletion of PVT1 (Pnphs2-Cre/Pvt1flox/flox) and confirmed that PVT1 deletion ameliorated diabetes-induced podocyte injury, glomerular pathology and proteinuria. We further demonstrated a novel role of PVT1 in regulating podocyte mitochondrial dysfunction and inflammation through TRIM56-mediated cGAS-STING signaling pathway. Similar results were validated in podocyte-specific deletion of Trim56 (Pnphs2-Cre/Trim56flox/flox) in DKD mice models. Mechanically, PVT1 was upregulated due to m6A demethylation under high glucose conditions, and the stabilized PVT1 provided mitochondrial dysfunction by interacting with TRIM56 post-transcriptionally to manipulate the ubiquitination of AMPKs, which subsequently induced mitochondrial injury. Meanwhile, the cytosolic mtDNA, released from damaged mitochondria, was recognized by the cGAS-STING pathway, linking mitochondrial homeostasis disruption to inflammatory responses in podocytes. Moreover, TRIM56 could catalyze STING in a ubiquitous manner to mediate inflammation directly in podocytes under high glucose environment.

Conclusions: Our study proposes the important role of PVT1 and TRIM56 in mitochondrial damage and inflammation, providing a potential therapeutic target against DKD.

Funding: Government Support - Non-U.S.
FR-OR38
NDUFS4 Regulates Cristae Remodeling in Diabetic Kidney Disease
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Background: Despite considerable progress in understanding the role of mitochondrial remodeling in kidney cells, the exact role and nature of mitochondrial electron transport chain (ETC) in the diabetic environment remains elusive.

Methods: We examined ETC remodeling in podocytes of established mouse models of diabetic kidney disease (DDK), and generated diabetic mice with podocyte-specific overexpression of Ndufs4 (NADH: ubiquinone oxidoreductase iron-sulfur protein 4, Ins2Akita/+;Ndufs4podTg), an accessory subunit of mitochondrial complex I, as a model to investigate the role of ETC integrity in DDK. APEX2 proximity labeling and complexome profiling were performed to seek the Ndufs4 interactome in the context of mitochondrial respiratory supercomplexes (RSCs).

Results: We found that diabetic mice with conditional overexpression of Ndufs4 in podocytes showed reduced albuminuria coupled with marked improvement in cristae morphology and mitochondrial dynamics. Importantly, primary podocytes from these mice exhibited increased ATP production, oxygen consumption rates, and complex I activity along with significantly reduced mitochondrial ROS and mitochondrial fission as compared to diabetic Ins2Akita/+ mice. Using cryo-electron tomography, we found that diabetes-induced cristae remodeling was significantly improved with the forced expression of NDUFS4. By coupling proximity labeling, structural cryo-electron microscopy complexome profiling, and super-resolution imaging approaches, we identified a possible interaction between STOML2, a 39 kDa cristae remodeling protein, and NDUFS4 in the context of improved supercomplex assembly as the main explanation for the NDUFS4-mediated improvement in the cristae morphology. We further validated this interaction and found that two regions of the β-plated sheet structures in STOML2 domain were crucial for its binding to NDUFS4.

Conclusions: Our findings uncover an unexpected role of NDUFS4 as a powerful regulator of cristae remodeling and mitochondrial dynamics. We propose that impaired mitochondrial cristae remodeling defining features of mitochondrial dysfunction in the diabetic environment, and targeting Ndufs4 could be a promising approach for developing therapies to slow the progression of DDK.

Funding: NIDDK Support, Private Foundation Support

FR-OR39
The Transcription Factor ChREBP Links Mitochondrial Lipid Metabolism and Morphogenesis to Progression of Diabetic Kidney Disease
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Background: Recent studies have suggested that both mitochondrial dynamics and lipid metabolism contribute to the pathogenesis of diabetic kidney disease (DKD). However, the precise interplay between these two key metabolic regulators is not fully understood. We recently showed that the expression of carbohydrate-response element-binding protein (ChREBP), a glucose-responsive transcription factor, and a master regulator of lipogenesis, is induced by high glucose in podocytes (Long et al., JBC 2020). Here we examine the role of ChREBP on progression of DKK in vivo and its role as a link between mitochondrial dynamics and lipid metabolism.

Methods: An inducible podocyte-specific ChREBP knockout mouse model was generated by crossing floxed ChREBP mice with tamoxifen-inducible Cre transgenic mice. The triple transgenic mice were assessed for kidney remodeling by microdissection (IS-LCM) using a Sglt2 ko-validated antibody (n=6 mice/group).

Results: We found that ChREBP deficiency in podocytes of diabetic mice improves key biochemical and histological features of DDK in addition to significantly reducing mitochondrial fission. Using mitochondrial lipidomic analysis, we find that the abundance of plasmalogens, but not other phospholipids such as PE or PC, is increased by high glucose and reversed with ChREBP knockdown, suggesting a modulatory role of ChREBP on plasmalogen phospholipids biosynthesis. Importantly, overexpression of ChREBP reverses the protective phenotype of ChREBP deficiency on mitochondrial fragmentation. Finally, our findings suggest that ChREBP bind to Gapat promoter to activates its transcription.

Conclusions: Our results uncover a distinct plasmalogen phospholipids as the mechanistic link between ChREBP-mediated lipid metabolism and mitochondrial remodeling.

Funding: NIDDK Support

FR-OR40
Transcriptomics of SGLT2-Positive Proximal Tubule S1 Segments in Mice: Response to Diabetics, SGLT1/2 Inhibition, or GLP1 Receptor Agonist
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Background: SGLT2 inhibitors (SGLT2i) and GLP1 receptor (GLP1R) agonists have kidney protective effects. However, their molecular effects on SGLT2-expressing early proximal tubule S1 segments, which have negligible SGLT1 expression, have not been fully understood.

Methods: Fourteen-week-old male wildtype (DBA) and diabetic (DBA-Akita) mice + systemic Sglt1 knockout (ko) were given vehicle or SGLT2i dapagliflozin (Dapa; 10mg/kg diet) for 2 weeks, while other DBA-Akita received GLP1R agonist semaglutide (Sema; 3nmol/kg body weight/day, s.c.). RNA sequencing was performed in SGLT2i-positive proximal tubule segments isolated by immunostaining-guided laser capture microdissection (IS-LCM) using a Sglt2 ko-validated antibody (n=6 mice/group).

Results: Bloodglucose in DBA-Akitawas significantly reduced by Dapa (254±11mg/dl) and Sglt1 ko (367±11mg/dl) but not by Sema (407±48mg/dl) vs. vehicle (480±35mg/dl). A total of 20,748 annotated protein-coding genes was detected by RNA sequencing, and robust enrichment of S1 segment genes was confirmed by ranking marker genes based on the number of transcripts. DBA-Akita showed 116 differentially expressed genes vs. DBA (DEGs; adjusted p<0.1, log2FC +/-0.6) suggesting downregulation of metabolic pathways like unsaturated fatty acid and carboxylic acid metabolism. Dapa restored lipid metabolic pathways and increased expression of genes coding for glucose metabolism, organic anion transport. Meanwhile, Dapa changed only 2 genes in DBA. Moreover, Sema and Sglt1 ko restored only 11 and 0 of the DEGs in DBA-Akita. Sglt1 ko enhanced the Dapa effect in DBA-Akita (207 DEGs and 64 restored genes) possibly due to additive effects on blood glucose (193±15mg/dl).

Conclusions: Transcriptomic profiling of SGLT2-positive S1 segments was established by IS-LCM. Despite SGLT2 expression in these segments, SGLT2i had little effect on transcriptomics in non-diabetic conditions. In diabetic mice, however, it restored transcriptomic changes many more ways, while targeting GLP1R or SGLT1 showed little effect. The approach warrants further studies in SGLT1-expressing S3 segments, which compensate during SGLT2i, and in glomeruli.

Funding: NIDDK Support, Other NIH Support - NIAMS, Commercial Support - Novo Nordisk

FR-OR41
Effect of Dietary Acid Reduction on Acid-Base Status of Patients with CKD but with Normal eGFR: A 5-Year Randomized Trial
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Background: Previous studies show that high acid-producing diets contribute to metabolic acidosis in subjects with chronic kidney disease (CKD) stage G3 and to eubicarbonatemic acidosis in those with stage G2, conditions of acid accumulation that have been associated with adverse outcomes. We tested the hypothesis that high acid-producing diets have discernible effects on acid-base status of those with CKD but with normal baseline eGFR.

Methods: One hundred fifty-three macroalbuminuric, non-diabetic G1 participants with eGFR >90 ml/min/1.73 m2 and baseline high acid-producing diets (potential renal acid load [PRL, mean (SE)] = 61.7 (0.83) mmol/day) were randomized to Usual Care (UC, n=51) or to base-producing fruits and vegetables (F+V, n=51) in amounts to reduce dietary PRAL by half, or oral NaHCO3 (HCO3, n=51) 0.4 mmol/kg bw/day. They were followed for 5 years, measuring eGFR (CKD-EPI equation) and plasma total CO2 (PTCO2) following the following at baseline and 5 years: plasma citrate (Pcit), 8-hour urine citrate (UcitV), 24-hour urinary creatinine excretion (UcitV), and acid retention by comparing observed to expected increase in PTCO2 in response to retained HCO3 (dose minus UHCO3V) 2 hours after oral NaHCO3 (HCO3, n=51) 0.4 mmol/kg bw/day, assuming 50% body weight HCO3 apparent space of distribution.

Results: Baseline values were similar among groups. For both F+V and HCO3 relative to UC, 5-year eGFR was higher (mean (SE)), F+V [96.5 (0.79)], HCO3 [95.9 (0.90)] vs. UC [92.1 (1.23), ml/min/1.73 m2, ps<0.001]. For both F+V and HCO3 relative to UC, 5-year PTCO2 was higher (PTCO2 [26.7 (0.08)], UC [26.0 (0.09)], mmHg, p<0.001). For both F+V and HCO3 relative to UC, 5-year Pcit and UcitV were higher (Pcit, F+V [0.159 (0.001)], HCO3 [0.158 (0.002)] vs. UC [0.157 (0.001), mmol/ml, p<0.02]; UcitV, F+V [1.163 (0.011)], HCO3 [1.141 (0.002)] vs. UC [1.124 (0.006), mmol/8 hours, ps<0.05]). For both F+V and HCO3 relative to UC, 5-year acid retention was lower (acid retention, F+V [1.19 (1.61)], HCO3 [-1.72 (1.56)] vs. UC [2.53 (1.55), mmol, p<0.003]).

Conclusions: In participants with CKD and normal eGFR high eating acid-producing diets at baseline, dietary acid reduction over 5 years with either F+V or NaHCO3 yielded small but discernible improvements in acid-base status that might mediate slower CKD progression.
Interventions to Reduce CKD Progression

FR-OR42
Supporting Self-Management of Healthy Behaviors (SMART-HABITS) in CKD and Hypertension: A Pilot Trial
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Background: Home blood pressure monitoring (HBPM) and physical activity monitoring may have health benefits, but the feasibility and acceptability among individuals with chronic kidney disease (CKD) and hypertension (HTN) are not known.

Methods: In a 12-week study among individuals with stage 3-4 CKD and HTN, we evaluated the acceptance and feasibility of SMART-HABITS, a smartphone-based intervention to support physical activity and HBPM. Participants were asked to perform HBPM and share results at least 3x/wk and share step counts daily for 6 weeks. Two approaches to communicate HBPM were: 1) text message and 2) a smartphone application (app) connected to a Bluetooth-enabled BP machine, with the sequence determined via randomization. Step counts were monitored with a wearable device (Fitbit) and communicated via the Fitbit app for 12 weeks. Primary outcomes were 1) acceptance-assessed through surveys and interviews, and 2) feasibility-assessed with measures of adoption, adherence, and usability with the System Usability Survey (SUS).

Secondary outcomes were maintenance (a HBPM or step count transmission a1x/wk), change in survey scores related to CKD knowledge, electronic health (eHealth) literacy, self-efficacy, self-management, QOL, BP, and daily step counts.

Results: Forty-seven participants were randomized. Mean age was 63 years, 49% were women, and 48% were Black. For HBPM, 44 participants (94%) completed the text phase and 43 (92%) completed the Bluetooth phase. Adoption was reflected in a 92% retention rate, HBPM adherence was 81% in the text phase and 69% in the Bluetooth phase, and step count adherence was >83% over 12 weeks. Usability was adequate (SUS score ≥ 70), with 43 (92%) participants communicated HBPM and/or step count data. Mean daily step counts significantly increased by 3414 steps, but BP did not change.

Conclusions: In this study of individuals with CKD and HTN, implementing a smartphone-based tool to support physical activity and HBPM is feasible and acceptable despite low eHealth literacy levels.

Funding: NIDDK Support

FR-OR43
Association of Leukotriene Antagonist Use with the Incidence of ESKD
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Background: Pro-inflammatory lipid mediators known as leukotrienes (LTR) have been implicated in the etiology of chronic kidney disease (CKD). We have found that short-term inhibition of cysteinyl LTRs in mice with metolukast inhibits CKD progression and accelerates acute kidney injury. Whether LTR antagonist use is associated with a reduction in kidney disease in humans is not known. We examined the association of LTR inhibitor (LTRi) therapies with the risk of developing end stage kidney disease (ESKD).

Methods: In a national cohort of 651,509 US Veterans with a diagnosis of asthma or allergic rhinitis, we identified 50,895 incident users of LTRi (montelukast or zafirlukast) and 600,614 patients who did not receive LTRi. We examined the association of LTRi with ESKD in competing risk regressions and cause-specific Cox models. We used propensity score matching to create comparable groups defined by baseline demographics, comorbidities, and health care utilization.

Results: Forty-three (91.5%) participants communicated HBPM and/or step count adherence was >83% over 12 weeks. Usability was adequate (SUS score ≥ 70), with 43 (92%) participants communicated HBPM and/or step count data. Mean daily step counts significantly increased by 3414 steps, but BP did not change.

Conclusions: In this study of individuals with CKD and HTN, implementing a smartphone-based tool to support physical activity and HBPM is feasible and acceptable despite low eHealth literacy levels.

Funding: NIDDK Support

FR-OR44
Initiation of ACE Inhibitor and ARBs in Patients with Advanced CKD
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Background: The treatment benefit of ACEi/ARB initiation on the risk of kidney failure with replacement therapy (KFRF) and mortality remains unclear in patients with CKD stage 4-5 who were not well-represented in individual trials evaluating the use of these agents.

Methods: We pooled individual-level data from 15 trials that included patients with eGFR<30 mL/min/1.73 m2 to examine the effect of ACEi/ARB use on the risk of the onset of KFRF, or secondarily, death using Cox models. We performed pre-specified subgroup analyses and tested for interaction to evaluate the effect of ACEi/ARB inhibitor use by baseline albuminuria (<300 mg/g versus ≥300 mg/g), eGFR (≤20 versus >20 mL/min/1.73 m2), age (<65 versus ≥65 years), race, and history of diabetes. All analyses were conducted in an intention-to-treat approach.

Results: We included 1752 participants from 15 trials, of whom 611 (35%) required KFRF and 215 (12%) died. Overall, ACEi/ARB use was associated with lower risk of KFRF (HR 0.71 [95% CI 0.60-0.83]) but not death (HR 0.95 [95% CI 0.72-1.24]). However, there was heterogeneity in the effect of the intervention on KFRF by baseline severity of albuminuria (p<0.08). ACEi/ARB initiation was associated with lower risk of KFRF in those with severe albuminuria (HR 0.68 [95% CI 0.57-0.80]), but not in those without severe albuminuria (HR 1.05 [95% CI 0.60-1.86]). There was no interaction between ACEi/ARB use and baseline eGFR, diabetes, race, or age for KFRF (all p>0.10).

Conclusions: Data from this pooled individual-level analysis demonstrated a benefit of ACEi/ARB use in delaying onset of KFRF, but not in death in patients with stages 4-5, regardless of the baseline eGFR.

Funding: NIDDK Support

FR-OR45
Sotagliflozin and Kidney and Cardiorenal Outcomes in SCORED
David Cherny,1 Deepak L. Bhatt,2 Michael Szarek,3 Michael J. Davies,4 Philippe Francès,1 Bertram Pitt,5 Philippe Gabriel Segh1 University of Toronto, Toronto, ON, Canada; 2Mount Sinai Heart, New York, NY; 3Ineha School of Medicine at Mount Sinai, New York, NY; 4University of Colorado Anschutz Medical Campus, Aurora, CO; 5Lexicon Pharmaceuticals Inc, The Woodlands, TX; 6University of Michigan, Ann Arbor, MI; 7Université Paris Cite, Paris, France; 8Hopital Bichat - Claude-Bernard, Paris, France.

Background: SGLT2 inhibitors reduce kidney and cardiovascular (CV) outcomes in patients with and without type 2 diabetes (T2D). The aim of this exploratory analysis was to evaluate the effect of sotagliflozin (SOTA), a dual SGLT1 and 2 inhibitor, on kidney and cardiorenal outcomes in patients with T2D and chronic kidney disease (CKD).

Methods: SCORED, a Phase 3, double-blind, placebo-controlled study, randomized 10,584 patients with T2D, CKD, and CV risk factors to SOTA or placebo (1:1). Kidney criteria for inclusion were an eGFR ≥25 to 60 mL/min/1.73m2 regardless of UACR. The composite in this analysis included kidney and cardiorenal outcomes derived using laboratory values, with treatment comparisons by proportional hazards models.

Results: At baseline, median eGFR was 45 mL/min/1.73m2 in 35 and 34, and 31% of patients were categorized as having normo-, micro-, and macroalbuminuria, respectively. Over a median follow up of 16 months, SOTA reduced the primary CV endpoint by 26% (p<0.001). SOTA reduced the risk of the composite of first event of 50% decline in eGFR, eGFR=15 mL/min/1.73m2, chronic dialysis, renal transplant, or renal or CV death (p=0.0023, Figure 1). Results were generally consistent when using different eGFR drop thresholds and/or on renal death (all p<0.01, Figure 2).

Conclusions: SOTA reduced the risk of kidney and cardiorenal endpoints in patients with T2D and CKD.

Funding: Commercial Support - Lexicon Pharmaceuticals, Inc.
Interventions to Reduce CKD Progression

Figure 1. First event within cardiorenal composite

Figure 2. Forest plot of various cardiorenal composites

FR-OR47
Effect of Tirzepatide on Kidney Function in People with Excess Body Weight: A Post Hoc Analysis of the SURMOUNT-1 Trial
Hidde J. Heerspink,1 Allon N. Friedman,2 Petter Bjornstad,2 Daniel H. van Raalte,2 Zhengyu Yang,3 Adam Stefanski,3 Farai B. Chiguuta,3 Ibrahim Turfandana,1 Mathijs Bunck,1 Carolina Piras de Oliveira,1 University Medical Center Groningen, Groningen, Netherlands; 2Indiana University School of Medicine, Indianapolis, IN; 3University of Colorado School of Medicine, Aurora, CO; 4Amsterdam Universitair Medische Centra, Duivendrecht, Netherlands; 5Eli Lilly and Company, Indianapolis, IN.

Background: The prevalence of chronic kidney disease due to obesity is rapidly increasing, but few proven effective therapies are available. Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, has shown potential in attenuating the decline in estimated glomerular filtration rate (eGFR) in people with type 2 diabetes (T2D) at high risk for cardiovascular disease. In the SURMOUNT-1 trial in people with obesity or overweight without T2D, tirzepatide significantly reduced body weight and blood pressure by week 72 (the primary endpoint) compared with placebo. This post-hoc analysis assessed the potential impact of tirzepatide compared with placebo on kidney function in SURMOUNT-1 trial participants.

Methods: Data from all participants randomly assigned to treatment were included (pooled tirzepatide [5, 10, and 15 mg], N = 1896; placebo, N = 643). Assessments included CKD-EPI creatinine- and cystatin-C-based eGFR (Cr-eGFR and CysC-eGFR, respectively), and urinary albumin-to-creatinine ratio (UACR). The change from baseline to week 72 was analyzed using a mixed model for repeated measures with on-treatment data.

Results: Baseline mean Cr-eGFR was 98.1 ± 18.0 mL/min/1.73m² and CysC-eGFR was 95.5 ± 19.1 mL/min/1.73m²; 27%-36% of participants had mean eGFR <90 mL/min/1.73m². Baseline median UACR was 6.0 mg/g (interquartile range 4.0-11.0 mg/g); 8.6% of participants had UACR ≥ 30 mg/g. The estimated treatment difference (ETD) between pooled tirzepatide groups and placebo on the change from baseline Cr-eGFR was -0.2 mL/min/1.73m² (95% confidence interval [CI] -1.2, 0.9; p=0.780). For CysC-eGFR the ETD was 3.2 mL/min/1.73m² (95% CI 2.1, 4.3; p<0.001). The change in percent change in UACR was -8.4% (95% CI -14.7, -1.6; p=0.017). In participants with baseline UACR ≥30 mg/g, the ETD was -42.3% (95% CI -60.8, -15.0; p=0.006).

Conclusions: Tirzepatide demonstrated an increase in CysC-eGFR and reductions in UACR compared with placebo, suggesting renoprotective effects. These results warrant a long-term, prospective kidney outcome trial for people with obesity or overweight.

Funding: Commercial Support - Eli Lilly and Company

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

**FR-OR49**

**Implications of Follow-Up Time on the Optimal Weighting of the Acute and Chronic Slopes to Predict Treatment Effects on Chronic End Points**

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1University of Utah Health, Salt Lake City, UT; 2Tufts Medical Center, Boston, MA; 3University of Groningen Afdeling Gezondheidswetenschappen, Groningen, Netherlands.

**Background:** We have shown in a meta-analysis of 66 randomized treatment comparisons (RTCs) that treatment effects on the established clinical endpoint (CE) based on doubling of serum creatinine (SCR), GFR ≥ 15 mL/min/1.73m² or kidney failure are in aggregate predicted accurately by the mean GFR slope over 3 years. We evaluate implications of follow-up time for the optimal weighting of the acute and chronic GFR slopes to predict treatment effects on the CE.

**Methods:** For each RTC, we used a mixed effects model to estimate treatment effects on the acute (evaluated from baseline to 3 months) and chronic (evaluated after 3 months) GFR slopes, and Cox regression to estimate treatment effects on the CE. We used an extended multivariable random-effects regression model to relate the treatment effects on the CE jointly to those on the acute and chronic slopes. The extended model expressed the optimal weighted average of the acute and chronic slopes as \( R^2 \) (Acute Slope) = \( \alpha \) (Acute Slope) + \( \beta \) (Chronic Slope), and allows \( \alpha \) to depend on the median follow-up time of each RTC.

**Results:** The multivariable model accurately predicted the treatment effect on the CE (median \( R^2 = 0.97 \) for a RTC with 3 years follow-up). The optimal weight \( \alpha \) for the acute slope relative to the chronic slope had a strong inverse relationship with the median follow-up time, decreasing from a median (95% Bayesian credible interval) of 0.90 (0.08, 0.94) at 2 years by 0.34 to 0.069 (0.049, 0.091) at 3 years and by 0.65% to 0.037 (0.013, 0.073) at 4.5 years.

**Conclusions:** The optimal weighting of the acute and chronic slopes for predicting the treatment effect on the CE assigns a major role to the acute effect when the CE is evaluated over longer follow-up times which are relevant to patients.

**Funding:** Private Foundation Support

**Effect of Follow-Up Time on Optimal Weighted Average of Acute and Chronic Slopes**

| Time | Model | CE
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<td>0.9% (0.7% to 0.7%) lower effect on optimal weighted average of the acute and chronic GFR slopes</td>
<td>0.5% (0.3% to 0.7%) lower effect on optimal weighted average of the acute and chronic GFR slopes</td>
<td>0.2% (0.0% to 0.4%) lower effect on optimal weighted average of the acute and chronic GFR slopes</td>
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<td>Optimal ( \alpha ) when evaluating CE over 3 years</td>
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<td>Optimal ( \alpha ) when evaluating CE over 3 years</td>
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<tr>
<td>Optimal ( \alpha ) when evaluating CE over 4.5 years</td>
<td>0.008</td>
<td>0.008 (0.007, 0.009)</td>
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**FR-OR50**

**Improvement in Anemia by SGLT2 Inhibitors Were More Prominent Among Those with Inflammation**

Miho Murashima, Takahisa Kasugai, Tatsuya Tomonari, Minamo Ono, Massashi Mizuno, Takayuki Hamano. Nagoya Shiroi Daigaku, Nagoya, Japan.

**Background:** SGLT2 inhibitors (SGLT2i) were reported to increase hemoglobin (Hb) by suppressing hepcidin and increasing erythropoietin, simulating the effect of hypoxia-inducible factor-1alpha (HIF-1α) inhibitors. We hypothesized that an increase in Hb by SGLT2i might be more prominent among patients with inflammation similar to HIF-1α inhibitors.

**Methods:** In this retrospective cohort study, diabetic outpatients from 2019 to 2020 at our hospital were enrolled. Exposure was the use of SGLT2i. The Hb slope within 6 months after initiation of SGLT2i (the first 6 months of the observation period for non-users) was analyzed using a mixed-effects model. Non-linear regression models were fitted with restricted cubic splines to investigate Hb levels at the last visit across different eGFR levels. Analyses were performed separately for those with higher and lower than the median baseline C-reactive protein (CRP) levels. The data were adjusted for potential confounders.

**Results:** Among 1,246 patients, 306 were on SGLT2i. During the first 6 months, CRP and eGFR trajectories were not significantly different between users and non-users of SGLT2i. Differences in Hb slope between users and non-users of SGLT2i were 0.14 (0.05–0.24) and 0.05 (-0.05–0.15) g/dL/month for those with higher and lower baseline CRP, respectively, after adjustment for confounders including time-dependent eGFR. Hb levels at the last visit were significantly higher among SGLT2 users across the range of eGFR levels, and it was more prominent among those with higher CRP (p for interaction=0.1).

**Conclusions:** SGLT2i use was associated with higher Hb levels, especially among those with inflammation across the range of eGFR levels. The results suggest that SGLT2i could improve anemia among patients with anemia of chronic kidney disease and inflammation which are refractory to treatment with erythropoiesis-stimulating agents.
Clinicopathologic features of MBGMID

FR-OR52
The Characteristics of Concurrent Anti-Glomerular Basement Membrane Nephritis and Membranous Nephropathy

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Background: Concurrent anti-glomerular basement membrane (GBM) nephritis and membranous nephropathy (MN) is rare and has been previously addressed only in case reports and small series (≤12 patients). Its true target antigen is unknown.

Methods: We studied the clinicopathologic characteristics and outcome of 28 patients with anti-GBM nephritis and MN diagnosed at a large nephropathy laboratory over a 23-year period. A pathologic diagnosis of anti-GBM nephritis was defined by the immunofluorescence finding of intense linear GBM staining for IgG, in the absence of (or much weaker) staining for albumin, and concurrent MN was defined by the presence of segmental or global subepithelial deposits by electron microscopy.

Results: These cases are among 449 (6.2%) anti-GBM nephritis and 5183 (0.5%) MN patients reviewed at our center. At diagnosis. Most (90%) patients presented with acute kidney injury with a median serum creatinine at biopsy of 7.8 mg/dL (range 1.2-24.0), proteinuria (median 3.5 g/day, range 0.4-11) and hematuria. Kidney biopsy showed classic (n=26) or atypical (n=2) anti-GBM nephritis. Most patients received immunosuppressive therapy. After a median follow up of 17 months, 11% had complete remission (including the 2 with atypical anti-GBM nephritis), 27% had persistent kidney dysfunction, 62% progressed to ESKD. The rate of progression to ESKD was 93% in those on dialysis at presentation. The dominant pathology was segmental or global subepithelial deposits by electron microscopy.

Conclusions: Concurrent classic anti-GBM nephritis and MN has poor prognosis, particularly in patients requiring dialysis at presentation, while atypical anti-GBM nephritis and MN has a favorable outcome. It is not associated with any of the known MN antigens and no novel target antigens were detected by mass spectrometry, favoring that the MN target antigen is likely an exposed structural GBM antigen.

FR-OR53
Clinicopathologic Features of Anti-Brush Border Antibody Disease: A Series of 66 Patients

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Background: Anti-brush border antibody disease (ABBA) is an autoimmune tubulointerstitial kidney disease that primarily affects older individuals and results in progressive kidney failure. It is a rare entity with only 20 cases reported to date. Therefore, the histopathologic spectrum, clinical associations, prognosis, and response to therapy are poorly understood.

Methods: We performed a retrospective clinicopathologic analysis of kidney biopsies and identified 66 cases with ABBA including 63 native and 3 recurrence in an allograft identified from 4 institutions. Demographics, clinical findings, and laboratory data were obtained. Histopathologic data included light, immunofluorescence, electron microscopy, and immunostaining for LR2P, CUBN, and AMN. Follow-up data was available from 49 patients, examining treatment(s), laboratory values, and outcome measures.

Results: Patients with ABBA were predominantly male (74%) with a mean age of 70.9 ± 12.3 years. Progressive chronic kidney disease was the most common biopsy indication. The mean serum creatinine was 3.5 ± 2.6 mg/dL, proteinuria 2.7 ± 2.9 g/day, and 66% had hematuria. Acute tubular injury with LR2P-positive tubular basement membrane deposits were seen in 94% patients, with one case demonstrating CUBN and AMN positivity in addition to LR2P. Thirty-eight patients (57.6%) had secondary diagnoses, most commonly glomerular diseases with high proteinuric states. These included podocytopenathy, membranous nephropathy, IgA nephropathy, lupus nephritis, crescentic glomerulonephritis, acute or chronic tubulointerstitial nephritis, and renal involvement by B-cell lymphoma. The majority of patients with available follow-up data were treated with immunosuppression (73.5%). Complete or partial remission was achieved for 32.7%, 67.3% had no remission, and 22.5% required dialysis or were deceased at follow-up. Patients not treated with immunosuppression were at the highest risk of kidney failure.

Conclusions: ABBA is frequently concurrent with other kidney diseases, which may lead to under-diagnosis of this important cause of kidney failure.

FR-OR54
Clinicopathologic Characteristics, Etiologies, and Outcomes of Secondary Oxalate Nephropathy

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Background: The characteristics of secondary oxalate nephropathy (ON) are not well defined, and the rate of recurrence after kidney transplant (Tx) and Tx outcome are unknown. We report the largest series on secondary ON to date.

Methods: Retrospective analysis of clinicopathologic and outcome characteristics of 113 patients with secondary ON in the native kidney diagnosed at a large tertiary care academic center.

Results: Biopsy incidence was 0.97%. ON was attributed to enteric hyperoxaluria in 60% (most commonly RYGB), excessive ingestion of foods high in oxalate or oxalate precursors in 23% (most commonly vitamin C), and was idiopathic in 17%. Most patients presented with AKI (particularly in the ingestion group) or AKI on CKD, and 63% with diabetic. Calcium oxalate (CaOx) crystals were more abundant in the ingestion than enteric group, and were accompanied by acute tubular injury, inflammation, and interstitial fibrosis and tubular atrophy (IFTA). Concurrent pathologic conditions were present in 53%, most commonly diabetic nephropathy. After a median follow up of 36 months, 27% had kidney recovery, 19% had persistent kidney dysfunction, 54% developed kidney failure, and 29% died. The mean kidney survival was worse for patients with a concurrent pathologic lesion (30 vs. 96 months for those without, p<0.001). Independent predictors of kidney failure were degree of IFTA and nade eGFR but not degree of crystal deposition. After a median follow up of 38 months in 23 patients who received kidney TX, 4 had graft loss (due to ON in 3). The 2-, 5-, and 10-year graft survival were 90%, 79%, and 50%.

Conclusions: ON is a rare cause of AKI or AKI on CKD. Most patients have co-morbid pathologic conditions, particularly diabetic nephropathy, which worsen the prognosis. Recurrence in the renal allograft and graft loss may occur if hyperoxaluria is not controlled.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR55

Computationally Derived Tubular Features Are Prognostic of Clinical Outcomes in Glomerular Kidney Diseases

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Background: The visual semiquantitative assessment of chronic and acute tubular damage has limited reproducibility and prognostic/predictive power. We hypothesize that sophisticated, computationally assessed, domain-inspired tubular pathomic features can enhance prognostication of proteinuria diseases.

Methods: We developed and applied tubular segmentation algorithms for tubular lumen (TL), epithelium (TE), nuclei, and basement membranes (TBM), to 235 PAS NEPTUNE/CureGN PAS-stained whole slide images (124 FSGS,111 MCD/MCD-like). From these segmentations, 56 features were extracted and summarized at the patient level. We used MMRM to select 10 features most prognostic for time from biopsy to 40% eGFR decline/kidney failure, and proteinuria remission, and Ridge regression models to estimate prognostic accuracy.

Results: Features (Fig.2-A), reflecting TE simplification and TBM thickening/shape, were most prognostic of disease progression; when added to other parameters, estimated prognostic accuracy of non-GS/SS glomerular features.

Conclusions: Computational quantification of tubular pathomic features provides prognostic information above routine measures in glomerular diseases.

FR-OR56

Quantitative Characterization of Nonsclerotic Glomeruli Is Prognostic of Clinical Outcomes in Proteinuric Diseases

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Background: Visual assessment of segmentally (SS), globally (GS) and non-GS/SS glomeruli is used clinically for the diagnosis and prognostication of glomerular diseases. We hypothesized that encoded in non-GS/SS glomeruli are computationally derivable subvisual features prognostic of outcome.

Methods: N=1186 (99 MCD/MCD-like, 87 FSGS) patients from the NEPTUNE/ CureGN cohorts with at least one PAS whole slide image (WSI) containing ≥4 non-GS/ SS glomeruli were included. A previously validated pipeline for glomerular segmentation and classification was applied to WSIs, yielding 272 GS, 113 SS, and 2661 non-GS/SS glomeruli. Percent of SS and GS was calculated. From non-GS/SS glomeruli, 108 intensity, shape, and texture features were computed. Patient-level summary statistics were produced using mean, standard deviation, kurtosis, minimum, maximum, and median. Maximum Relevance Minimum Redundancy (MRMR) selected the 10 most prognostic features for time from biopsy to disease progression (eGFR decline with last eGFR<90 or kidney failure) and to first complete proteinuria remission (UPCR<0.3). Ridge regression models estimated prognostic accuracy of non-GS/SS glomerular features.

Results: Prognostic features (Table 1) reflect the heterogeneity of intra-glomerular organization. These features were the most prognostic of disease progression compared to other models and increased the prognostic accuracy of both clinical outcomes when added to conventional parameters (Table 2).

Conclusions: Computational methods allow for extraction from non-GS/SS glomeruli of information prognostic of clinical outcomes above and beyond conventional
Kidney Pathology: From Classic Clinicopathologic Studies to Computational Pathology

**FR-OR57**

A Spatial Atlas of the Human K�nels of Cell Types and Functional Tissue Units Identified in Highly Multiplexed Immunofluorescence Images

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**Background:** Kidney tissue can be defined at the cell level and at the level of unique functional tissue units (FTUs, e.g. glomeruli and tubules). FTUs are tightly linked to the spatial organization of the kidney. Several single cell transcriptomic atlases have been developed for the kidney, but a spatially anchored comprehensive atlas for cell types and FTUs based on protein expression has yet to be described.

**Methods:** Mesoscale sequential sections from reference kidney tissue spanning from cortex to papilla were imaged using Fusion-Phenocycler, a mesoscale highly multiplexed fluorescence imaging platform. Major markers were used to identify major cell types (epithelial, immune, endothelial), states (stress, repair, cycling) and FTUs. An analytical pipeline was developed to perform image registration, followed by cell and FTU segmentation, labeling, mapping, and neighborhood definition.

**Results:** Over 4 million cells from 5 donors and 18 tissue sections were incorporated in the analytical pipeline, which resulted in the identification of over 30 cell types distributed across the kidney and localized in structures that align with FTU ontologies. A cell-based neighborhood analysis captured tubular niches unique to the renal cortex and outer or inner stripe of the medulla. This spatial segregation was complemented with interstitial niches unique to the cortex or medulla. FTU segmentations mapped the 3D FTUs of the kidney, including vasculature, glomeruli, several tubules and interstitium. Using sequential sections interrogated with Fusion-Phenocycler, FTU segmentation were used to generate 3D models of renal FTUs highlighting the 3D arrangement of kidney FTUs.

**Conclusions:** We establish a reference mesoscale spatial atlas to define anatomically and functionally distinct compartments of the kidney with single cells and FTUs. This work begins to define: 1) the 3D relationship of FTUs, including the relationship between vasculature and tubules, 2) a comprehensive map of cell-types in the human kidney and their organization into FTUs and the bow cellular niches vary across the kidney. This atlas provides a cellularly resolved and spatially anchored reference to understand kidney function in health and disease.

**Funding:** Other NIH Support - Common Fund, HubMAP

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**FR-OR58**

Multiplexed Single-Nucleus RNA and ATAC Sequencing in the Renal Biopsy Specimen

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**Background:** Multi-omic technology allows simultaneous transcriptomic and epigenomic profiling in various kidney cell types, bringing about opportunities to identify crucial pathways, novel biomarkers, and physiology-relevant disease subtypes, while limited by cost and the amount of tissue required.

**Methods:** We developed a novel multiplexed droplet-based single-cell/nucleus sequencing technique to achieve higher throughput and lower cost with less tissue. We applied this method to simultaneously profile transcriptomic (RNAseq) and chromosomal access (ATACseq) data in 27 patients who underwent renal biopsy due to various kidney diseases, ten time-zero transplant biopsy samples, and seven paracancerous kidney samples.

**Results:** After quality control, we yielded about 120,000 single-nuclei (mean nuclei number 2727 per sample) with both transcriptomic and epigenomic profiling data. For snRNAseq, the median gene number per cell is more than 1100. For snATAC-seq, the median fragments number per cell is about 6000, and the TSS enrichment score is 8.83. Major renal cell types including proximal tubule cells, descending thin limb cells, thick ascending limb cells, distal convoluted tubule cells, connecting tubule cells, principal cells, intercalated cells, podocytes, endothelial cells, vascular smooth muscle cells, as well as infiltrating B cells, T cells, and fibroblasts can be robustly identified from the snRNAseq dataset.

**Conclusions:** We developed a novel single-nucleus multi-omic approach that offers rich transcriptomic and epigenomic data, showing promise as a molecular renal pathology technique.

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

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**FR-OR59**

T Cell-Receptor (TCR)-Independent Activation of CD8 Effector T Cells by IL-15 and IFNβ Drives Kidney Damage in Lupus Nephritis

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**Background:** Lupus nephritis (LN) implies morbidity in Systemic Lupus Erythematosus (SLE). A T cell-rich infiltrate parallels deposition of antibodies. How infiltrating T cells contribute to kidney damage is unclear. They can also be observed in urine, which thus can be used as a “window into the kidney” to investigate the cellular pathogenesis of LN. We report analysis of kidney infiltrating T cells found in urine to test if a renal autoimmune reaction contributes to tubulointerstitial inflammation (TII).

**Methods:** Urinary T and tubular epithelial cells (TEC) were quantified by flow cytometry (FC) in LN patients. T cells were subjected to single cell RNA sequencing after FC sort from urine and blood of five LN patients at flare. Comparison of gene transcription revealed putatively pathogenic genes. 67 T cell receptors (TCR) from expanded clonotypes were cloned to test specificity; T cell subsets from blood were subjected to in-vitro experiments. T cell stimulating cytokines were determined in urine from LN and healthy donors, reflecting the renal milieu.

**Results:** Majority of urinary T cells in LN are of CD8 lineage, the amount of which correlates with urinary TEC, a proxy for kidney damage. Mainly being of effector memory phenotype they are recruited partially from a CX3CR1 positive subset in blood which has a type I interferon (IFN) signature. TCR analysis revealed expanded CD8 clonotypes which reactivated both autologous TEC (018). Reactivity to viral CMV and EBV epitopes was shown for 15/67 clones. CMV or EBV was not detectable in respective kidney biopsies. In kidney tissue and/or urine we detected elevated levels of T cell stimulating cytokines, like IL-15. In-vitro, stimulation of CD8 T cells with IL-15 and IFNβ caused TCR-independent activation, degranulation and secretion cytokines TNF and IFNβ, almost exclusively by CX3CR1 positive CD8 effector T cells.

**Conclusions:** Contribution of CD8 T cells to TII and TEC damage in LN is antigen and TCR independent. In-vivo stimulation with IL-15 and type I IFN may be sufficient to trigger effector functions of a CX3CR1 positive subset. Targeting these cells in the blood, their migration, their response to cytokines or reducing renal cytokine levels may prevent LN flares and represent a tailored treatment.

**Funding:** None.

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**FR-OR60**

Adaptive Cellular Immunotherapy for the Control of Primary Membranous Nephropathy

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**Background:** Primary membranous nephropathy (PMN) is an autoimmune podocytopathy caused by subepithelial immune deposits that thicken the glomerular basal membrane and fusion of podocyte processes, causing proteinuria. It is the most common cause of non-diabetic nephrotic syndrome in adults. It is caused in 80% of cases

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

**Underline** represents presenting author.
Kidney Transplantation: Biomarkers, New and Old

FR-OR62
Validation of Diagnostic, Prognostic, and Predictive Performances of a Novel Urinary Exosomal mRNA Clinical Test
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Background: Urinary Exosomes contain a biological payload of proteins and nucleic acids that reflect the physiology of the parent cells (kidney cells and immune infiltrates). Here we further characterize diagnostic performances of a novel urinary exosomal mRNA multigene signature for the diagnosis of any-cause rejection in kidney transplant, and describe its prognostic and predictive performances.

Methods: A total of 411 urine samples -from 366 patients- were collected at time of clinically indicated or protocol kidney biopsy. The transcript of 17 gene targets were pre-amplified and evaluated by RT-qPCR. Cross validation was applied to estimate the performance of the gene signatures. A composite endpoint of subsequent events was determined using the electronic medical records, and outcomes were subjects with positive and negative exosome signature were compared.

Results: The multi-gene classifier accurately distinguished any-cause rejection from no rejection, in the for-cause cohort (AUC 0.731) and the protocol biopsies cohort (AUC 0.781). We further identified a 5-gene signature (IL18BP, CXCL11, CD74, CD44, C3) that accurately distinguishes TCMR from ABMR with an AUC of 0.756. Majority of rejection negative by biopsy classified as positive by our model (false positive) showed significant and underlying inflammation on biopsy such as lymphoproliferative infiltrate, moderate to significant lymphocytic infiltration, interstitial nephritis (BKV nephritis or acute interstitial nephritis), glomerulopathy or immune complex deposition. Furthermore, the remaining inflammation negative but positive urinary exosome scores were associated with increase-fold increase in risk development of composite outcomes of subsequent rejection and increase of decrease eGFR and loss of allograft at 3 years. The exosomal score showed a mean decrease of -0.0566 (p=0.0431) in responders to rejection treatment.

Conclusions: Urinary exosomal mRNA is an non-invasive clinical test that offers an interrogate the status of the innate and adaptive immune responses and involve the differential regulation of leukocyte mediated cytotoxicity" were among top GO Terms in hypomethylated genes compared to non-rejection in kidney transplant recipients. These differences include

FR-OR63
Differential cfDNA Methylation in Kidney Allograft Rejection
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Background: Acute allograft rejection (AAR) is a risk for kidney allograft failure, however, knowledge of the molecular pathophysiology of rejection is lacking. Allograft life is limited and organ availability is scarce, emphasizing the need to understand rejection pathophysiology to preserve the primary allograft. Cell-free DNA (cfDNA) serves as a real-time marker of organ injury and immune response. DNA methylation patterns dictate gene expression. Generally, hypermethylation silences gene expression and hypomethylation indicates active transcription. We propose methylation changes in cfDNA during AAR inform the biologic pathways involved in its development and sequelae.

Methods: Methylation status of total plasma cfDNA samples from 20 pediatric kidney transplant recipients at the time of allograft biopsy was assessed using whole genome bisulfite sequencing. 7,789 differentially methylated CpG sites (DMCs) between individuals with vs without AAR were determined through logistic regression analysis (≥20% difference in methylation rate, q-value <0.05) and were assessed for gene associations and pathway functional enrichments.

Results: AAR was present in 7 patients. 3,390 DMCs were relatively hypermethylated in the setting of AAR and 4,399 were relatively hypomethylated; these DMCs were associated with 114 and 138 genes, respectively. On enrichment analysis, "Relationship between inflammation, COX-2 and EGF"; "Negative regulation of mononuclear cell proliferation"; "Regulation of cytokine-type endopeptidase activity in apoptosis process"; "Regulation of interleukin-8 production"; and "PID CD8 TCR Pathway" were among the most significant WikiPathways, canonical pathways, and Gene Ontology (GO) Terms in hypermethylated genes (P < 0.005). "Response to oxidative stress" and "Regulation of leukocyte mediated cytotoxicity" were among top GO Terms in hypomethylated genes (P < 0.01).

Conclusions: Our data implicate differential immune responses in acute rejection compared to non-rejection in kidney transplant recipients. These differences include the innate and adaptive immune responses and involve the differential regulation of leukocytes and mediation of cytokines. These results provide evidence that methylation differences of cfDNA inform the mechanisms of AAR.

Funding: Private Foundation Support
FR-OR64

Urinary Endothelin Excretion Is Associated with Graft Failure and Mortality in Kidney Transplant Recipients
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Background: Kidney fibrosis is a suggested cause of kidney failure and premature mortality, regardless of the underlying cause. Since collagen type VI is closely linked to kidney fibrosis, we aimed to evaluate whether endothelin, a profibrotic signaling molecule that reflects collagen type VI formation, in the urine was independently associated with graft failure and mortality among kidney transplant recipients (KTR).

Methods: We used data of KTR with a functioning graft one year that were enrolled in the TransplantLines Biobank and Cohort Study. Endothelin was measured by the PRO-C6 enzyme-linked immunosorbent assay in the 24h urine.

Results: There were 621 KTR (age 53 ± 13 years old, 43% female, 5.2 [2.0-12.0] years after transplantation, eGFR 45 ± 19 mL/min/1.73 m²) included in the analyses. The 24h urinary endothelin excretion at baseline was 5.6 [3.1-13.5] μg/24h. During median follow-up of 5.3 years, 70 KTR (11.3%) developed graft failure and 134 KTR (21.6%) died. 24h urinary endothelin excretion was prospectively associated with both increased risk of graft failure and mortality, independent of potential confounders (Table). Cox proportional-hazards analyses for the association of 24h urinary endotrophin excretion with graft failure and mortality.

Results:

<table>
<thead>
<tr>
<th>Graft Failure</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>Model 2</td>
</tr>
<tr>
<td>p-value</td>
<td>p-value</td>
</tr>
<tr>
<td>Cyto</td>
<td>1.79 (1.44-2.23)</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.61 (1.37-1.88)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.12 (1.06-1.20)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.19 (1.04-1.40)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.22 (1.05-1.42)</td>
</tr>
</tbody>
</table>

Model 1 was adjusted for age, sex, and time after transplantation at inclusion. Model 2 was further adjusted for estimated glomerular filtration rate and log2 24h urinary protein excretion with graft failure and mortality. Model 3 was further adjusted for body mass index and diabetic nephropathy as primary kidney disease. Model 4 was further adjusted for donor age and history of delayed graft function.

FR-OR65

Elevated Glycolytic Markers in Urinary Extracellular Vesicles in Kidney Transplant T Cell-Mediated Rejection
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Background: Urinary extracellular vesicles (UEV), containing components of their parent cells, are released from cells lining the kidney and urinary tract. Changes in kidney protein expression are reflected in the proteome of UEV and its use as a non-invasive marker of allograft function is of particular interest in kidney transplantation. Under stress, renal energy metabolism switches from fatty acid oxidation to glycolysis. We evaluated changes in glycolytic metabolites and proteins in UEV at the time of clinically indicated kidney transplant biopsies and correlated this with histological lesions described in the Banff classification.

Methods: This prospective observational study involved collection of pre-transplant urine samples from kidney transplant recipients who were indicated by the Banff classification. UEV were isolated by differential ultracentrifugation. Western blots were performed to confirm vesicle markers (CD9, TSG101 and Tamm-Horsfall protein) and then probed for confirm glycolytic markers.

Results: The cohort of 25 subjects (mean age 50.6 years, 60% male) included 5 cases of T-cell mediated rejection (TCMR), 4 cases of borderline TCMR and 16 normal biopsies. TCMR and borderline TCMR were analysed as one group (n = 9) and the following glycolytic markers were detected in this group: phosphofructokinase-mouse, isozymes of α-2-ketoglutaric, α-2-ketoglutaric dehydrogenase, α-2-ketoglutaric dehydrogenase (PKFB), phosphorylated ser483 PKFBF2, phosphorylated ser483 PKFBF2, PKFBF3, PKFBF4) and pyruvate kinase (PK-M2, PK-LR). There was significantly increased expression of PKFBF3+ UEV in 3/9 (33%) of TCMR samples compared to 0/16 of normal biopsy samples (p=0.04).

Conclusions: This study demonstrates elevated expression of PKFBF3 and PKFBF4 in UEV in kidney transplant recipients with biopsy-proven TCMR. This may represent altered energy metabolism in the form of increased renal glycolysis in association with cell mediated rejection.

FR-OR66

Proenkephalin A119-159 as a Novel Biomarker for Early Detection of Delayed Graft Function After Kidney Transplantation
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Background: Delayed graft function (DGF) frequently occurs following kidney transplantation and adversely affects patient outcomes such as length of hospital stay, impaired long-term graft function and ultimately quality of life. Though a universal definition of DGF is lacking, a common classification is the need for dialysis in the first postoperative week excluding the first 24 hours. The aim of this study was to evaluate the capabilities of the novel kidney function biomarker proenkephalin A119-159 (penKid) to predict DGF compared to serum creatinine (SCr).

Methods: In the currently ongoing study, penKid has been quantified from plasma using a chemiluminescence immunoassay in our daily routine in all freshly transplanted patients since November 2022. PenKid is quantified the day of transplantation and every weekday following transplantation. For this preliminary analysis, penKid levels were compared to SCr. The end of data collection is June 30, 2023.

Results: In a preliminary analysis including 70 kidney transplant recipients (70% cadaveric transplants), results suggest, that penKid may discriminate patients with delayed graft function from patients with primary graft uptake earlier than SCr. In contrast to SCr, penKid was able to distinguish between DGF and no DGF as early as 24 hours after transplantation (Figure 1). In addition, other than SCr, penKid levels do not seem to be affected by dialysis.

Conclusions: PenKid is a promising new biomarker for the early prediction of DGF after kidney transplantation and may enable clinicians to adjust their treatment in high-risk patients accordingly. However, more clinical data is needed to validate our findings and to establish the clinical utility of penKid in the management of kidney transplant patients.

FR-OR67

Uncontrolled Hypertension Is Associated with Increased Risk of Graft Failure in Kidney Transplant Recipients: A Nationwide Population-Based Study
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Background: Hypertension is highly prevalent in patients with kidney transplantation caused by transplantation-related immunologic or non-immunologic risk factors. However, whether a strict definition of hypertension (≥130/80 mmHg) and subdivided blood pressure (BP) groups were associated with an increased risk of graft failure after kidney transplantation using a nationwide large cohort study are still unknown.

Methods: Using Korena National Health Insurance Service data, we included 14,249 patients who underwent kidney transplantation from 2002 to 2016. Patients were categorized into five BP groups according to the 2021 Kidney Disease: Improving Global Outcomes practice guidelines for BP management: normal BP (BPN; ≤120/80 mmHg), elevated BP (≥120–129/≥80 mmHg), incident hypertension (≥130/80 mmHg), and controlled or uncontrolled hypertension with anti-hypertensive medications. Results: The primary outcome was graft failure, which occurred in 1,914 (13.6%) participants during the 6-year follow-up. After adjusting for covariates, hypertension was associated with a higher risk of graft failure [Adjusted hazard ratio (AHR), 1.70; 95%
Kidney Transplantation: Biomarkers, New and Old

FR-OR68
The Molecular Microscope Diagnostics System (MMDx) Does Not Identify T Cell-Mediated Rejection (TCMR) in Cases with Borderline Changes or Isolated Intimal Arteritis in the Absence of Microvascular Inflammation


Background: Borderline changes suspicious for T-cell mediated rejection (TCMR) and isolated intimal arteritis (v-lesion) represent a particular challenge. Even though the Molecular Microscope Diagnostics System (MMDx) has not been trained on borderline changes and v-lesions, it has been suggested that MMDx may reclassify a subgroup of cases to molecular TCMR.

Methods: In this single-center cohort of 326 kidney allograft biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 153 cases with isolated tubulitis (i0, i1-3; n=114), borderline changes (n=10), and isolated intimal arteritis (i0, i0-2; v1; n=39) in the presence (n=81) and absence (n=72) of microvascular inflammation (MVI). 83 cases without histologic lesions suspicious for TCMR (i0, t0, v0) were used for comparison of rejection phenotype scores. Any cases with overlapping pathologies were excluded from the analysis.

Results: 41 of 81 cases (51%) with suspicion for TCMR and MVI showed molecular rejection (30 cases with molecular ABMR, 4 cases with molecular ABMR/TCMR), 1 case with isolated tubulitis, 1 case with borderline changes, 7 cases with isolated intimal arteritis, and 7 cases with minor ABMR (p=0.003). However, 1 of 72 cases (1%) only with suspicion for TCMR, but no MVI showed molecular rejection (1 case with minor ABMR). No pure molecular TCMR was identified in any group. 11 of 153 cases (7%) with suspicion for TCMR showed a TCMR phenotype score (R2) ≥0.10 (7 cases with isolated tubulitis and 4 cases with isolated intimal arteritis) compared to 5 of 83 cases (6%) without suspicion for TCMR (p=0.1).

Conclusions: MMDx may identify molecular TCMR among cases with MVI irrespective of histologic suspicion for TCMR. MMDx does not identify molecular TCMR in cases with isolated tubulitis, borderline changes, or intimal arteritis without MVI. TCMR phenotype scores do not differentiate between isolated tubulitis, borderline changes, isolated intimal arteritis, or no histologic lesions suspicious for TCMR.

FR-OR69
Donor-Derived Cell-Free DNA (dd-cfDNA) in Kidney Transplant Recipients with Indication Biopsy: Results of a Prospective German Single-Center Trial

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Background: Donor-derived cell-free DNA (dd-cfDNA) identifies allograft injury and discriminates active rejection from no rejection. With a number of studies investigating the benefit of dd-cfDNA in US American transplant cohorts, we aimed at evaluating the performance of dd-cfDNA in a cohort of German kidney transplant recipients.

Methods: We enrolled 106 kidney transplant recipients with clinically indicated biopsy between November 2020 and March 2023 at the Department of Nephrology at Heidelberg University Hospital. dd-cfDNA was quantified using the AlloSeq cfDNA assay (CareDx) at time of biopsy to correlate dd-cfDNA levels with histopathological reporting and on days 7, 30, and 90 following biopsy to assess the utility of dd-cfDNA in monitoring treatment response.

Results: Of the 106 allograft biopsies, 36 (33%) were classified as different types of rejection. Patients with ABMR or TCMR (N=13) showed significantly higher dd-cfDNA levels with a median (IQR) of 1.60% (0.38–3.35) compared to the 0.44% (0.20–1.10) in patients with borderline changes (N=23) and the 0.2% (0.11–0.53) in patients with no sign of rejection (N=72) (P<0.01). The AUC for dd-cfDNA to differentiate any type of rejection including Borderline changes from no rejection was at 0.72 (95% CI 0.62–0.83). The optimal cut point for dd-cfDNA to discriminate active rejection was at a threshold of 0.57%, yielding a sensitivity of 53% (95% CI 37–68%), a specificity of 81% (95% CI 70–88%), a PPV of 58% (95% CI 41–73%), and a NPV of 77% (95% CI 67–85%). In patients receiving anti-rejection treatment, dd-cfDNA levels decreased significantly during the 7-, 30-, and 90-day follow-up compared to levels at the time of biopsy (P<0.006, P<0.002, and P<0.001, respectively).

Conclusions: Our data verify the good performance of dd-cfDNA to correctly identify kidney transplant recipients with active rejection at a German transplant center. We show that dd-cfDNA may aid the clinician in recognizing patients at risk and in decision-making regarding the need for a graft biopsy. The potential benefit of dd-cfDNA to assess response to therapy needs further validation.

Funding: Commercial Support - CareDx

FR-OR70
Pretransplant HbA1C as a Predictor of Kidney and Pancreas Allograft Survival in Simultaneous Pancreas-Kidney Transplantation: A Retrospective Nationwide Study

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Background: Simultaneous pancreas-kidney transplant (SPKT) is a therapeutic option for patients with end-stage kidney disease (ESKD) and diabetes mellitus (DM). Hemoglobin A1C (HbA1C) is a widely used biomarker for glycemic control in DM patients. However, its role in predicting SPKT outcomes remains unclear. This study aimed to investigate the association of pre-transplant HbA1C levels with kidney and pancreas allograft survival in patients with SPKT.

Methods: Using data from the United Network for Organ Sharing (UNOS) database, a total of 3,351 SPKT recipients were included in the analysis. Cox proportional hazards regression models with time varying covariates were used to model the association between HbA1C and allograft survival.

Results: Our results showed that higher pre-transplant HbA1C levels were significantly associated with lower kidney and pancreas allograft survival rates. Compared to patients with HbA1C levels ≤7%, patients with HbA1C levels >7% had a hazard ratio of 3.38 (95%CI: 2.40-4.75, P<0.01) and 7.99 (95%CI: 6.02-10.60, P<0.01) for kidney and pancreas allograft failure, respectively (Figure 1A and 1B). Moreover, this association remained significant after adjusting for relevant potential confounders, including age, gender, body mass index, and donor types.

Conclusions: Pre-transplant HbA1C is a strong predictor of both kidney and pancreas allograft outcomes in SPKT recipients. Our findings highlight the importance of glycemic control in uremic diabetic patients as one of the pre-transplant preparation strategies to improve allograft survival after successful SPKT.
Managing the Many Facets of Home Dialysis

FR-OR71
The Standardized Discontinuation Ratio: A Novel Measure for Real-Time Monitoring of Home Dialysis Discontinuation
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Background: Home dialysis attrition is a significant challenge. Attrition slows growth, and discourages both nurses and patients who devote great effort to training. Many measures, including the “churn rate” and the cumulative incidence of all-cause attrition, are not ideal for real-time quality monitoring, due to slow evolution and the inclusion of kidney transplantation, a positive outcome. We developed a novel measure, the standardized discontinuation ratio (SDR), that facilitates ongoing assessment of whether the composite event of conversion to in-center hemodialysis or death is occurring more or less frequently than is expected.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. On any given day, we defined the SDR as the ratio of actual versus expected discontinuations from home dialysis during the past 13 weeks. Discontinuation was defined by either conversion from home dialysis to in-center hemodialysis or death. The expected number of discontinuations was summed from patient-day probabilities of discontinuation, estimated as a function of age, modality, and time since home dialysis initiation.

Results: During the 4-year period ending on May 15, 2023, there were 288 discontinuations among 1011 home hemodialysis (HHD) patient-years and 1557 discontinuations among 5430 peritoneal dialysis (PD) patient-years. C-statistics for modality-specific models of discontinuation were 0.61 for HHD and 0.58 for PD. As displayed, the organization-wide SDR from April 2020 to March 2023 varied widely, ranging from 0.77 on July 11, 2020, to 1.34 on March 30, 2021. The SDR was between 1.1 and 1.2 on 12.2% of days during the 3-year period ending in March 2023, and greater than 1.2 on 6.5% of days.

Conclusions: The SDR can be used in real-time to monitor trends in home dialysis discontinuation for the purpose of organizational quality improvement.

FR-OR72
Breaking Through Barriers with Home Hemodialysis (HHD) Group Training, Enhancing Access and Improving Patient Experience: A Single-Center Experience
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Background: Despite emerging evidence supporting greater quality of life (1) and improved cardiovascular outcomes (2, 3), HHD remains underutilized in the U.S. (4) Two barriers to widespread adoption are delayed access to HHD due to shortage of units and staff; and patient apprehension about taking dialysis in their own hands. Group training for HHD remains underutilized in the US with less than 5% of units implementing this training strategy. Given lack of experience, little is known about group training in HHD. We describe a single center experience of instituting group training for HHD.

Methods: All patients and their care-partners currently enrolled in HHD program who underwent group training were surveyed. We evaluated the impact of group training on duration of training, unit census growth, need for retraining, incidence of complications and patient experience.

Results: A total 6 consecutive groups of 2 and 3 patients at a time for a total of 16 patients were trained in HHD over a period of 7 months. Training time averaged 30-40 days and was similar for all groups and comparable to solo training. Unit census tripled during this period going from 7 patients to 23. Demographic characteristics are described in table 1. 14 (87.5%) patients had no missed treatments over a 3 month period and no patient needed retraining after the follow up period. 1 patient transitioned to in-center dialysis and 1 died. All patients who were surveyed agreed that group training was an enjoyable experience and strongly recommended to others.

Conclusions: In our experience, group training has proven to be an effective strategy for scaling HHD training. It has helped overcome two major barriers to HHD: prompt access to training and patients’ need for strong support in the early training phase. Ongoing longitudinal data collection will help us evaluate association of group HHD training with outcomes including missed treatments, need for retraining and respite care, and patient quality of life scores. Group training has the potential to be an empowering tool for our patients and to enhance our ability to cross train nurses in HHD thus potentially helping with nursing attrition.

References:

FR-OR73
Hospitalization Risk in the Integrated Home Dialysis Model: Analysis of the Canadian Organ Replacement Register
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Background: The integrated home dialysis model proposes the initiation of dialysis with peritoneal dialysis (PD) followed by transition to home hemodialysis (HHD) after PD ends. Outcomes of integrated home dialysis versus a “direct to HHD approach” are poorly known. We aimed to compare the hospitalization risk of patients in integrated home dialysis (before, during and after transfer to HHD) with patients directly initiating HHD.

Methods: We studied patients in the Canadian Organ Replacement Register who initiated PD or HHD between 2005 and 2018. A 1:1 propensity score was used to match patients transitioning from PD to HHD in less than 90 days after PD (“PD+HHD” group) to patients with HHD as the first home-dialysis modality (“HHD” group). Our outcome was all-cause hospitalization, assessed from the beginning of home dialysis (PD or HHD) until transfer to facility HD, death, end of follow-up (December 31st 2019) or kidney transplant. Hospitalizations were compared between groups with shared frailty models in three periods: before PD-HHD transition, during transition, and after transition (Fig 1).

Results: From 63,327 patients, 13,726 initiated PD and 745 initiated HHD. 4,420 patients transferred from PD to facility HD and 163 transferred to HHD (3.6% of transfers; median time on PD 1.9 years). Hospitalization risk was similar between groups in the period before and after the PD-HHD transition but was significantly increased during the transition period (Table). Similar trends were observed when these periods were sub-divided by year (Fig 2).

Conclusions: Patients transitioning from PD to HHD do not have an increased hospitalization risk outside their transfer period when compared with patients who start dialysis directly in HHD.

Funding: Government Support - Non-U.S.
FR-OR74


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Background: Life participation is a core patient-reported outcome for people receiving peritoneal dialysis (PD) that is dependent on physical activity engagement and adequate physical function. Little is known about exercise practice patterns or perceptions of people receiving PD. The aim was to describe the physical activity and exercise practices and perceptions of people receiving PD to inform patient education, future areas of research, and clinical recommendations.

Methods: A cross-sectional, descriptive, web-based 25 item survey (16 perception and practice questions, 9 demographic questions) was co-developed and pilot tested by persons living with kidney disease, PD clinicians and exercise specialists. Adults who currently or previously received PD were invited to participate in the survey. Recruitment was completed through national and international kidney organization websites and social media platforms. All variables were reported descriptively, and free text responses were collated and summarized.

Results: There were 114 respondents, 6 excluded due to duplication or incompletion, the majority were from Canada (68%), United Kingdom (25%) and 7% other. Women represented 53% of respondents, with most 50-64 years old (43.5%). Forty-one percent received PD for 1-3 years and 72.9% had post secondary education. Physical activity was felt to be beneficial by 91.8% of respondents and 40% reported they had good physical function (could walk an unlimited distance without stopping). Variable medical advice regarding swimming and weightlifting emerged: 44% were told they could or could not swim, and respondents were told to limit weight lifting from 2 to 45 kg. A minority of respondents reported receiving instructions on draining PD fluid prior to physical activity (28% yes, 53% no, 19% unsure).

Conclusions: Survey respondents were knowledgeable regarding benefits of exercise and physical activity on physical and mental health for people receiving PD. Knowledge gaps emerged including maximum weightlifting, whether exercise was safe with or without intrabdominal PD fluid in situ, and whether swimming is allowed. Education for both health care providers and patients is needed regarding the practice of exercise for people receiving PD.

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

FR-OR75

Decreasing the Burden: A Single-Centre Experience of Decremental Peritoneal Dialysis (PD) in Toronto, Canada

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Background: The 2020 International Society of Peritoneal Dialysis (ISPD) recommendations on providing high-quality peritoneal dialysis (PD) prescriptions highlight shared-decision making principles that emphasize the focus on Kt/V clearance targets. As a result, incremental PD has gained popularity amongst care providers in recent history. However, “decremental PD”, a practice in which PD dose is reduced after patients are started on high dose PD (>10L/day), has not been well described in the literature. Decremental PD utilizes the principles of goal-directed therapy as outlined by the ISPD to reduce prescriptions where possible; particularly when treatment is burdensome for patients. We describe our experience with this approach and potential benefits to both patients and the healthcare system.

Methods: Nine prevalent patients on high-dose automated PD prescriptions seen between August 1-December 31, 2019, were included in this analysis. All patients reported prescriptions were burdensome. Patients were offered a reduced dose in their prescription after clinical assessment and laboratory investigations were reviewed.

Results: Patients were compared 6 months before and after the change in prescription for any significant differences in hospitalization, peritonitis rates and technique failure. Small solute clearance using Kt/V and creatinine clearance along with residual urine output were also compared.

Conclusions: Total dialysis volume and time on cyclers were significantly reduced from a mean of 12.6 L to 9.2 L (p < 0.0001) and from 8.7 to 8.2 hours (p < 0.035). No statistically significant differences in Kt/V or CrCl values 6 months after the change in prescription were observed. There were no observed peritonitis episodes or hospitalizations six months after prescription change. All patients remained on PD 12 months after the intervention with no further prescription changes. The reduced prescription resulted in a 19.2% cost reduction per patient at six months compared to high-dose prescription.

Conclusions: We demonstrate that decremental PD prescriptions align with ISPD recommendations in maintaining patient-centered care while reducing cost.
Conclusions: Worldwide, CKD-aP is highly prevalent among PD patients and associated with poor quality of life. Efforts to better identify and manage CKD-aP are needed for PD patients are urgently needed.


Managing the Many Facets of Home Dialysis

Outcomes of an Assisted Peritoneal Dialysis Program in the United States

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Background: Staff-assisted peritoneal dialysis (PD) can support patients to initiate or remain on PD following challenges to self-care. These programs are not currently supported by Medicare in the United States (US) despite the intentions put forward in the Advancing American Kidney Health initiative to increase home dialysis utilization.

Methods: Assistance was provided by trained non-nurse healthcare personnel to patients with short-term limitations to self-care who lacked adequate support by family or friends. Descriptive statistics are provided on indications, services, and outcomes.

Results: A total of 121 referrals were received. Mean patient age was 71 (SD 14) years, and 45% were female. Forty-five percent of the referrals were before completion of PD training, while the remaining 55% were for prevalent patients. The main indications for referral were physical function limitations (57%), cognition (47%), and psychosocial reasons such as anxiety (46%). A total of 48 referrals were cancelled due to resolved needs or inability to continue PD. A total of 604 visits (12% virtual) were provided for 73 patients, with a median of 5 (interquartile range [IQR]: 3 to 10) visits per patient over a median of 8 (IQR 2 to 21) days. Services provided included setting up and observing PD exchange and to validate the effects of biocompatible dialysates in animal models.

Conclusions: QuickCheck is a reliable point-of-care method for rapid diagnosis and treatment of PD-associated peritonitis. Its speed, simplicity, and portability make it an attractive option for use at the point-of-care.
FR-OR80

Pregnancies in Women with Kidney Failure on Home Dialysis
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Background: Women with kidney failure have impaired fertility and are at a higher risk of maternal and fetal morbidity and mortality. Little is known about pregnancies in women receiving maintenance home dialysis in the United States.

Methods: Using data from the United States Renal Data System, a cohort of 26,387 women aged 15-49 years with kidney failure receiving maintenance home dialysis in 2005-2015 was examined. We calculated pregnancy rates and identified factors including the modality associated with pregnancy on home dialysis.

Results: Overall, 437 pregnancies were identified in 26,837 women on home dialysis. Unadjusted pregnancy rate was 8.6 per 1000 person-years (PTPY). The unadjusted pregnancy rate was higher on home hemodialysis (16.0 vs. 7.5 PTPY) than on peritoneal dialysis. Women on home hemodialysis had a higher adjusted likelihood of pregnancy than women on peritoneal dialysis (HR, 2.34; 95% CI, 1.79-3.05). Compared with women aged 20-24 years, the likelihood of pregnancy was lower in women 30-34 years (HR, 0.64; 95% CI, 0.43-0.96) and 35-39 years (HR, 0.53; 95% CI, 0.35-0.79), 40–44 years (HR, 0.32; 95% CI, 0.21-0.49), and 45–49 years (HR, 0.21; 95% CI, 0.13-0.33). While Black women had a higher likelihood of pregnancy (HR, 1.40; 95% CI, 1.07-1.83), there was no difference in likelihood of pregnancy in Asian, Hispanic, and Native Americans as compared to Whites. Body mass index, cause of kidney failure, socioeconomic status, rurality, pre-dialysis nephropathy care, or dialysis vintage were not significantly associated with pregnancy on home dialysis.

Conclusions: The pregnancy rate in women with kidney failure undergoing home dialysis is higher with home hemodialysis than with peritoneal dialysis. Younger age and Black race/ethnicity are associated with a higher likelihood of pregnancy among women on home dialysis. This information can guide clinicians in preconception counseling and making informed treatment decisions for pregnant women on home dialysis.

Funding: Other NIH Support - NHLBI K23 career development award, under Award Number 1K23HL151816-01A1

FR-OR81

Representativeness of Randomized Control Trials in Kidney Transplantation
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Background: Differences between participants in randomized controlled trials (RCTs) and the target patient population may impact the intervention effect of trial findings in clinical practice. The purpose of this study was to determine the extent to which participants in clinical trials were similar to transplant recipients who underwent transplantation in the U.S. at the time of clinical trial enrollment.

Methods: We undertook a systematic search of PubMed, Embase and ClinicalTrials.gov for RCTs completed between 1990 to 2020 that included adults ≥18 years of age in kidney transplant recipients. Trials were included if at least one U.S. center participated and were randomized. For each trial, the inclusion and exclusion criteria were extracted and applied to the scientific registry of transplant recipients (SRTR) to identify patients undergoing transplantation during the trial enrollment period. Demographics of interest included participant age, the proportion of women, and the proportion of patients from race and ethnicity minority groups.

Results: Our search identified 5206 records, 43 trials met the study inclusion criteria. Participants characteristics included age, sex, race/ethnicity, cause of kidney failure, donor source, and comorbid conditions. From the trials, a total of 13591 participants enrolled, 74% enrolled patients only in the U.S., and 52% were multicenter studies. After searching each trial’s inclusion and exclusion criteria during the trial enrollment period, 1,011,861 transplant recipients were identified in the SRTR who were potentially eligible for trial participation. Trial participants were younger, more likely to be White, and less likely to be Black or Asian (table 1). Demographic differences between trial participants and transplant eligible transplant recipients in the U.S. persisted in more recent trials.

Conclusions: We conclude that women and non-White patients are under-represented in kidney transplant trials. These differences may limit the applicability of trial findings to the U.S. real-world setting. Efforts to improve the representativeness of transplant trials are needed.

FR-OR82

Primary Care Clinician Perspectives on APOL1 Testing for Kidney Diseases
Dinushika Mohottige, Rennie Negron, Michelle Ramos, Tatiana Sabin, Miguel Gomez, Carol R. Horowitz. Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Black and Hispanic individuals experience a disproportionate burden of ESKD and CKD progression compared to White counterparts. These disparities are multifactorial and related to health-harming socio-contextual factors and partly explained by high-risk genetic alleles including APOL1, and gene-environment interactions.

Methods: We conducted, recorded, and transcribed 15 semi-structured interviews in 2018-2016 with general internists and family physicians in New York, NY. Two independent trained researchers coded transcripts, modified discrepancies through consensus, and used modified grounded theory to identify themes.

Results: Interviewed clinicians had a mean age of 38 years, 10 (67%) were female, 8 (53%) self-identified their race as White, 3 (20%) as Asian, 2 (13%) as Black, and 1 (7%) self-identified as Hispanic. Participants mentioned environmental and behavioral factors as contributors to kidney risk and patients’ fear of dialysis as a primary driver of HTN-related behavioral change. Additional emergent themes included 1) desires for additional training opportunities to effectively communicate testing considerations and implications of genetic testing, including potential stigma, 2) challenges identifying individuals appropriate for testing based on race/ethnicity and other sociodemographic characteristics 3) the need for low literacy, culturally-tailored, action-oriented post-testing instructions and guidance for patients, 4) fears that APOL1 disclosure would result in fatalism and decreased engagement in health promoting behaviors, and 5) the importance of ensuring APOL1 testing discussions are attentive to patient-level barriers including racial discrimination and medical mistrust.

Conclusions: Primary care physicians describe a broad interest in clinical decision-support for APOL1 genetic testing and return of results, as well as clear guidance regarding effective communication about risk and modifiable actions to reduce risk.

Funding: Other NIH Support - National Human Genome Research Institute (NHGRI) (Grant Nos. 5U01HG007277 and U01HG006380) and the National Center for Advancing Translational Sciences (NCATS) (Grant No. UL1TR000067). Neither the NHGRI nor the NCATS was involved in the study design, collection, analysis or interpretation of data, writing of this article, or decision to submit it for publication. The authors thank the genomics board; the Genetic Testing to Understand Renal Disease Disparities team of academic, community, and clinical partners as well as the study coordinators and staff members at the study sites; and their partners in the Implementing Genomics in Practice (IGNITE) Network for their valuable contributions to this project.

FR-OR83

Association of Unmet Social Needs with Blood Pressure Severity and Target Organ Injury: Interim Analysis of the SUPERHERO Study
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Background: Hypertension (HTN) is a leading cause of cardiovascular disease and is best controlled if associated with increased risk for target organ injury (TOI). The burden of HTN disproportionately falls on individuals of low socioeconomic status (SES) and racial and ethnic minorities. Studies in adults have shown that low, including income, and neighborhood characteristics are linked to poor blood pressure (BP) control. Data in youth relating to the influence of SES factors on HTN epidemiology are sparse.

Methods: Cross-sectional analysis of baseline electronic health record data from the SUPERHERO Registry in youth referred to subspecialists for ICD-10 code-defined HTN disorders from 1/1/2015 – 12/31/2022. We excluded those with pregnancy, kidney transplantation, or dialysis. We examined the association of individual-level social drivers (transportation, financial, food access, housing, education, employment, occupational exposures, physical environment, social environment, family, and crime) by ICD-10 codes with BP severity and risk of TOI in youth using unadjusted generalized linear models.

Results: Of our cohort of 11,580 participants, 56% (6,508 of 11,580) were Caucasian and 27% (3,114 of 11,580) African American. Of the 47 with documented unmet social needs, 57% (n = 27) were African American vs 26% (n = 12) were Caucasian. Stage 2
Navegating a Path to Diversity and Equity in Kidney Health

FR-ORT84

Association of Unmet Social Determinants of Health (SDOH) with Quality of Life (QoL) in Patients on Hemodialysis (HD)

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**Background:** Patients on hemodialysis (HD) have low quality of life (QoL). Social determinants of health (SDOH) are the non-medical aspects of a patient’s life that affect their health. Whether unmet SDOH are associated with QoL in patients on HD has not previously been studied.

**Methods:** We prospectively surveyed patients on their living situation, food security, transportation, utilities, and safety using the AHC-IRSN and their QoL using the KDQOL-36. From the KDQOL-36, we calculated the physical component score (PCS), mental component score (MCS), and scores for effect, burden, and symptoms of kidney disease. Patients were included if they were over the age of 18, had been on HD for more than 30 days, and was able to complete the surveys with minimal assistance. Patients completed the surveys during their HD treatments. Laboratory values of hemoglobin, albumin, calcium, phosphorus, intact parathyroid hormone, and K/V were obtained from the monthly blood work closest to the survey administration. QoL scores were compared using Student’s T-test. We used linear regression to evaluate the association between SDOH and QoL, while adjusting for age and gender.

**Results:** A total of 138 patients participated in the study, 53% were female, 50% were Black, and 43% were Hispanic. Unmet SDOH were common in our patients, with 40% of patients reporting food insecurity and 23% of patients reporting housing insecurity (Figure 1A). Patients with unmet SDOH had lower scores for PCS and MCS, and higher scores for effect, burden, and symptoms of kidney disease, although these were not statistically significant (Figure 1B&C). There was no clinically or statistically significant difference in laboratory values between patients with and without unmet SDOH. There was no significant association between SDOH measures and the PCS or MCS of the KDQOL-36.

**Conclusions:** Unmet SDOH are common in patients on HD, particularly food and housing insecurity. Patients with unmet SDOH report lower QoL and higher effect, burden, and symptoms of kidney disease. While not statistically significant, this may be related to a small sample size.

**Funding:** NIDDK Support

FR-ORT85

Exploring Unconscious Bias in Peer-to-Peer Interactions in Medical Conferences: A Retrospective Analysis

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**Background:** Unconscious bias in academic interactions has garnered increased attention across several disciplines, including the field of medicine. We explored the presence of these biases using speakers’ introductions at ASN (American Society of Nephrology) Kidney Week.

**Methods:** We screened 535 archived sessions from ASN Kidney Week 2019 and 2020 to conduct this study. The moderators’ gender and academic title were documented, along with the presence of the speaker’s academic title, first name, and last name in each announcement. R.4.2.2 was used for inferential and descriptive statistics.

**Results:** The professional title announcement frequency from highest to lowest were female moderators introducing female speakers (85%), female moderators introducing male speakers (77%), and male moderators introducing male speaker (73%) or female speakers (72%). A multivariate logistic regression using variables “speaker rank,” “moderator rank,” “speaker gender,” “moderator gender,” “first name announcement,” and “last name announcement” found female moderators had the highest odds ratios of title announcement (OR = 1.76 Female vs Male, p = 0.01) and high academic rank had the lowest odds ratio of title announcement (OR = 0.66 higher rank, p = 0.01). Another multivariate analysis combining variables of “moderator gender” with “speaker gender” and “moderator rank” with “speaker rank” found that males (moderators) introducing females (speakers) had the lowest (OR = 0.48, p = 0.05), whereas associate professors professors introducing professors had the highest title announcement odds (OR = 4, p = 0.001).

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

**Underline represents presenting author.

FR-ORT86

County-Level Structural Racism Predicts Black-White ESKD Patient Mortality Disparities

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**Background:** Despite numerous call for structural racism (SR) research in nephrology, no prior research has employed multidimensional, empirical measures of SR to racial disparities in ESKD mortality. We estimate the first-ever analysis of the role of SR in racial disparities in ESKD patient mortality.

**Methods:** We analyze data from United States Renal Data System (USRDS), American Community Survey 2006-10 (ACS), and Vera Institute (VI), linked by county. USRDS ESKD who were alive on Jan. 1, 2001 and lived in a county with at least 100 White and Black residents were included. SR was constructed from ACS and VI county Black-White disparities in imprisonment, homeownership, college graduation, median income, unemployment, poverty, and segregation. Black-White disparities in each measure were converted to county z-scores and summed. Patient person-months through Dec. 2019 were analyzed using complementary log-log discrete time survival models. Monthly ESKD treatment was assigned based on treatment received on 1st day of each month (hemodialysis, peritoneal dialysis, deceased donor kidney transplant, living donor kidney transplant). Models controlled for region, county racial composition, and patient gender and birth cohort.

**Results:** Black race statistically significantly interacted with SR to predict monthly mortality risk among ESKD patients. Black patients experienced survival advantages compared to Whites at higher levels of SR. When stratified by monthly treatment, the core finding that Black survival advantages were erased or increased at higher SR levels was replicated within each treatment group.

**Conclusions:** County-level SR is a significant determinant of ESKD patient mortality. Future research should prioritize including area-level measures of SR in ESKD disparities research.

**Title Announcement Odds Predictors (Only Statistically Significant Results Included)

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FR-ORT87

Significant Variation in Kidney Disease Indicators Within Cook County, IL: Findings from Geospatial Analysis of 2022 National Laboratory Data

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**Background:** Chronic Kidney Disease (CKD) is frequently diagnosed through routine laboratory tests. There is not currently a source for population-level data on kidney disease and it is therefore difficult to assess prevalence at the local level. We sought to assess the feasibility of analyzing data from one of the largest clinical laboratory networks in the US to measure the extent of variation in kidney disease indicators found within a single county by ZIP code.

**Conclusions:** Our findings suggest the possibility that unconscious bias exists in peer-to-peer interactions in renal academic circles, though larger studies are necessary to understand the extent of this issue and the interplay of additional variables.

**Funding:** NIDDK Support

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Navigating a Path to Diversity and Equity in Kidney Health

Methods: Data from approximately 600,000 Labcorp tests, resulted in 2022, for estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (UACR) in the greater-Chicago area of Cook County, IL. were utilized. The presence of a kidney disease indicator was defined as an eGFR < 60 ml/min/1.73m² or a UACR > 30 mg/g. The overall ZIP code percentage of lab results with kidney disease indicators were visualized with ArcGIS, stratified by Jenks Natural Breaks (5 classes). ZIP codes with less than 10 results were suppressed. Optimized hotspot analyses were conducted with the Getis-Ord G* statistic and Moran’s I statistic was applied for the outlier analysis. The interstate system was included to aid visualization.

Results: Kidney disease indicators varied markedly at the ZIP code level across Cook County, IL. The ZIP code percentage of lab results with kidney disease indicators ranged from a low of 0% to a high of 67%. Hotspot analysis indicated a clear high-high cluster in south and southeastern sections of the county. The northeastern section of the county appeared to be a low-low cluster, or cold spot. Both high-high and low-low outliers were found.

Conclusions: We demonstrate the feasibility of utilizing a large national laboratory database for mapping kidney disease indicators and identification of hotspots of kidney disease within a county. This work has the potential to support CKD surveillance systems to guide area-level CKD prevention and population health improvement initiatives.

Funding: Other U.S. Government Support

FR-OR89

Experiencing Discrimination Reduced the Effectiveness of the TALK Intervention on Kidney Failure Patients

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Background: Although kidney transplantation (KT) is the optimal treatment for patients with kidney failure, few patients receive it. We studied the effect of an empirically-developed culturally-concordant education intervention on increasing KT evaluation completion rates for patients starting the evaluation process. We also examined the impact of novel social determinants of health (e.g., experience of discrimination) on outcomes.

Methods: We recruited patients for a baseline interview before their first KT evaluation appointment. We randomly assigned patients to receive the Talking About Live Kidney Donation (TALK) intervention or no intervention at their evaluation appointment. The TALK group received an educational booklet and video encouraging shared decision making and informed consideration of kidney failure treatment options. We called patients after two weeks to address questions and encourage review of materials. We conducted a second interview to assess intervention engagement and other outcomes after patients completed or discontinued evaluation.

Results: Our study sample included 1028 participants (63% male; mean age=56.7 yrs; 45% ≤ high school graduates; 71% non-Hispanic White; 21% Black). Using a Fine-Gray proportional subdistribution hazards model for time to evaluation completion, and controlling for demographic, medical, cultural, psychosocial, and transplant knowledge covariates, we found no significant difference in the likelihood of evaluation completion between TALK and no-TALK (SHR=1.13, 95% CI = 0.96-1.34, p=0.153). Interaction analyses showed that the TALK intervention increased the rate of evaluation completion among people who reported never experiencing discrimination in healthcare (SHR=1.26, 95%(CI=1.04-1.52, p=0.019), but not among those who reported ever experiencing discrimination.

Conclusions: Our findings suggest that TALK education materials alone did not promote higher KT evaluation completion rates and that the impact of experiencing discrimination in healthcare may be particularly relevant. Patients, especially those who have experienced discrimination, may need additional or different support to encourage their completion of KT evaluation, such as a social worker, peer mentor, or community health worker.

Funding: NIDDK Support, Private Foundation Support

FR-OR88

Barriers and Opportunities to Increase Home Dialysis Among African American Patients

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Background: Home dialysis offers patients another treatment option for kidney failure. Home dialysis use is lower in African American patients. In this study we sought to understand the experiences that patients and care partners face and uncover influencing factors and barriers to home dialysis use.

Methods: A total of 29 participants (African American patients at a dialysis provider, both in-center and home, and their care partners) were recruited to join in-person focus groups held in December 2022 and February 2023. Focus groups were audio and video recorded and transcribed verbatim. Responses were analyzed using inductive thematic analysis.

Results: Patients reported that physicians did not make a clear connection between poor management of underlying health conditions and kidney failure; irrespective of a patient’s access to primary care. Patients and care partners want improved additional education, especially regarding modality selection as some information was lost or never recorded and transcribed verbatim. Results were analyzed using inductive thematic analysis.

Conclusions: Opportunities exist for early and direct linkage of co-morbidities with kidney disease and consideration of patient concerns in home dialysis modality education.

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

FR-OR90

Regional Variation in the Use of Percutaneous Kidney Biopsy in Japan

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Background: Several studies have conducted questionnaires on kidney biopsies performed in Japan, but there is no exhaustive survey of all kidney biopsies in Japan. Moreover, it is unknown whether there is a regional variation in the use of percutaneous kidney biopsies in Japan.

Methods: The number of percutaneous kidney biopsies stratified by the demographic data of the patients was obtained from the National Database of Health Insurance Claims and Specific Health Checkups of Japan. Data from other nationwide surveys, including the population census, kidney transplant registry, dialysis registry and statistics of physicians, were also used. Pearson’s product-moment correlation coefficient was calculated using the R system for statistical computing.

Results: A total of 22,419 health insurance claims for percutaneous kidney biopsy in the fiscal year 2020 was registered in the database. The majority (99.9%) was inpatient percutaneous kidney biopsy. There was a large difference in the number of inpatient percutaneous kidney biopsies per population among prefectures, which could be up to 4.8 times as large in one prefecture than in another, even after adjusting for age. The number of inpatient percutaneous kidney biopsies per population positively correlated with the number of annual kidney transplants per population (R = 0.39, p = 0.006) and the number of annual kidney biopsies (R = 0.47, p < 0.001). There was a weak negative correlation between the number of inpatient percutaneous kidney biopsies per population and the prevalence of reduced kidney function in the population aged 40–74 years (R = −0.36, p = 0.013). The frequency of kidney biopsy had no correlation with the number of patients on hemodialysis or the number of nephrologists or urologists per population.

Conclusions: The National Database of Health Insurance Claims and Specific Health Checkups of Japan revealed for the first time that more than 20,000 kidney biopsies were performed per year in Japan, as of 2020. Percutaneous dialysis and kidney transplant are offered more frequently in prefectures with a higher frequency of kidney biopsy. Further research is warranted to understand the reason for the wide regional variation in the frequency of kidney biopsy.
One-Month Treatment with Dapagliflozin Triggers Renal Water Conservation and Thus Prevents Osmotic Diuresis in Patients with Chronic Heart Failure

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Background: It is unclear whether SGLT2 inhibitors improve cardiac outcomes due to their osmotic-diuretic potential. We tested the hypothesis that SGLT2 inhibition with dapagliflozin does not promote renal water excretion in patients with chronic heart failure.

Methods: DAPA-HF trial was a mechanistic, double-blind, randomized trial which investigated the early (48h) and late (4 weeks) effects of dapagliflozin on urine volume generation and body solute handling. Participants with chronic heart failure NYHA class III/IV were randomly assigned to receive dapagliflozin 10mg daily or placebo for 4 weeks. The primary endpoint was change from baseline in urine osmolyte concentration.

Results: 29 participants (placebo n=14; dapagliflozin n=15) completed the study (age 59.6±11.3 yrs). Dapagliflozin increased glucoseuria by 3.3±0.4 mmol/kg/d (p<0.001) without 48h; this effect persisted after 4 weeks (2.7±0.4 mmol/kg/d, p<0.001). Dapagliflozin did not increase natriuresis (early: p=0.68; late: p=0.64), and did not change MRI-determined generation and body solute handling. It is unclear whether SGLT2 inhibitors improve cardiac outcomes due to their osmotic-diuretic potential. We tested the hypothesis that SGLT2 inhibition with dapagliflozin does not promote renal water excretion in patients with chronic heart failure.

Conclusions: SGLT2 inhibition with dapagliflozin triggered a vasopressin-driven water conservation response in patients with chronic heart failure, and thereby prevented a 800-1000 mOsmol/kg/d glucose-driven increase in urine volume. In contrast to saline diuretics, which promote solute excretion to increase free water excretion in the urine, SGLT2 inhibitors reduce solute-free water excretion, abolishing the osmotic-diuretic effect of glucosuria.

Funding: Commercial Support - AstraZeneca

FR-OR93

Polygenic Scores for Incident Myocardial Infarction in CKD

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Background: Improving prediction of cardiovascular events in CKD has focussed on integrating kidney biomarkers to existing models. In the general population, genetic data may provide orthogonal information to clinical variables, identifying individuals at high risk of coronary artery disease (CAD) even in the absence of classical risk factors. In CKD, where cardiovascular risk is elevated and underlying aetiology may differ, the utility of CAD polygenic scores (PGS) has not been assessed.

Methods: Individuals with genetic data at risk of incident myocardial infarction (MI) in the Chronic Renal Insufficiency Cohort (CRIC) were included. Following relevant quality control and imputation of array-derived genotypes, variants with an imputation quality R2 0.3 or R2 0.8 with minor allele frequency <0.01 were retained. Individuals were stratified as European (EUR) or African (AFR) ancestry (based on self-report and genotype). We applied PGS derived in European and multi-ancestry populations (pgscatalog.org), for CAD and for estimated glomerular filtration rate (eGFR), to Cox-proportional hazard models sequentially adjusted for: first 10 PCs, age, sex, baseline eGFR and statin use. The primary outcome was incident MI, over the follow-up period and after censoring at dialysis initiation.

Results: 1175 AFR and 1607 EUR individuals in CRIC included, had 142 (12.1%) and 156 (9.7%) MI events, respectively, including 79 (6.7%) and 113 (7.0%) events were retained. Individuals were stratified as European (EUR) or African (AFR) ancestry (based on self-report and genotype). We applied PGS derived in European and multi-ancestry populations (pgscatalog.org), for CAD and for estimated glomerular filtration rate (eGFR), to Cox-proportional hazard models sequentially adjusted for: first 10 PCs, age, sex, baseline eGFR and statin use. The primary outcome was incident MI, over the follow-up period and after censoring at dialysis initiation.

Conclusions: Current PGS for CAD predicts incident MI in European ancestry individuals with CKD but no significant effect was revealed in African ancestry individuals. As PGS is being considered as a potential tool for prediction in clinical practice, there is a pressing need to understand the genetic architecture of CAD in the milieu of CKD and how PGS perform in the context of diverse ancestry.

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

FR-OR94

Kidney Function Trajectories, Risk Factors, and Outcomes in Left Ventricular Assist Device (LVAD) Recipients

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Background: LVAD (Left ventricular assist device) implantation can improve or worsen kidney function due to several known and hypothesized causes. However, competing risks of death and transplantation, patterns of missing data, and inaccuracy of estimating equations complicate kidney outcome assessment. To enable additional insight into the effects of LVAD implantation on kidney health, we investigate use of a continuous metric (trajectory of log eGFR) to summarize long-term post-LVAD kidney health.

Methods: We identified 15,052 LVAD recipients (median age 59 years, 21.2% female, median pre-LVAD eGFR 62 ml/min/1.73m2). The median eGFR trajectory slope was approximately -5.6% over one year; only 23.3% had a positive trajectory slope. The ten baseline factors most associated with worse than average kidney function trajectory are shown in Figure 1A: ‘older age’ was the most significant risk factor; ‘no prior cardiac operation’ was the most significant protective factor. In addition, mortality was progressively higher with worse kidney function trajectory (Figure 1B).

Conclusions: A log eGFR trajectory measure over one year may be a useful summary outcome metric of LVAD outcomes on kidney health/function. As a continuous summary metric, this may provide improved power to study determinants of kidney outcomes in LVAD recipients. In addition, as a log trajectory measure, it may be less susceptible to the imprecision and non-kidney-related confounding inherent in estimating GFR.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-OR95

Associations Between Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Disease in Three Prospective CKD Patient Cohorts

Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition characterized by the clonal expansion of blood cells carrying somatic mutations to specific driver genes. Although CHIP has been established as an important contributor to cardiovascular diseases (CVD) in the general population, its association with in a pro-inflammatory chronic kidney disease (CKD) setting has not been examined.

Methods: We examined prospective associations between CHIP status and CVD events in three cohorts that included a total of 3,414 CKD patients: the Chronic Renal Insufficiency Cohort (CRIC), the African American Study of Kidney Disease (AASK), and the Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT). Primary analyses tested associations between CHIP status and a composite CVD endpoint of myocardial infarction (MI), stroke, congestive heart failure (CHF), or peripheral artery disease (PAD). Cox proportional hazards regression models were used, adjusting for demographic, lifestyle, and clinical covariables, including cardiovascular risk factors. Secondary analyses investigated individual CVD endpoints. Random-effect meta-analyses were employed to combine effects across studies.

Results: Study participants had an average age of 68.8 years and a mean eGFR of 40.2 ml/min/1.73m². As expected, participants had a high frequency of hypertension (95%) and diabetes (49%), with CHIP identified in 25% of participants. Those with large CHIP clone size (≥10%) had a non-DNMT3A CHIP mutation explained 38% (95% CI 2-85%) and 42% (95% CI 6-90%) higher risks of the composite CVD endpoint, respectively, compared to non-carriers. Compared to non-CHIP status, large clone size was further associated with incident CHF (HR: 1.53, 95% CI: 1.13-2.00).

Conclusions: CHIP carrier status may be an important risk factor for CVD among CKD patients, with associations mirroring those observed in the general population.

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

FR-OR96

Effects of Apropterin on Blood Pressure Lowering and Proteinuria in Patients with CKD and Resistant Hypertension

Background: Hypertension is often difficult to control in patients with CKD. In the phase 3 PRECISION trial, the dual endothelin receptor antagonist apropterin (APRO) at 12.5 and 25mg once-daily demonstrated significant BP reductions vs placebo (PBO) in patients with resistant hypertension. We evaluated APRO in patients with CKD enrolled in PRECISION.

Methods: Participants had unattended automated office systolic BP (SBP) ≥140mmHg despite use of ≥3 antihypertensive drugs. This subgroup analysis included patients with an eGFR of 15 to <60mL/min/1.73m². Reductions in office SBP, ambulatory BP monitoring (ABPM), and urinary albumin-to-creatinine ratio (UACR) were assessed following the double-blind treatment phase (Week 4), after 32-week single-blind APRO 25mg treatment (Week 36), and after 4 weeks of randomized withdrawal (Week 40).

Results: Changes in office SBP and UACR in 162 CKD patients included in this analysis are summarized in the table below. Both doses of APRO resulted in a more pronounced BP reduction from baseline to week 4 compared to PBO. This was confirmed by ABPM. At Week 4, edema or fluid retention occurred in 18% and 24% of patients receiving APRO 12.5mg and 25mg, respectively, vs 2% with PBO; this rate was 34% in subjects exposed to APRO 25mg during the trial. 55% of treated patients (90% loop); 2 discontinued treatment due to this event. Five patients receiving APRO 25mg and 1 receiving placebo had heart failure leading to hospitalization; all but one had a history of heart failure.

Conclusions: In patients with CKD stage 3 or 4 and resistant hypertension, APRO 12.5 and 25mg added to a3 antihypertensive drugs resulted in a substantial reduction of both office and ambulatory BP and UACR. Edema and fluid retention were manageable with additional diuretics.

Funding: Commercial Support - Janssen Pharmaceuticals and Idorsia Pharmaceuticals, Ltd

FR-OR97

Increased Coronary Artery Pathology in Type 2 Diabetes Without Cardiovascular Disease but with Albuminuria

Background: Advances in non-invasive imaging enables combined structural and functional assessment of coronary artery pathophysiology. We evaluated sub-clinical coronary artery pathology using multimodal imaging in persons with type 2 diabetes.

Methods: Cross-sectional study including persons with type 2 diabetes, without known cardiovascular disease or symptoms. Coronary microcalcification activity was measured using 99mTc-sodium fluoride positron emission tomography/computed tomography (PET/CT). Plaque inflammation was measured using 18F-DOTATATE PET/CT and estimated as coronary inflammation activity. Myocardial flow reserve was calculated using 82Rubidium PET/CT, and the coronary artery calcium score was quantified using CT.

Results: We included 90 participants, 30 had normoalbuminuria (urine albumin creatinine ratio (UACR) <30 mg/g) and 60 had current albuminuria or a history of albuminuria (UACR ≥ 30 mg/g). Mean age was 65 (SD 7.5) years, 19 % were females. Participants with albuminuria had increased microcalcification activity (median 0.75 [IQR: 0.30 - 1.85]) compared to normoalbuminuria (0.43 [0.24 - 0.87]; p=0.04), but no difference in assessment for clinical risk factors for cardiovascular disease (p=0.09). Microcalcification activity was positively associated with the current level of UACR (standardized β=0.53, p=0.008), and a trend remained after adjustment (β=0.44, p=0.05). Mean myocardial flow reserve was lower in participants with albuminuria (2.5 (SD 0.7)) compared to normoalbuminuria (2.9 (0.7); p=0.02), but not after adjustment (p=0.07). Coronary inflammation activity and coronary artery calcium score were similar between albuminuria groups (p=0.40). Higher current level of UACR was associated with lower myocardial flow reserve (β=0.42, p=0.03) and higher coronary artery calcium score (β=0.40, p=0.03) in unadjusted analysis. Current level of UACR was not associated with coronary inflammation activity (p=0.74).

Conclusions: In persons with type 2 diabetes, without cardiovascular disease, the presence of albuminuria was associated with sub-clinical coronary artery pathology microcalcifications when compared to normoalbuminuria.

Funding: Private Foundation Support

FR-OR98

Podoecte-Specific Knockout (KO) of the Natriuretic Peptide Clearance Receptor (NPRC) Ameliorates Glomerular Injury in a Mouse Model of Focal Segmental Glomerulosclerosis (FSGS)

Background: Natriuretic peptides (NPs) have podocyte protective effects by stimulating cGMP generation (J Am Soc Nephrol 28: 260, 2017). NPs stimulate cGMP production by binding to NP receptors (NPRs). Atrial NP (ANP) and the C-type NP (CNP) stimulate cGMP generation by binding to NPRA and NPRB, respectively.

Conclusions: In patients with type 2 diabetes, without cardiovascular disease, the presence of albuminuria was associated with sub-clinical coronary artery pathology microcalcifications when compared to normoalbuminuria.

Funding: Private Foundation Support
hemoglobinuria in a mouse model of FSGS (Physiological Reports. 2021;9:e15095).

In this study, we investigated the effects of podocyte specific KO of NPR in FSGS using the same mouse model.

Methods: NPRC was deleted specifically in podocytes in a transgenic (TG) mouse model of FSGS created in our laboratory (J Clin Invest 125:1913, 2015). These TG mice express a constitutively active Gq subunit specifically in podocytes (Gq mice). In these Gq mice, treatment with a single dose of the podocyte toxin puroycin, amniosculeous (PAN) causes robust albuminuria, but only mild disease in wild type (WT) mice.

Results: Podocyte specific KO of NPRC significantly reduced albuminuria in Gq mice 10 days following a single PAN injection (6094 ± 1130 [NPRC/+] vs. 2740 ± 627 [NPRC/-]/mg creatinine; P = 0.007). KO of NPRC also significantly reduced the number of Gq mice with glomerular sclerosis (GS) (85% [NPRC/+] vs. N = 20 vs 46% [NPRC/-]; N = 13; P = 0.026). Consistent with the GS results, there was a significant increase in mRNA and protein levels of the myelofibrotic marker alpha-smooth muscle actin (alpha-SMA) in NPRC/- Gq mice, and this increase in alpha-SMA expression was significantly reduced in NPRC/- Gq mice. Treatment with PAN also decreased expression of both nephrin and podocin in NPRC/+/ Gq mice, which was prevented by podocyte specific KO of Gq.

Conclusions: Podocyte specific KO of NPRC significantly decreased albuminuria, reduced GS, decreased myelofibrotic activation and preserved expression of the podocyte proteins nephrin and podocin in a mouse model of FSGS. These data suggest that strategies to augment the effects of NPRs might be a useful therapeutic approach for treating FSGS.

Funding: Other NIH Support - NCTATS; Veterans Affairs Support

FR-OR99

Hemizygous Loss of Vegfa in Cap Mesenchyme Is Associated with Thrombosis Microangiopathy and Metabolic Reprogramming of the Tubule Epithelium

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Background: Tonic secretion of VEGF from nephron progenitors and their epithelial derivatives plays a key role in both development and homeostatic maintenance of kidney microvascular beds. Reduction of Vegfa production by podocytes or tubular epithelial cells in the nephron specific endothelial cell lineage of peritubular capillaries, respectively. Here, we report a kidney epithelial-specific, hemizygous Vegfa knockout mouse model. Fifty per cent reduction of Vegfa in Sis2-progenitor cells results in a progressive loss of glomerular filtration function after 4 weeks of age.

Methods: Vegfa floxed mice were used generating the CRISPR-Cas9 system and were crossed with transgenic Sis2-eGFPCre mice to generate Vegfafl/+; Sis2-Cre mice, leading to excision of Vegfa from nephron progenitor cells of cap mesenchyme. Kidneys from 1, 2 and 4 week old mice were examined histologically using light and electron microscopy and single-cell RNAseq libraries were generated from knockout and control kidneys at 2 and 4 weeks which were analyzed in R using Seurat. Results: Vegfafl/++; Sis2-Cre mice began to develop albuminuria at 2 weeks. On light microscopy, kidneys from Vegfafl/++; Sis2-Cre mice were indistinguishable from those of their control littermates at 1 week. Electron microscopy at 2 weeks showed evidence of glomerular injury, with subendothelial expansion and podocyte foot process effacement. At 4 weeks, Vegfafl/++; Sis2-Cre glomeruli exhibited florid thrombocytopenia and microangiopathy. In single-cell RNAseq data from Vegfafl/++; Sis2-Cre mice exhibited decreased expression of transcripts encoding markers of glomerular identity. Analysis also identified a new population of thick ascending limb (newTAL) cells expressed cytokeratin 19 as well as classic genes such as uM0D. Pathway analysis of differentially expressed genes in the newTAL showed downregulation several metabolic pathways with enrichment of growth factor signaling.

Conclusions: Vegfa gene dosage in renal epithelium is important for the maintenance of the glomerular endothelium and plays a role in the metabolic programming of the TAL.

FR-OR100

SMPD3.3 Modulates Podocyte Innate Immunity via Stimulator of Interferon Genes (STING) Activation in CKD

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Background: Chronic kidney disease (CKD) is a global problem with rising incidence, prevalence and poor understood pathogenesis. Our prior studies support the hypothesis that sphingolipids are major determinants of podocyte function and survival, where sphingomyelin phosphodiesterase acid like 3b (SMPDL3b) plays an important role. However, little is known about the role of SMPDL3b in podocyte injury through activation of STING.

Methods: Immortalized control or overexpression (SMP OE) human podocytes were used. Illumina sequencing RNA data analysis, qRT-PCR and Western blot analysis were used to characterize the cells: c-dAMP, a STING specific agonist, treatment (10µM) was performed for 24h. Glomerular podocytes from 1, 2, and 4 week old mice with podocyte specific Smib3 deficiency (pSMPfl/fl) or overexpression (pSMPfl/+) were used to evaluate STING activation. pSMPfl/+ and pSMPfl/fl mice were intraperitoneally injected with a single dose of c-diAMP, 50mg/kg or 5% DMSO and sacrificed 24h later, followed by urinary albumin-to-creatinine ratio (ACR), histological analysis and flow cytometry. One Way ANOVA followed by Tukey’s post-test were used to detect statistical changes.

Results: Genes involved in the cytosolic DNA sensing pathways in SMP OE podocytes are significantly regulated. In vitro and in vivo studies demonstrated that SMP OE podocytes are more sensitive to activation of STING than wild type podocytes. Furthermore, treatments with c-diAMP reduced proteinuria, albuminuria, and glomerular injury in SMPfl/fl and SMPPfl/+ mice treated with BMP6.

Conclusions: Our data indicate that SMPDL3.3 overexpression is associated with STING activation in podocytes in vitro and STING-dependent proteinuria in vivo.

Funding: NIDDK Support, Private Foundation Support

FR-OR101

Podocyte-Derived Endothelin-1 and Cross-Talk with Endothelial Cells Through Edn1A Is Essential for Glomerular Injury

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Background: Crosstalk between activated podocytes and glomerular endothelial cells (GECs) has been demonstrated in mouse models of focal segmental glomerulosclerosis (FSGS). However, it is presently unclear that podocyte-derived ET-1 can affect GECs and progression. We reported that activation of the stimulator of interferon genes (STING), an important innate immune signaling protein, contributes to alterations in podocyte foot processes, proteinuria and CKD progression. Here we test the hypothesis that increased STING expression leads to injury through activation of STING.

Methods: Immunohistochemical and immunofluorescence staining for ET-1 and EDN1 in podocytes and glomeruli isolated from pSMPTg mice were examined histologically using light and electron microscopy, and glomerular injury, albuminuria and podocyte depletion were assessed.

Results: Genes involved in the cytosolic DNA sensing pathways in SMP OE podocytes are significantly regulated. In vitro and in vivo studies demonstrated that SMP OE podocytes are more sensitive to activation of STING than wild type podocytes. Furthermore, treatments with c-diAMP reduced proteinuria, albuminuria, and glomerular injury in SMPfl/fl and SMPPfl/+ mice treated with BMP6.

Conclusions: Our data indicate that SMPDL3.3 overexpression is associated with STING activation in podocytes in vitro and STING-dependent proteinuria in vivo.

Funding: NIDDK Support, Private Foundation Support

FR-OR102

Conditional Knockout of Yap Decreases Podocyte Adhesion and Exacerbates FSGS Progression Through α3β1 Integrin

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Background: The occurrence of proteinuria in FSGS patients is closely related to the decreased adhesion and further loss of podocytes. Previous studies showed Yap nuclear exclusion contributes to podocyte apoptosis and FSGS progression, but its role in the podocyte adhesion remains unclear.

Methods: We generated podocyte-specific Yap gene knockout mice (Yapfl/fl) by crossing Yapfl/+ mice with NPHS2-Cre mice. We then constructed Adriamycin induced YappodoKO mice by using YappodoKO mice. Furthermore, we treated the above mice with pyrvinium, an agonist of α3β1 integrin.

Results: By 16 weeks of age, compared to Yapfl/+ mice, Yapfl/fl mice developed decreased podocyte adhesion including reduced α3β1 integrin and focal adhesion (examined by double immunofluorescence staining of vinculin and F-actin), with some decrease in ECM hyperplasia and electron microscopy, although showed no significant difference in morphology by light microscopy, proteinuria, serum creatinine and BUN. Compared to Adriamyacin treated Yapfl/+ mice, Yapfl/fl mice aberrantly aggregated decrease in α3β1 integrin, focal adhesion and podocyte number induced

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

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by Adriamycin, with markedly increased segmental or global glomerulosclerosis, foot process effacement and proteinuria. Of note, pyrinatin treatment largely improved the podocyte adhesion and ameliorated the disease progression of FSGS caused by Adriamycin treatment with or without podocyte-specific Yap knockout.

**Conclusions:** This study, for the first time, demonstrated that podocyte-specific Yap gene knockout can reduce podocyte adhesion and mitigating the process of FSGS via α3β1 integrin. This is important to report because, so far, there is no clinical strategy to treat FSGS by targeting α3β1 integrin and its regulatory factors.

**FR-OR103**

**Paracrine Effects of Injured Podocytes on the Transcriptome of Neighboring Cells**

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**Background:** Knowledge gaps in glomerular diseases include how podocytes respond to different forms of injury and the crosstalk between injured podocytes and neighboring cells (healthy podocytes or parietal epithelial cells (PECs)). The goal of this study was to establish in vitro microfluidic coculture model to distinguish podocyte’s responses to different injuries, and to determine what mediators from injured podocytes cause paracrine damage to neighboring cells in the glomeruli.

**Methods:** We engineered an open microfluidic coculture device consisting of two separate but interconnected chambers. The outer chamber was seeded with primary human podocytes and the inner chamber was seeded with human podocytes or PEC’s in different conditions of expression. Following the induction of podocyte injury in the outer chamber by cytotoxic sheep anti-podocyte IgE (IgE), purmorphin (PAN), Adriamycin (ADR), chambers were connected to study the paracrine effects between injured podocytes and naïve podocytes or PECs. Imaging, cell viability and RNA-sequencing were temporally measured in cells of both chambers.

**Results:** Injured human podocytes displayed foot process effacement, cell body shrinkage, and decreased cell viability. In the podocyte-podocyte coculture, gene set enrichment analysis showed several common pathways for injury by IgE, PAN, and ADR, including apoptosis, complement, p53, TNFα, IFN, Wntβ-catenin, and reactive oxygen species (ROS). IgG and ADR but not PAN increased TGFβ1 or inflammatory response (IL2, IL6, KRAS). ADR and PAN but not IgE increased DNA repair. The naïve podocytes cocultured with injured ones showed similar enrichments. Among the 65 ligand-receptor pairs shared by all three injuries were CSF1 & CSF1 receptor, BMP2 & BMP type I receptors, IL1A & IL1 receptor, and GDFN & RET receptor. The transcriptomic results from podocyte-PEC experiments are pending.

**Conclusions:** The in vitro open microfluidic coculture device represents a new model for studying autocrine and paracrine signaling between injured podocytes and healthy neighboring cells. The paracrine injury response of podocytes is similar to the direct injury response. Mechanistic studies are currently ongoing to identify which ligands from the injured podocytes and which receptors on naïve podocytes mediate these paracrine effects.

**Funding:** NIDDK Support, Other NIH Support - R35GM128648, ABT; NIA 5R01AG046231, SJS, OW, Other U.S. Government Support

**FR-OR104**

**A Novel Small Therapeutic Peptide with Potential for Treating αvβ3-Mediated Glomerular Damage**

Yan Xu,1 Ryan Spear,1 Yanxia Cao,1 Kwi Hye Koh,2 Steve Mangos,1 Alexis P. Jimenez Uribe,1 Jochen Reiser,1 Eunsl Hahn.1 Dr. Eunsla Hahm’s Lab. Rush University Medical Center, Chicago, IL; 3 Morphic Therapeutic, Boston, MA.

**Background:** αvβ3-mediated podocyte injury represents an initial pathological event observed in several glomerular diseases. However, effective clinical strategies targeting αvβ3 integrin remain elusive. Our recent research has unveiled a new function of inducible costimulatory ligand (ICOSL), which acts as an endogenous antagonist of αvβ3 integrin through its RGD motif. In this study, we identified a novel 19-mer peptide derived from ICOSL and evaluated its therapeutic potential for mitigating αvβ3-mediated podocytopathy.

**Methods:** The binding affinity of human ICOSL and its small linear peptide (hICOSL-peptide) to αvβ3 Integrin was assessed using surface plasmon resonance (SPR) at the molecular level, along with podocyte adhesion assays at the cellular level. Subsequently, we evaluated the therapeutic potential of hICOSL-peptide using proteinuria assay in vitro and in vivo with rats treated with LiCl or with saline, corresponding to a treatment with or without ICOSL-mimicking proteinuria by five-fold increment, further emphasizing its augmented therapeutic promise.

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

**Underline represents presenting author.**

**FR-OR105**

**Prevention of Proteinuria by a Novel, Subnanomolar ApoL1 Inhibitor**

Brett M. Antono,1 Nathan Zahler,2 Ingrid Mechin,1 Jonathan W. Thiele,3 Robert L. Dow,2 Robert A. Vollmann,2 Shannon G. Zellmer,1,3 Lhoucine Ch eid,1 Anil Nair,1 Douglas Kraffe.3 Ohm Ab, Durham, NC; 3 BioPharmaWorks, Groton, CT.

**Background:** Genetic variants of human ApoL1, which have arisen under evolutionary pressure to target mutant trypanosomes, have also been associated with an increased risk of developing chronic kidney diseases (CKD) in people of African ancestry. Recently reported clinical results suggest inhibition of ApoL1 ion channel function may produce clinical benefit in patients with ApoL1-induced nephropathies1. 1. doi: 10.2215/CJN.15161210.2, doi: 10.1056/NEJMoa2202096.

**Methods:** We established stable HEK-TREX cell lines in the EIK haplotype expressing human G1 and G2 variants under control of an inducible promoter and identified compounds for evaluation via high throughput screening, in silico profiling and medicinal chemistry design. T1 flux and electrophoresis assays were used to assess in vitro efficacy of compounds against ApoL1 function. A transgenic mouse model expressing ApoL1-G1 EIK and exhibiting a significantly elevated urinary albumin/creatinine ratio (uACR) following IFNγ challenge was used to assess in vivo efficacy. Compound efficacy was determined by assessing inhibition of proteinuria.

**Results:** Our lead compound, ICA-264 demonstrated concentration-dependent inhibition of ApoL1-G1 mediated T1 flux with an IC50 value of 4 nM (95% CI 3.5-4.4 nM, n=196). The potency was similar against ApoL1-G2 (IC50 = 5 nM, 95% CI 4.4-6.0 nM, n=77). Directly measuring ApoL1 current in electrophysiological experiments demonstrated potent inhibition with IC50 values at 40 nM and 60 nM of 0.6 nM and 0.4 nM (95% CI 0.35-0.47 and 0.49-0.65, respectively). Analogos of ICA-264 were identified with IC50 values as low as 0.26 nM in electrophysiological assays. In our in vivo model oral dosing of ICA-264 (BID) at 3, 10, and 30 mg/kg decreased the IFNγ-induced rise in uACR by 73%, 92%, and 91%, respectively (n=6) on day 2.

**Conclusions:** ICA-264 is a novel ApoL1 inhibitor with excellent drug-like properties and in vivo efficacy. This merits further consideration as a potential novel therapeutic for the treatment of ApoL1-induced nephropathies.

**Funding:** Commercial Support - Ohm Ab, Inc.

**FR-OR106**

**Dyn11-P313 Facilitated Proteasome-Mediated Degradation as a New Therapeutic Target for Interferon 2 (INF2)-Related FSGS**

Jillian Williquett, Hua Sun. University of Iowa Hospitals and Clinics, Iowa City, IA.

**Background:** Mutations in Inverted form 2 (INF2) gene leads to treatment lacking, autosomal dominant Focal Segmental Glomerulosclerosis (FSGS). We found the R218Q mutation in INF2 disrupts the INF2-Dynll1 interaction, leading to dysregulation of dynin-mediated trafficking and degradation of nephrin in vitro and in vivo models of INF2-mediated podocytopathy. Our previous study found Dyn11 facilitates lysosomal degradation of nephrin via adaptor Histone deacetylase 6 (HDAC6). Here, we identified Proteasomal Inhibitor of 31K (P313) as a new adaptor protein which mediates dynin-driven proteasome-mediated degradation. We hypothesized that the INF2-R218Q disrupts dynin-mediated trafficking of nephrin to the proteasome for degradation via enhanced Dyn11-P313 interaction and treatment with Bortezomib (a proteasome protease inhibitor), could become a therapeutic target for INF2-related FSGS.

**Methods:** Proteasome-mediated degradation of nephrin was studied in immortalized podocytes harboring INF2 R218Q mutation, with or without siRNA silencing of Dyn11 or P313. Purinomycin aminonucleoside nephropathy (PAN) was established in INF2 R218Q knockin (KI) mice and effects of Bortezomib versus normal saline control among the different genotypes were evaluated by quantifying severity of proteinuria and podocytopathy.

**Results:** Increased Dyn11-P313 interaction was shown in R218Q KI podocytes, correlated with the R218Q disrupted Dyn11-INFP interaction. The nephrin protein in R218Q KI cells could be stabilized by 1) dynin inhibitor Cilobrevin D and by...
Bortezomib, suggesting an enhanced dynin-mediated degradation of nephrin via protocadherin-5 (PCDH-5) and knockdown of either Dynll1 or PI31, suggesting a critical role for Dynll1-PI31 interaction in nephrin degradation caused by INF2-R218Q. The Bortezomib treatment rescued the PAN of the INF2-R218Q KI mice by attenuating the dynin-facilitated degradation of nephrin via proteasome and preserving the surface trafficking of nephrin that is needed to maintain the slit diaphragm.

**Conclusions:** The R218Q mutation disrupts the Dynll1-INF2 interaction and facilitates dynin-mediated trafficking of nephrin to the proteasome via an increased Dynll1-PI31 interaction. Enhanced dynin facilitated proteasome-mediated degradation of nephrin represents a new therapeutic target for INF2-related FSGS.

**Funding:** Other NIH Support - NIH K12HD027748, Private Foundation Support

**FR-OR107**

**Fasting-Mimicking Diet and Podocyte Protection**

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**Background:** Dietary management is of particular importance in the context of kidney disease. Our data indicate that periods of fasting and intermittent caloric restriction (FMD) can ameliorate kidney damage by preventing podocyte loss. Using different tools and animal models, we showed the renoprotective role of FMD in the context of glomerulopathies. We also showed, in a small pilot clinical trial that FMD is safe, feasible, and potentially beneficial to patients with CKD.

**Methods:** In rats was established by paroxymic (PAN). Rats were fed with six cycles of FMD or ad-lib. Morphological, physiological, and spatial transcriptomics (ST) data were collected at long term. Early molecular changes induced by the FMD were studied by snRNA-seq after one cycle. We used our Alport-podocyte-FUCCI (Fluorescence Ubiquitin Cell Cycle Indicator) mice to study the podocyte cell cycle. We administered 3 cycles of FMD to a small cohort of 13 patients (9 men and 5 women, 38-63 years) with stage III CKD.

**Results:** FMD downregulated proteinuria, ameliorated glomerular sclerosis, and protected podocyte number. ST showed that ctrl and FMD-rats present very similar spatial gene maps vs the PAN-rats. snRNA-seq showed that in PAN-rat, the FMD activated podocyte-specific genes, revealing the important role of fasting followed by refeeding in inducing transcriptional changes in podocytes after damage. In the Alport-podocyte-FUCCI mice, FMD lowered the podocyte number in G1 and increased the podocyte number in G0. In CKD patients, FMD downregulated KGF1, protein C, aminopeptidase, epidermal factor, and upregulated flow-mediated dilatation value (indicating amelioration of endothelial function).

**Conclusions:** These results indicate that FMD promotes the maintenance of glomerular structure and function by inducing podocyte repair and by preserving the G0 state in these cells. FMD cycles could represent a potential treatment for patients affected by progressive kidney disease.

**SA-OR01**

**IMPROVE AKI: Sustainability of Team-Based Coaching Interventions to Improve AKI in a Cluster-Randomized Trial**

Michael E. Matheny,1,2 Richard J. Solomon,1 Sharon E. Davis,1 Kevin C. Cox,1 Meagan E. Stabler,1 Dax Westerner,1 Chad A. Dorn,1 James O’Malley,1 Jeremiah R. Brown,1 Tandem Health University Medical Center, Nashville, TN; 1VA Tennessee Valley Healthcare System, Nashville, TN; 2University of Vermont Medical Center, Burlington, VT; 3Dartmouth College Geisel School of Medicine, Hanover, NH.

**Background:** Up to 14% who undergo cardiac catheterization procedures in the U.S. each year may experience acute kidney injury (AKI). An absence of standards for implementing known interventions hinder efforts to prevent AKI. In a 2x2 factorial cluster-randomized trial, we found the combination of team-based coaching and a data-driven surveillance dashboard reduced the odds of AKI by 46%. We hypothesized these improvements would persist in the period following the active intervention phase of the trial.

**Methods:** A 2x2 factorial cluster-randomized trial was conducted that randomized 20 Veteran Affairs hospitals to receive team-based coaching in a Virtual Learning Collaborative (VLC) compared to Technical Assistance with an AKI Prevention Toolkit (TA), both with and without Automated Surveillance Reporting (VLC/ASR and TA/ASR). Patient outcomes were collected over 18 months following the active intervention phase. Multilevel logistic models for AKI were fit with site-level random effects to account for the clustered design.

**Results:** Across 20 randomized sites, 440 of 4,160 patients experienced AKI during 18-months following the active intervention phase, including 216 of 1,260 patients with pre-existing chronic kidney disease (CKD). We observed a substantial reduction in AKI within the VLC/ASR cluster compared to the TA cluster (aOR=0.60; 0.42-0.86) consistent with the effect previously reported for the active intervention phase (aOR=0.54; 0.40-0.74).

**Conclusions:** Team-based coaching along with data-driven surveillance dashboard can sustainably reduce AKI by 45%, even after active participation in the trial is complete. These combined interventions are an effective, scalable framework to establish aggressive AKI prevention protocols.

**Funding:** NIDDK Support
SA-OR03
Effect of Terlipressin Treatment on the Incidence of Renal Replacement Therapy in Patients with Hepatorenal Syndrome and Fluid Overload: A Post Hoc Analysis of the Phase 3 CONFIRM Study
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Background: Terlipressin (terli) is an FDA-approved vasopressin analogue for the treatment of patients with hepatorenal syndrome (HRS). However, in the Phase III CONFIRM study, terli use was associated with respiratory failure in 10% of terli-treated patients; this could have been due to increased intravascular volume, which is often managed with renal replacement therapy (RRT). In this analysis, we retrospectively examined the subgroup of patients in CONFIRM with fluid overload to determine the incidence, indications, and modality of RRT.

Methods: This post hoc analysis of the Phase III, randomized, placebo-controlled (pbo)-controlled CONFIRM study (NCT02770716) evaluated the incidence of RRT, indications, and modes of RRT used, in the subgroup of patients with fluid overload (pooled term for: hemodynamic edema, effusions, and fluid overload), as determined by investigator assessment. Incidence of RRT was determined on Days 14, 30, 60, and 90 in patients treated with terli or pbo; RRT was initiated after treatment discontinuation. Indications and mode of RRT were determined up to Day 14. Statistical analysis was determined using a Chi-square or Fisher Exact test.

Results: The CONFIRM study enrolled 300 patients (terli, n=199; pbo, n=101), of which 88 patients had fluid overload (terli: n=69; pbo, n=19). RRT incidence was significantly lower in the terli versus pbo group by Day 14 (22.6% [6/28] vs 47.4% [9/19], P<0.03), and similar results were observed by Days 30, 60, and 90 (Table S5). The indications for RRT up to Day 14 did not differ significantly between treatment groups, and the most common indications for both terli and pbo were fluid overload (14.5% [10/69] vs 15.8% [3/19]); P=1.00) and pulmonary edema (5.8% [4/69] vs 10.5% [2/19]; P=0.60). Hemodilution (terli vs pbo: 10.1% [7/69] vs 36.8% [7/19], P=0.05) was the only mode of RRT with a significant difference between treatment groups.

Conclusions: This analysis from the CONFIRM study demonstrated that the incidence of RRT in patients with HRS and fluid overload was lower in terli-treated patients compared with pbo-treated patients. Improved renal function with terli may lead to reduced RRT requirements in patients with HRS and fluid overload.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals

SA-OR04
Niacinamide and Renal Recovery After AKI: A Randomized, Controlled Trial
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Background: Incomplete recovery following community acquired acute kidney injury CA-AKI may be seen in 15-20% of patients. Strategies to improve recovery rates and follow-up of such patients are required. The impaired NAD+ biosynthesis pathway has been recently implicated in AKI. Niacinamide, which bypasses the salvage denovo pathway and produces NAD, could be protective. Its role in recovery following AKI has been postulated. In this pilot phase of clinical trial, role of niacinamide supplementation in recovery after CA-AK was investigated.

Methods: The study was an open label, randomized, controlled trial. Patients of CA-AK aged 18-70 years were enrolled. Underlying CKD, urinary tract obstruction, malignancy, heart failure, pregnancy, lactating women or poor performance status were excluded. Underlying CKD, urinary tract obstruction, malignancy, heart failure, pregnancy, lactating women or poor performance status were excluded. Patients were randomized to receive either niacinamide (500 mg BD for 14 days) or no intervention. Follow-up visits were at 1 and 4 months after hospital discharge. Secondary outcome measures were differences in eGFR between the intervention group as compared to control group. No major drug-related adverse events were recorded.

Conclusions: Niacinamide supplementation improved renal recovery at 4 months after hospital discharge in patients with severe AKI.

Funding: Government Support - Non-U.S.

SA-OR05
Impact of Using Blood Warmer During Continuous Kidney Replacement Therapy on Adverse Kidney Events and Mortality
Aisha Abbas, Akshith Doddi, Ambika Ramesh, Ankit Sakhuja, Khaled Shawwa, West Virginia University Health Science Centers, Morgantown, WV.

Background: Hypothermia is a complication of continuous kidney replacement therapy (CKRT). Blood rewarming is often used to prevent hypothermia; however, its impact on adverse kidney outcomes is unknown.

Methods: Patients with acute kidney injury (AKI) who required CKRT between 1/1/2012 and 1/1/2021 and admitted at a tertiary academic hospital were included. Major adverse kidney events (MAKE) is a composite outcome of need of kidney replacement therapy, doubling of the serum creatinine from baseline or death. We assessed MAKE at 30 and 90 days after CKRT initiation.

Results: There were 669 patients with AKI that required CKRT during the study period. There were 324 (48%) patients in whom a blood warmer was used on first day of CKRT. Patients where a blood warmer was used were more likely to be diagnosed with sepsis/septic shock (91% vs 74%, p<0.04), and were in a less positive fluid balance at the time of CKRT initiation (1.0 vs 1.3 L, p<0.03) compared to patients where a blood warmer was not used. There was no difference in hypotensive episodes during first day of CKRT between the two groups. MAKE-30 and MAKE-90 occurred in 376 (50%) and 472 (65%) of the patients, respectively. Patients who developed MAKE-30 were older (62 vs 56) and had higher SOFA score (10.5 vs 9), higher norepinephrine equivalent (NEE) requirement (0.15 vs 0.07 mcg/kg/min), higher lactate (5.5 vs 3.3 mmol/L), higher Charlson comorbidity index (CCI) (8 vs 7), lower mean arterial pressure (MAP) (74 vs 80 mmHg) and were more likely to be requiring mechanical ventilation (75% vs 63%) at CKRT initiation compared to patients who did not develop MAKE-30, p<0.001.

Baseline creatinine was not different between the two groups (1.2 mg/dL). After adjusting for age, CCI, baseline serum creatinine and SOFA score, lactate, MAP, mechanical ventilation and NEE at CKRT initiation, the use of a blood warmer was independently associated with MAKE-30 (OR: 1.6, 95% CI: 1.1-2.2, p=0.009) but not MAKE-90 (OR: 1.3, 95% CI 0.9-1.9, p-value=0.1). In adjusted Cox proportional hazard model, use of blood warmer was independently associated with mortality: hazard ratio 3.3 (95% CI 2.0-5.0).

Conclusions: Blood warming techniques were associated with worse outcomes in patients with AKI on CKRT. More studies are required to explain this relationship.

Funding: Other NIH Support - National Institute of General Medical Sciences of the NIH under Award Number 2U54GM104942-07. Dr. Ankita Sakhuja disclosed funding from NIH/NIDDK IK08DK131286.

SA-OR06
Machine Learning-Guided Personalized Diuretic Strategy in Patients with Sepsis-Associated AKI
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Background: Fluid overload is common in patients with sepsis associated acute kidney injury (SA-AKI) and is associated with worse outcomes. Loop diuretics are commonly used to manage fluid overload, but their role in patients with SA-AKI is unclear. In this study we aimed to develop a personalized strategy for use of loop diuretics in patients with SA-AKI using machine learning.

Methods: This was a retrospective study using MIMIC IV database. We defined AKI using both creatinine and urine output based KDIGO criteria. We identified patients with sepsis who developed AKI within 48 hours of ICU admission. The primary outcome was AKI recovery within 48 hours of AKI onset. We used available features for demographics, comorbidities, SOFA score, vital signs, laboratory measurements, fluid balance, vasopressors and mechanical ventilation to estimate time varying individual treatment effects (ITE) using a two-model approach employing gradient boosting. The policy tree algorithm with pruning was then employed to identify subpopulations with the highest average treatment effects (ATE) for loop diuretic therapy, enabling a personalized diuresis strategy.

Results: Of 10,739 patients with SA-AKI, 37.8% had AKI recovery within 48 hours. Loop diuretics were used in 3,661 patients within 48 hours after onset of SA-AKI. ATE of loop diuretics was HR 0.935 (95% CI, 0.934, 0.937). Further policy tree analysis identified a personalized strategy for use of loop diuretics with goal to increase AKI recovery within 48 hours (Fig 1a). Specifically, patients with SA-AKI with Blood Urea Nitrogen (BUN)>18 and red cell distribution width (RDW)<14.2 benefited from loop diuretic therapy with an ATE for HR 1.094 (CI 1.080, 1.100) (Fig 1b).

Conclusions: In this study we identified subgroups of patients with SA-AKI who may benefit from loop diuretic therapy to improve the likelihood of recovery of AKI within next 48 hours. This study shows the potential of machine learning to help personalize therapies for patients with AKI.

Funding: NIDDK Support, Other NIH Support - Wo: T32DK077577 T1LD13K16048, AS: l05DK131286, GN: R01DK18083 U1HG007728 U1HG009610 U10DK116100
SA-OR07

Association of Post-Hospitalization Vascular Biomarker Clusters with Future Heart Failure
Audrey Shi,1 Anna Simone Andrawis,1 Wassim Obeid,2 Alan S. Go,3 Kathleen D. Liu,4 Mark M. Wurfel,4 Jonathan Himmelfarb,5 Chirag R. Parikh,5 Pavan K. Bhattraja,6 Vernon M. Chinchilli,7 Paul L. Kimmel,8 James S. Kaufman,9 Steven R. Liu,3 William B. Reeves,3 Amit X. Garg,10 Edward D. Siew,4 Talat Alp Izkiler,2 Heather Thiessen Philbrook,2 Chi-yaun Hsu,2 David K. Prince,3 Francis P. Wilson,1 Sherry Mansour.1 1Yale School of Medicine, New Haven, CT; 2Johns Hopkins University, Baltimore, MD; 3University of California San Francisco, San Francisco, CA; 4University of Washington, Seattle, WA; 5VA New York Harbor Healthcare System, New York, NY; 6Vanderbilt University, Nashville, TN; 7National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 8The Pennsylvania State University, University Park, PA; 9Icahn School of Medicine at Mount Sinai, New York, NY; 10The University of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: Individual vascular biomarkers helped elucidate the connections between acute kidney injury (AKI) and future heart failure (HF). The role of combined vascular biomarkers in recently discharged patients with risk of future hospitalizations with HF is unknown.

Methods: Using the ASSESS-AKI cohort, we performed an unsupervised spectral cluster analysis with 9 plasma biomarkers measured at 3 months post-hospitalization [Angiopoietin (angpt)-1, angpt-2, vascular endothelial growth factor (VEGF)-A, VEGF-C, VEGF-D, VEGF receptor 1 (R1), solubleTie-2 (sTie-2), placental growth factor (PIGF), and basic fibroblast growth factor (bFGF)] in 1,497 patients, half of whom had AKI. We used a Cox regression analysis to evaluate the associations between clusters and future hospitalizations with HF. Models were adjusted for demographics, cardiovascular disease, co-morbidities, medications, ICU status, lung disease, sepsis, serum creatinine, proteinuria, and admission center.

Results: 3 biomarker-derived clusters were identified: Cluster 1 [n=302, Vascular Injury (VI) phenotype] had higher levels of vessel injury markers, whereas Cluster 2 [n=728, Vascular Repair (VR) phenotype] had higher levels of vessel repair makers. Cluster 3 [n=467] had lower levels of both repair and injury markers (dormant phenotype). The median time to HF was 4.7 years (IQR: 2.93-5.93). Participants with the VI phenotype were twice as likely to have a HF event [aHR 2.23 (1.56, 3.18)] compared to the VR phenotype. The dormant phenotype was also significantly associated with HF [HR 1.19 (1.01-1.38)] compared to the VI phenotype. The odds of AKI were higher in males in all 3 age categories but was strongest in adults (Table 1). Adjustment for comorbidity attenuated the male risk in adults only, adjustment for socio-economic status did not change the strength of the association meaningfully.

Conclusions: Men are more likely than women to develop AKI. The attenuation of sexual dimorphism in AKI incidence before puberty and after menopause suggests that female sex hormones are protective in AKI.

SA-OR09

Dialysis Weaning Is Uncommon in the Treatment of Outpatient AKI Requiring Dialysis (AKI-D)
Ian E. McCoy,1 Eric D. Weinhandl,2 Wael F. Hussein,2 Chi-yaun Hsu.1 1University of California San Francisco, San Francisco, CA; 2Satellite Healthcare, San Jose, CA.

Background: Recovery from dialysis-requiring acute kidney injury (AKI-D) often occurs after discharge from the hospital, following treatment in outpatient hemodialysis units. The dialysis weaning strategies employed during outpatient recovery (weaning dialysis frequency, weaning dialysis session duration, or proceeding directly to a trial of complete dialysis cessation) have not been described.

Methods: We examined outpatient dialysis orders for a cohort of 1,754 AKI-D patients initiating in-center hemodialysis between 7/1/2017 and 6/30/2022 across 67 different dialysis units operated by a medium-sized, not-for-profit dialysis provider. We followed patients for 5 months after first outpatient hemodialysis treatment. AKI-D patients were stratified by need for dialysis at time of discharge (0-42 days) and stratified by gender and age categories (18-44 years, 45-54 years, >54 years). We assessed changes in prescribed hemodialysis frequency and session duration.

Results: 95% of AKI-D patients were initially ordered for ≥3x/week dialysis frequency. At 3 months after first outpatient hemodialysis treatment, 41% had recovered, 9% continued to receive dialysis, and 10% had died. During follow-up, 70% had no changes to either prescribed dialysis frequency or session duration. Among those who recovered, dialysis frequency was weaned in 18% and dialysis session duration was weaned in 9% of all others discontinued dialysis without a change from their initial prescription. Among those who remained on dialysis or died, frequency was weaned in 11%.

Conclusions: In this contemporary cohort of patients with AKI-D in outpatient hemodialysis centers, dialysis weaning was uncommon. That many patients were able to transition directly from thrice-weekly treatment to no hemodialysis suggests there may be substantial opportunity to wean dialysis more often (e.g., to twice weekly treatment), likely resulting in cost savings and quality of life improvement.

Funding: NIDDK Support, Commercial Support - Satellite Healthcare Inc., not-for-profit dialysis provider

Outpatient dialysis prescriptions for AKI-D patients, stratified by outcomes 3 months after first outpatient dialysis

<table>
<thead>
<tr>
<th>Status</th>
<th>Recovered</th>
<th>Continued receiving dialysis</th>
<th>Died without recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis frequency</td>
<td>59/56</td>
<td>62/81</td>
<td>42/68</td>
</tr>
<tr>
<td>Dialysis session duration</td>
<td>55/59</td>
<td>62/70</td>
<td>44/61</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR10
Prediction of Postdischarge Kidney Disease Progression Among Patients with Hospitalized AKI: The ASSESS-AKI Study
Steven Menez,1 Kathleen F. Kerr,1 Yi Chen,2 David Hu,3 Heather Thiessen Philbrook,4 Dennis G. Molelida,2 Sherry Mansour,2 Alan S. Go,6,7 Talat Alp Ikizler,8 James S. Kaufman,9 Paul L. Kimmel,10 Jonathan Himelfarb,11 Steven G. Coca,12 Ching R. Cherkly1;1;1;1
1Johns Hopkins University School of Medicine, Baltimore, MD; 2University of Washington School of Medicine, Seattle; WA; 3Yale School of Medicine, New Haven, CT; 4University of California San Francisco, San Francisco, CA; 5Kaiser Permanente, Oakland, CA; 6Vanderbilt University School of Medicine, Nashville, TN; 7New York University Grossman School of Medicine, New York, NY; 8National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; 9Icahn School of Medicine at Mount Sinai, New York, NY.

Background: Acute kidney injury (AKI) occurs frequently during hospitalization, but only a small fraction of patients progress to chronic kidney disease (CKD) after discharge. Biomarkers of kidney injury, inflammation, and repair have been shown to be informative of long-term kidney disease risk.

Methods: We evaluated data from 723 hospitalized patients with AKI and post-discharge follow-up in the National Kidney Disease Education Program, Chronic Kidney Disease: Assessment, Serial Evaluation, and Subsequent Sequelae of AKI (ASSESS-AKI) Study. We investigated 75 candidate predictors, including 11 urinary and 28 plasma biomarkers measured at 3-month post-discharge follow-up. We employed both random forests and least absolute shrinkage and selection operator (LASSO) regression to predict major adverse kidney events (MAKE: CKD incidence, CKD progression, or development of end-stage kidney disease). The data was split into training (80%) and test (20%) datasets. We used multiple imputation to handle missing data and independent test data for unbiased estimates of model performance.

Results: A total of 235 patients developed MAKE over 3 years of follow-up. While a prediction model containing 9 key clinical variables yielded an area under the receiver-operating characteristic curve (AUC) of 0.75 (0.63-0.87), random forest and LASSO models using all 75 variables yielded AUC values of 0.81 (0.71-0.92) and 0.80 (0.70-0.91). The top 5 clinical biomarkers based on random forest modeling were sTNFR1, sTNFR2, NT-proBNP, FGF-23, and Ang-2, all measured in the plasma and yielded an AUC of 0.75 (0.63-0.88). A combination model leveraging both clinical variables and the top 5 biomarkers demonstrated an AUC of 0.77 (0.65-0.89).

Conclusions: A parsimonious predictive model using a combination of key clinical variables and top biomarkers offers moderately strong discrimination in identifying patients with hospitalized AKI at highest risk of progression of kidney disease long-term.

Funding: NIDDK Support

SA-OR11
Development of Physiologically Relevant In Vitro Model of Human Kidney Collecting Duct System Toward a Functional Kidney Replacement
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Background: A significant number of patients with end-stage kidney disease face a restricted supply of kidney donors. Urgently needed alternatives are necessary due to the shortening of dialysis. Engineered kidney models have mainly focused on the proximal nephron. In this work, we present a method to recapitulating the kidney collecting duct (CD) system. The collecting system refines faturine urine and is vital for regulating acid-base balance, Na+ and K+ handling, and body water homeostasis. Applying microfluidic and 3D bioprinting methods to the development of kidney CD systems can potentially lead to a more understandable and functional in human disease, as well as serve as an important component of functional kidney replacement.

Methods: PDMS soft lithography was employed to create a three-compartment cell culture device in which channels are separated by phase guides. These phase guides allow for in situ hydrogel formation while enabling substrate-attached cells to be patterned. The fluidic exchange channels were designed to support both 2D cell culture for preliminary tests and as an enclosed system for fitting 3D bioprinted tubes. Each channel is connected to a peristaltic pump channel, enabling shear stress in 2D or 3D culture. Ureteric bud-derived CD cells were seeded in the central channel, while the surrounding channels can be potentially used to culture stromal cells and endothelial cells to resemble the in vivo setting.

Results: Preliminary testing of the fabricated devices exhibited high cytocompatibility and the ability to withstand shear stress values up to 10 dynes/cm² in the channels without mechanical failure or cell detachment. In situ hydrogel formation demonstrated the ability of the phase guides in preventing mixture before crosslinking, while allowing fluidic transfer between the channels. The hydrogel structures within the devices showed sustained resistance to flow forces with no structural defects.

Conclusions: Our human kidney CD system can be used to model the CD in health and disease, as well as serve as a potential component for kidney functional replacement. Our initial studies involve demonstrating the functionality of this system to study human CD system physiological function in health and in models of genetic disease.

Funding: NIDDK Support, Other NIH Support - T32EB016652-09-UH3 TR002155, R01 DK59373, R01 DK72381

SA-OR12
Induced Pluripotent Stem Cell (iPSc)-Derived and Primary Podocyte-Like Cells Are Capable of Macromolecular Sieving After Culture in Scalable Scaffolds
Thomas F. Gallegos, Aneta J. Przepiorka, Mohsen Sarikhani, Ivjiva Medical, Woburn, MA.

Background: With the growing demand for donor kidneys and insufficient donor organs, there is an urgent need for alternatives to dialysis and kidney transplantation. Our team has developed a biocompatible engineered glomerular tissue construct comprising hollow vascular and epithelial networks separated by a porous biomimetic membrane. The scaffolds are seeded with endothelial cells and podocytes that when perfused under vascular pressure, recapitulate glomerular function to produce a primary filtrate. The glomerular units are seeded with primary cells isolated from non-transplantable human donor kidneys of by isolation of cells from human induced pluripotent stem cells (iPSCs), that have been differentiated into endothelial cells and podocyte-like cells. We evaluated filtration dynamics and cell characteristics of podocytes.

Methods: Human primary podocytes and endothelial cells are isolated by enzymatic digestion and glomerular isolation by sieving. Podocytes and endothelial cells were isolated by subsequent glomerular digestion and FACS sorting. Isolates were pursued as a monolayer. iPSCs were differentiated into endothelial and podocyte-like cells. Human kidney organoids were generated using published methods with modifications.

Results: Aqecular camouflage scaffolds are highly permeative to transmembrane fluid flux and produce filtrates which contain micro- and macromolecules. Histological analysis of this construct and iPSC scaffolds shows cellular coverage within the endothelial and podocyte channels, indicating good cellular attachment and survival under perfusion for a minimum of 7 days. Pressure saturated pure filtered scaffolds with a blood-like buffer containing physiologic albumin and hematocrit through the vascular channel, produced RBC-free filtrate which resists macromolecule loss from the vascularule.

Conclusions: Our results demonstrate that both primary and iPSC derived endothelial and podocyte-like cells are viable option for physiologically relevant engineered renal tissues.

Funding: Commercial Support - Ivjiva Medical

SA-OR13
A Novel Vascularized Human Kidney Organoid to Study Podocyte and Endothelial Health and Disease
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Background: Recapitulating vasculature in in vitro kidney systems is critical for mechanistic studies due to its important role in health and disease. Many methods for vascularizing have been taken, however, few have been robust, reliable, high-throughput, and can be used to study podocyte/endothelial morphology and morphological changes in injury settings.

Methods: Here, we generate vascularized human kidney organoids by mixing an inducible ETS translation variant 2 (ETV2) human induced pluripotent stem cell line (iETV2-hiPSC), which directs endothelial fate, with a non-transgenic iPSC line in suspension organoid culture.

Results: We demonstrate that the addition of iETV2-hiPSCs to an established kidney organoid protocol generates a vascularized human kidney organoid with a 10-fold increase in endothelial cells and a 60% increase in organoid diameter. Podocyte and endothelial differentiation were consistently evidenced with a network of endogenous ETS and with immunohistochemistry. On untrained we found vascularized podocytes exhibit enhanced VEGF signaling, basement membrane maturation, and endothelial differentiation markers. Additionally, we demonstrate that vascularization of human kidney organoids enables the formation of a functional interstitium with drug responsive renin-angiotensin. These renin cells existed within the podocyte clusters of vascularized organoids only. Finally, we show that iETV2-hiPSCs undergo co-development with kidney organoid parenchymal tissue, thus generating mature differentiated kidney-specific endothelial networks.

Conclusions: We generated a vascularized human kidney organoid with increased maturation of neprhon structures including more mature podocytes with improved foot process interdigitiation, a fenestrated endothelium, and the presence of renin+ cells. This represents the first demonstration of renin+ cells in a kidney organoid without the use of exogenous supplementation. The creation of an engineered vascular niche capable of improving kidney organoid maturation and cell type complexity is a significant step forward in the path to clinical translation.

Funding: NIDDK Support, Other NIH Support - T32EB001026, R01 EB028532

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Background: Glomeruli are anatomically complex structures essential to kidney function. Much of our current understanding of glomeruli comes from optical microscopy, for general physiology and molecular distributions, and electron microscopy, for ultrastructure. While powerful, these methods yield uncorrelated results obtained on different pieces of tissue and typically for thin sections at random angles. Researchers therefore generally study small regions of glomeruli, rather than viewing them as distinct, functioning units. We are creating a Glomerular Nanoscale Spatial Atlas (GNSA) that will provide a detailed, annotated collection of high-resolution 3D reconstructions of whole mouse glomeruli. Our goals are to identify previously unknown glomerular phenotypes and to create a rich, downloadable resource.

Methods: We used optical super-resolution microscopy methods at 50-100nm resolution together with advanced tissue labeling techniques and a mix of manual and deep-learning-based data analysis techniques to image and segment major structures in mouse glomeruli. Our results are to identify previously unknown glomerular phenotypes and to create a rich, downloadable resource.

Results: We have reconstructed and analyzed 7 glomeruli (3F, 4M) from healthy adult mice (3–6mo), whose models reveal Bowman's capsule, Bowman's space, blood space, all cell types and locations, glomerular basement membrane and mesangial matrix.

Conclusions: We have established a pipeline for creating detailed 3D models of whole renal glomeruli. We are performing a detailed spatial analysis of the models and acquiring new results for aged and model diseased mice with a focus on identifying spatial correlations between components of glomeruli. Once published, the unique data sets of the GNSA may be mined for diverse purposes by the nephrology community.

Funding: NIDDK Support

SA-OR15

A Novel Glomerular Endothelium-Targeting Adeno-Associated Virus (AAV) Delivers Bacterial Proteinase to Treat Glomerulonephritis

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Background: The breakdown of glomerular filtration barrier (GFB) is relevant to the pathogenesis of most kidney diseases. Targeting the GFB by conventional drugs is challenging due to the lack of cell-targeting specificity, which consequently compromises the therapy efficacy. Adeno-associated virus (AAV) as a promising in vivo gene delivery platform shows the advantage in delivering therapeutic molecules to those difficult or non-druggable cells. However, natural AAV serotypes have insufficient targeting specificity and transduction efficiency in kidney cells, thus approaches to broaden the tropism of AAV and screenings for kidney-specific AAV vectors are particularly needed.

In this study, we aimed to discover new AAV vectors targeting the renal glomeruli. The targeting specificity and transduction efficiency of the selected AAV were evaluated in vivo under both physiological and pathological conditions.

Results: We identified a new AAV vector termed AAV2-GE, which specifically and efficiently targeted the glomeruloid endothelial cells (GEC) after systemic administration. AAV2-GE exhibited robust GEC tropism in C57BL/6J, BALB/c mice and Sprague Dawley rats, as well as in disease models causing GEC damage. The potential of AAV2-GE for kidney-targeting therapy was evaluated by delivering a bacterial cysteine proteinase originally purified from Streptococcus pyogenes (Idex) to the GEC. Idex, also known as an inalidase, is an antibiotic-elevating enzyme used in the clinic to eliminate pathogenic IgG. We showed that AAV2-GE-Idex transduction efficiently produced Idex in GEC, which provided sustained clearance of kidney-bound IgG and successfully prevented the progression of anti-glomerular basement membrane glomerulonephritis.

Conclusions: This study establishes an AAV in vivo screening approach for renal glomeruli. It identifies a novel GEC-targeting AAV vector with robust tropism maintained across species in both physiological and pathological settings. The identification of AAV-GE demonstrates the feasibility of future GFB-tatrophe strategies for novel kidney therapies.

Funding: Government Support - Non-U.S.

SA-OR16

Comprehensive Single-Cell Transcriptomic, Epigenomic, and Metabolomic Profiling Reveals Anatomical and Metabolic Heterogeneity in Human Kidneys

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Background: The human kidney has a distinct spatial organization, with multiple anatomic structures constituted by diverse cell types and performing unique metabolic functions. We lack a large-scale spatially-resolved multimodal (transcriptome, epigenome, metabolome) single-cell atlas for the human kidney.

Methods: We developed an optimized, split-pool barcoding-based multimodal profiling method based upon SHARE-seq (concurrent scATAC/RNA-seq). We profiled 50 human kidney samples from cortex, medulla, papilla, ureter and renal artery. Computational analysis (e.g. gene regulatory network, module enrichment analysis) identified molecular signature of different anatomic regions. Mass spectrometry spatial metabolomics was used to identify region-specific metabolites at single-cell resolution. Clinical data were used to identify novel genes in kidney disease progression.

Results: We generated transcriptomes of 446,000 cells, chromatin accessibility profiles of 401,000 cells & spatially resolved metabolomes of 408,000 cells. Multimomic analysis revealed cell types in different anatomic regions are characterized by markedly different transcriptome & chromatin accessibility profiles depending on the region (e.g. cortical vs. medullary vs. papillary TAL cells). Healthy PT (proximal tubule)-to-maladaptive PT transition is accompanied by acquisition of a distinct metabolic signature (e.g. reduced fatty acid oxidation, elevated lipid accumulation). Tubular cell types had non-overlapping metabolomic profiles. We developed MALDipy, a package for single-cell analysis of imaging mass spectrometry data.

Conclusions: Our optimized SHARE-seq achieved single-cell multiome profiling at 20-fold lower cost compared to 10X Genomics. We developed a comprehensive single-cell multimomic atlas of human kidneys covering diverse anatomic structures. Distinct signatures of cells in different regions suggest cellular plasticity and metabolic heterogeneity. Genes (e.g. PFTHP1) correlated with disease severity were identified as potential therapeutic targets.

Funding: NIDDK Support
SA-OR18
The Effect of a Novel Digital Physical Activity Intervention on Health-Related Quality of Life in People with CKD: A Multicenter Randomized Controlled Trial (Kidney BEAM)
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Background: Evidence-based and theory-driven resources to support self-management are lacking but digital health interventions (DHIs) may offer cost-effective and equitable education delivery. We co-produced My Kidneys & Me (MK&M), an educational DHI, and tested its effect on patient activation in a multicenter randomized control trial. Methods: Participants from 26 sites in England were randomized 2:1 to intervention (MK&M) or control groups. MK&M provided theory-based education sessions and trackers for goals, symptoms, physical activity and clinical measures. The Patient Activation Measure (PAM-13) was collected at baseline, 10 and 20 weeks. A 4-point increase in PAM-13 was deemed a meaningful important difference. Intention-to-treat (ITT) and per-protocol (PP) analyses (including patients who used MK&M at least once) were conducted.

Results: 421 patients (mean age 59.9±13.4 years, 60% males, eGFR 39.5±24.6 ml/min/1.73m²) were recruited: 281 randomized to receive MK&M, 140 to control. 205 (73%) participants used MK&M at least once. Changes in PAM-13 are shown in Figure 1. Significant between group differences in PAM-13 were observed at 20 weeks in PP analysis. In those with low PAM-13 at baseline, MK&M significantly improved PAM-13 by 9.3-11.4 points. No changes were seen in those with high baseline PAM-13 scores. Conclusions: Use of the MK&M DHI increased patient activation (measure of self-management). Greater benefit was seen with frequent and sustained usage, and in those with low PAM-13. As higher patient activation is associated with better outcomes, MK&M may improve CKD healthcare management.
and lower adjusted Charlson Comorbidity Index (5.0 vs 5.3) (p=0.001). The percentage of participants achieving an albumin target (≥2.5 and ≤5.5 mg/dL) was higher in app users (68.9%) compared to non-users (66.4%) (p=0.001). Phosphate control improved after 1 year of app usage from 62.2% to 69.4% (p<0.001). Hospitalisation rate (events per patient year) was 1.55 for app users and 1.97 for non-users (p=0.001). The number of hospitalisations per patient year for users and non-users were 10.2 and 10.9 days, respectively (p=0.001). The impact of app usage on patients' interdialytic weight gain was not statistically significant.

Conclusions: HD patient app promotes patient empowerment and self-care. Additionally, app usage may improve medical outcomes such as phosphate and hospitalisation.

Funding: Commercial Support - Fresenius Medical Care

SA-OR20

Integrated Proteomic and Metabolomic Modules Associated with Risk of Kidney Function Decline

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Background: Proteins and metabolites play crucial roles in various biological functions and are frequently interconnected through enzymatic or transport processes. Many molecules have been linked to kidney disease, and several of them are potentially representing pathways or endophenotypes.

Methods: We present an integrated analysis of proteomics (4,091 proteins) and metabolomics (634 metabolites) via a dimensionality reduction clustering method in the Chronic Renal Insufficiency Cohort (CRIC) Study. We split the 1,708 participants (mean age 59; mean eGFR=42.8 mL/min/1.73 m²) with a random split in discovery (2/3) and replication (1/3). Linear regressions (eGFR decline) and Cox proportional hazards models (CKD progression, ESKD) were comprehensively adjusted for demographies and risk factors including eGFR and PCR. Multiple testing in discovery and replication was accounted for by Bonferroni adjustment. Identified modules were characterized through pathway enrichment analyses.

Results: We identified 139 modules of correlated proteins and metabolites in the discovery data. The mean module size was 34 proteins / metabolites. There were 286 principal components (PCs) used to represent the 139 modules. Module membership and PC directions were projected onto the replication dataset. The average follow-up period was 9.5 and 7.4 years for eSKD and CKD progression respectively (537 and 685 events). Eight out of 12 initially identified modules replicated in the replication dataset. Two new modules were replicated (1 eGFR decline; 3 CKD progression; 4 ESKD). Multiple testing in discovery and replication was accounted for by Bonferroni adjustment. Identified modules were characterized through pathway enrichment analyses.

Conclusions: In summary, this study demonstrates that the integration of the proteome and metabolome can identify functions (patho-) physiologic importance in human health and disease. Specifically, the ephrin receptor activity pathway might play a role on a systemic level.

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

SA-OR21

A Soluble ACE2 Protein Improves Survival and Lowers Viral Titers in a Lethal Mouse Model of SARS-CoV-2 Infection with the Delta Variant

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Background: Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) utilizes Angiotensin Converting Enzyme 2 (ACE2) as its main receptor for cell entry. Several recent studies have revealed that a biotinylated and humanized soluble ACE2 protein designed to have increased binding to the SARS-CoV-2 spike protein and with extended duration of action can neutralize SARS-CoV-2 in the k18hACE2 mouse model infected with the ancestral SARS-CoV-2 strain (Washington isolate). Here we investigated the preventative/therapeutic potential of the biotinylated ACE2 protein in the k18hACE2 mouse model infected with the SARS-CoV-2 delta variant which causes severe disease in humans.

Methods: k18hACE2 mice were inoculated with SARS-CoV-2 delta variant (2x10⁴ PFU) and followed for up to 14 days in a BSL-3 facility. ACE2-618-ABD-DDC or PBS as vehicle control (n=10 per group) were administered intranasally 6h prior as well as 24 and 48hrs after viral inoculation. Infected animals were observed for weight loss, a clinical score, and mortality. Viral load was assessed by plaque assay in brain, lung, and kidney tissue.

Results: All untreated animals had succumbed to the disease at day 6, whereas survival at day 14 was 90% in mice receiving ACE2-618-ABD-DDC (Fig, left panel). Brain and lung viral titers were markedly reduced in mice receiving ACE2-618-ABD-DDC (Fig, middle panels). Despite uniform lethality of the disease in untreated animals, infected mice showed absence of kidney viral titers in all groups (Fig, right panel).

Conclusions: This study demonstrates the protective effect of ACE2-618-ABD-DDC in a lethal mouse model of SARS-CoV-2 infection with the delta variant. This soluble ACE2 protein markedly improved survival in the otherwise lethal model and reduced viral titers in lungs and brains to almost undetectable levels. It also shows a consistent lack of replicating virus in the kidney of animals infected with the delta variant. Taken together with our previously published experiments, the data supports a universal protective effect of our soluble ACE2 protein against infections with different SARS-CoV-2 variants.

Funding: Private Foundation Support

SA-OR22

University of California Health Systems Kidney COVID-19 Study Inpatient Cohort

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Background: Understanding long term changes in kidney function following moderate to severe COVID-19 is important. The aim of our study was to compare changes in eGFR between people hospitalized with and without COVID-19 to better understand its longer-term kidney sequelae.

Methods: We conducted a retrospective cohort study of adults receiving care within the five major University of California (UC) Health Systems, who underwent PCR testing for SARS-CoV-2 between March 1, 2020, and December 31, 2021, and were hospitalized within 10 days of testing. The cohort was restricted to those without ESKD, with a serum creatinine (sCr) within 12 months prior to SARS-CoV-2 testing or normal kidney function on admission. Length of stay was calculated by subtracting the admission date from the date of discharge. The percentage of patients achieving the phosphate target (≤2.7 mg/dL) compared to non-users (66.4%) (p<0.001). Phosphate control improved after 1 year of app usage from 62.2% to 69.4% (p<0.001). Hospitalisation rate (events per patient year) was 1.55 for app users and 1.97 for non-users (p=0.001). The number of hospitalisations per patient year for users and non-users were 10.2 and 10.9 days, respectively (p=0.001). The impact of app usage on patients' interdialytic weight gain was not statistically significant.

Conclusions: HD patient app promotes patient empowerment and self-care. Additionally, app usage may improve medical outcomes such as phosphate and hospitalisation.

Funding: Commercial Support - Fresenius Medical Care

SA-OR23

Machine Learning-Based Multi-Omics Analyses Predict Disease Severity and Identify Molecular Mechanisms of COVID-Associated Kidney Injury

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Background: Studies show a higher prevalence of acute kidney injury (AKI) in COVID-19 patients, however mechanisms leading to severe kidney outcomes are unclear. Identifying these mechanisms may help develop therapies for the management of COVID-associated AKI.

Methods: We conducted a retrospective cohort study of adults receiving care at the five major University of California (UC) Health Systems, who underwent PCR testing for SARS-CoV-2 between March 1, 2020, and December 31, 2021, and were hospitalized within 10 days of testing. The cohort was restricted to those without ESKD, with a serum creatinine (sCr) within 12 months prior to SARS-CoV-2 testing or normal kidney function on admission. Length of stay was calculated by subtracting the admission date from the date of discharge. The percentage of patients achieving the phosphate target (≤2.7 mg/dL) compared to non-users (66.4%) (p<0.001). Phosphate control improved after 1 year of app usage from 62.2% to 69.4% (p<0.001). Hospitalisation rate (events per patient year) was 1.55 for app users and 1.97 for non-users (p=0.001). The number of hospitalisations per patient year for users and non-users were 10.2 and 10.9 days, respectively (p=0.001). The impact of app usage on patients' interdialytic weight gain was not statistically significant.

Conclusions: In summary, this study demonstrates that the integration of the proteome and metabolome can identify functions (patho-) physiologic importance in human health and disease. Specifically, the ephrin receptor activity pathway might play a role on a systemic level.

Funding: Other NIH Support - UC Davis School of Medicine

LME Models

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

Underline represents presenting author.
Longitudinal Kidney Outcomes of COVID-19-Associated AKI

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Background: COVID-19 infection is associated with a high incidence of acute kidney injury (AKI). The long-term impact of COVID-associated AKI on kidney function trajectory remains unknown.

Methods: This was a longitudinal health record cohort study that included 9624 adults hospitalized with AKI within a large New England health system assessing the association of COVID-19-associated AKI with the slope of estimated glomerular function rate (eGFR) for up to 2 years after discharge using multivariable linear mixed effects models. Three groups were compared: 1) patients hospitalized with COVID-19-associated AKI; 2) patients hospitalized during the COVID pandemic who tested negative for SARS-CoV-2 and had AKI due to other causes (Other-AKI); and 3) patients hospitalized with influenza-associated AKI in the 5 years before the COVID pandemic (Flu-AKI). A key secondary outcome included 2-year major adverse kidney events (MAKE—a composite of mortality, ≥50% eGFR decline from discharge or end-stage kidney disease diagnosis) assessed using multivariable time-to-event analyses.

Results: The adjusted eGFR slope was -0.79 mL/min/1.73 m² per year (95% CI -1.23, -0.35) following COVID-AKI, -0.13 (95% CI -0.73, 0.47) following Flu-AKI, and -0.29 (95% CI -0.52, -0.06) following Other-AKI. COVID-AKI was associated with lower 2-year MAKE (adjHR: 0.67, 95% CI: 0.59-0.75), with lower 2-year mortality (adjHR: 0.31, 95% CI: 0.24-0.39, p<0.001) and lower 2-year renal progression (adjHR: 0.78, 95% CI: 0.69-0.88, p<0.001) compared to Other-AKI.

Conclusions: While survivors of COVID-AKI experience an initial faster eGFR decline compared to AKI due to other causes, they have higher eGFR on discharge and exhibit lower rates of longitudinal renal progression and mortality.

Funding: Other U.S. Government Support

SA-OR25

Monovalent and Bivalent mRNA Vaccine Effectiveness Against Severe COVID-19 Associated with Omicron Variant in Maintenance Dialysis Patients

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Background: Recent data suggest that SARS-CoV-2 bivalent (BV) booster is more effective than monovalent (MV) booster against severe Omicron infection. We compared the effectiveness (VE) of BV and MV booster regimens in a national population of maintenance dialysis patients.

Methods: All adult patients receiving maintenance dialysis during the Omicron era (12/19/21-2/12/23) at Dialysis Clinic, Inc. (DCI) facilities who had COVID-19 during this time were included. Vaccination status was categorized as unvaccinated or received MV or BV booster before COVID. A logistic model was used to determine odds ratio (OR) of hospitalization/death within 30 days of infection by vaccination status. The model was adjusted for COVID prior to the Omicron period, age, sex, dialysis vintage, COPD, thyroid disease, PVD, diabetes, and immunocompromising conditions, and weighted by the natural log transformation of exposure time at risk.

Results: Among 3,853 eligible patients, mean age was 63 (±15) years; 55% were male and 31% Black. Figure 1 shows ORs of hospitalization or death within 30 days of infection by vaccination status. Relative to unvaccinated, the VE, defined as 100*(1-OR%), was 44% (95% CI 30-56%) for MV booster doses received more than 180 days prior to COVID. Among patients who received MV or BV booster within 180 days of infection; was 55% (42-65%) for MV received within 180 days; and was 83% (62-93%) for BV received within 180 days of infection. Relative to MV received more than 180 days before infection, the VE for MV and BV received within 180 days of infection were 20% (0.2-35%) and 70% (33-87%), respectively. The VE was 63% (16-84%) for BV relative to MV when both were received within 180 days of infection.

Conclusions: Bivalent SARS-CoV-2 vaccine is more effective than monovalent vaccine against severe Omicron infection in maintenance dialysis patients. Vaccine effectiveness declines after 180 days in this population suggesting a need for revaccination.

Funding: Other U.S. Government Support

SA-OR4
SA-OR26
Excess Mortality During the COVID-19 Pandemic in a Mid-Sized Dialysis Provider
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Background: Before widespread availability of vaccination, the coronavirus disease 2019 (COVID-19) pandemic incited a sharp increase in the all-cause death rate among chronic dialysis patients. Whether excess mortality has persisted during 2022 and early 2023 remains uncertain.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. During each epidemiologic week from week 1 of 2017 to week 16 of 2023, we identified all chronic dialysis patients in centers in California, Hawaii, Tennessee, and Texas. For each patient-day, we collected age, sex, and duration of end stage kidney disease (ESKD). We fit a logistic regression of death with generalized estimation equations, adjusted for age, sex, duration of ESKD, state, and seasonality; and estimated excess mortality in 9 pandemic intervals, relative to the interval from week 1 of 2017 to week 11 of 2020, overall and by setting (in-center, home).

Results: During the pandemic era, there were 4175 deaths, or 16.5 deaths per 100 patient-years; in contrast, there were 14.5 deaths per 100 patient-years during the pre-pandemic era. As displayed, the rate of death was initially elevated between September 2020 and March 2021 (excess mortality factor, 1.34; 95% CI, 1.24-1.45), and remained elevated from July 2021 to October 2022, with excess mortality factors ranging from 1.11 to 1.18. From November 2021 to February 2023, excess mortality was more pronounced among home dialysis patients (range of excess mortality factors, 1.20-1.35 among home patients versus 1.07-1.14 among in-center patients). Since March 2023, the rate of death has been in line with the pre-pandemic norm (excess mortality factor, 0.96; 95% CI, 0.81-1.14).

Conclusions: Excess mortality during the pandemic has gradually decreased since Winter 2020-2021, although it dissipated more slowly among home dialysis patients. In Spring 2023, excess mortality is absent.

SA-OR28
Abrupt Estimated Glomerular Filtration Rate Decline After Initiating Sodium-Glucose Cotransporter-2 Inhibitors Predicts Clinical Outcomes: A Systematic Review
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Background: The initiation of sodium-glucose cotransporter-2 inhibitors (SGLT2i) typically leads to a reversible initial decline or “dip” in estimated glomerular filtration rate (eGFR). However, the implications of this phenomenon on clinical outcomes are not well-defined.

Methods: We searched MEDLINE, Embase, and Cochrane Library from inception to March 23, 2023 to identify randomized controlled trials and cohort studies comparing kidney and cardiovascular outcomes in patients with and without initial eGFR dip after initiating SGLT2i. Pooled estimates were calculated using random-effect meta-analysis.

Results: We included seven studies in our analysis, which revealed that an initial dip in eGFR following the initiation of SGLT2i was associated with less annual eGFR decline (mean difference: 0.64, 95% confidence interval [CI]: 0.437-0.843 mL/min/1.73m²). The risk of major adverse kidney events was similar between non-dipping and dipping groups but reduced in patients with a 0-10% eGFR dip (hazard ratio [HR]: 0.915, 95% CI: 0.865-0.967). No significant differences were observed in the composite of hospitalized heart failure and cardiovascular death (HR: 0.824, 95% CI: 0.633-1.074), hospitalized heart failure (HR: 0.959, 95% CI: 0.574-1.592), or all-cause mortality (HR: 0.83, 95% CI: 0.589-1.170). However, trial sequential analysis indicated that the required sample size had not been reached to make conclusive claims about cardiovascular and mortality outcomes. The risk of serious adverse events (SAEs), discontinuation of SGLT2i due to AEs, kidney-related AEs, acute kidney injury, and vascular complications was similar between the two groups. However, patients with >10% eGFR dip had a higher risk of hyperkalemia compared to the non-dipping group.

Conclusions: The findings of this study suggested that the initial dip in eGFR following the initiation of SGLT2i might be associated with less annual eGFR decline. Additionally, there were no significant differences in the risks of adverse kidney and cardiovascular outcomes between the dipping and non-dipping groups.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-OR29
Global Burden of CKD and Attributable Risk Factors in 38 Organization for Economic Cooperation and Development (OECD) Countries: Results from GBD 2019
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Background: CKD was the 8th leading cause of death in Organization for Economic Cooperation and Development (OECD) nations in 2019, accounting for 3.5% of all fatalities.

Methods: This study utilized the Global Burden of Disease methodology to analyze CKD incidence, mortality, disability-adjusted life years (DALYs), and associated risk factors in OECD countries.

Results: In 2019, OECD countries accounted for 35.06% of total global incident cases, 27.7% of deaths, and 19.6% of DALYs attributed to CKD. Within the combined OECD countries, CKD incident cases increased by 103%, deaths by 179%, and DALYs by 120% from 1990-2019. Age-standardized incidence rates (ASIR) increased by 18%, ASIR by 29%, and ASMR by 37% between 1990-2019. In absolute counts, the United States (US) had the highest numbers with 1.7 million incident cases (95% UI: 1.5–1.8 million), 106,954 deaths (95% CI: 95,861–114,383), and 2.2 million DALYs (95% CI: 2.1–2.4 million) in 2019. Japan, Mexico, Germany, and Turkey followed suit. When comparing ASR, the US had the highest ASR (1.8 million), followed by Japan, Mexico, and Germany, and then Turkey. When comparing ASMR, the US had the highest ASMR (1.03 million), followed by Japan, Mexico, and Germany, and then Turkey.

Conclusions: CKD represents a significant burden in the 38 OECD countries. The high prevalence rates, association with cardiovascular disease, economic costs, health disparities, and impact on quality of life emphasize the need for comprehensive strategies to address CKD.

SA-OR30
The Risk of CKD in Lithium-Treated Individuals
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Background: The use of lithium may contribute to chronic kidney disease (CKD) but studies have yielded conflicting results. The aim of this study was to examine the risk of developing CKD stage 3 and above among persons treated with lithium.

Methods: This was a retrospective cohort study of all persons in Iceland using lithium in the years 2008-2018. Patients with affective disorders (ICD-10 codes F30-F39) attending the outpatient clinics of the Landspítali–The National University Hospital Mental Health Services in 2014-2016 who had not been prescribed lithium served as controls. CKD stages 3-5 was defined as eGFR <60 mL/min/1.73 m², eGFR was calculated using the serum creatinine (SCr) based CKD-EPI equation. Individuals with fewer than 2 SCr measurements during the study period and those with CKD stages 3-5 prior to 2008 were excluded. Cox regression was performed to assess the risk of CKD associated with lithium treatment in a time dependent manner, adjusting for important confounding factors where acute kidney injury (AKI), hypertension, diabetes mellitus (DM) and cardiovascular diseases were treated as time-dependent covariates.

Results: A total of 2760 persons received lithium treatment during the study period, of whom 2046 (74.1%) were included in the study. Of those, 221 (10.9%) developed CKD stages 3-5. Of the 1615 persons in the control group, 1220 (75.6%) were included, of whom 39 (3.2%) developed CKD 3-5. Lithium use was associated with incident CKD (hazard ratio [HR] 1.93, 95% confidence interval [CI] 1.37–2.74) in the adjusted model. Age per year (HR 1.03, 95% CI 1.02–1.04), initial eGFR per mL/min (HR 1.73 m²[HR 0.96, 95% CI 0.92–0.99]), DM (HR 1.73, 95% CI 1.15–2.48) and AKI (HR 1.89, 95% CI 1.32–2.74) were other significant CKD risk factors. When compared to individuals not exposed to lithium the HR for CKD in adjusted analysis was 1.24 (95% CI 1.08–1.41) for those with mean lithium concentration of 0.8–0.99 mmol/L, 2.89 (95% CI 1.97–4.22) for those with mean lithium concentration of 0.60–0.79 mmol/L, and 5.23 (95% CI 3.31–8.26) for those with mean lithium concentration of 0.8–0.99 mmol/L.

Conclusions: Long-term lithium use is associated with risk of CKD in a concentration-dependent manner among patients with bipolar and unipolar mood disorders. Therefore, the mean blood concentration of lithium should be kept as low as possible for adequate mood stabilization and treatment.

Funding: Government Support - Non-U.S.

SA-OR31
CKD Among Childbearing Age Women in the United States: NHANES 1999-2018
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Background: Previous studies reported 3% and up to 6% prevalence of CKD among pregnant women and women of childbearing age in high income countries, respectively. However, the prevalence and severity of CKD among women of childbearing age (20-49) in the US has not been well characterized. We aimed to examine this epidemiology evidence gap in a representative sample of the US adult population.

Methods: We analyzed data from the National Health and Nutrition Examination Survey (NHANES), 1999-2018. The definition of childbearing age was derived from the CDC vital and health statistics report. We used KDIGO guidelines to define CKD and the prognosis risk categories. We examined common kidney risk factors in the age group between 20 to 49, including eGFR, albuminuria, blood pressure, HbA1c, glucose, hemoglobin, BMI, and lipids. We used Poisson regression to estimate the CKD prevalence ratio comparing women to men in this age group.

Results: The weighted period prevalence of CKD among childbearing age women in the US was 7.51%, while the prevalence of CKD among men in the same age group was 5.08%. Non-Hispanic black and Hispanic women of childbearing age had higher prevalence of CKD (9.10%). Fig 1 shows that more than 1 in 5 CKD patients had moderately increased KDIGO risk and more than 1 in 14 CKD patients had high/very high KDIGO risk were women of childbearing age. The percentage of Hispanics was higher among childbearing age females (20.2%) compared to females 50 (36.4%) in CKD patients. After adjusting for race/ethnicity and age, female gender was independently associated with 47% increased prevalence for CKD in the childbearing age group (PR=1.47, 95% CI 1.32, 1.63), yet female CKD patients showed largely more favorable profiles of common kidney risk factors compared to their male counterparts.

Conclusions: Our study highlighted that women of childbearing age had disproportionately higher prevalence of CKD in the US, especially among Hispanic women, than previously reported. Our findings quantify disparities and highlight the need and gaps in kidney/reproductive health among one of the most vulnerable populations in CKD patients.
SA-OR32
Mortality and Transplant After Delivering on Hemodialysis: A Matched Cohort Study
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Background: Rates of successful pregnancies among women with ESKD on hemodialysis (HD) are increasing, however, more risk of preeclampsia and cesarean delivery remain high. Subsequent mortality and transplantation after delivery on HD are unknown.

Methods: Using USRDS data, women treated with HD who delivered an infant between 2002 and 2019 were identified from ICD-9-10-CM codes and matched up to 1:4 by age, vintage, race and ethnicity, and diabetes as primary cause of ESKD to contemporary women on HD who did not deliver. We assessed mortality and transplantation rates over time. A Cox proportional hazards model was fit to compare mortality and transplantation rates between delivering and non-delivering women. Logistic regression was used to evaluate 1 and 5 year transplant rates for delivering vs. non-delivering female patients. All models were adjusted for age, vintage, BMI, race, Hispanic ethnicity, incident comorbidities, area deprivation index, rural-urbanicity, nephrology care pre-ESKD, Medicare insurance, and prior transplant history; patient waitlist status and PRA values were also adjusted in the transplant models.

Results: 1,109 delivering women were matched to 4,404 non-delivering women. Unadjusted mortality and transplantation rates for delivering vs non-delivering women were 4.5 vs 7.2 and 6.0 vs 8.6 per 100 patient-years, respectively (Figure). In adjusted models, the HR (95% CI) for mortality and transplant are 0.69 (0.64, 0.74; p<0.0001) and 0.76 (0.71, 0.81; p<0.0001), respectively, in delivering compared to non-delivering women. 1 and 5 year transplantation rates were lower in delivering women compared to non-delivering women.

Conclusions: While pregnancy on hemodialysis is associated with significant risk of preeclampsia and preterm delivery, delivery on hemodialysis was associated with a lower risk of subsequent mortality. Residual confounding may explain superior survival of delivering women vs. non-delivering women, however persistently lower transplant rates in delivering women warrant further research.

Funding: NIDDK Support

SA-OR33
Performance of Creatinine-Based GFR Estimating Equations in Young Adults
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Background: In the United States, GFR is estimated using serum creatinine and the 2021 CKD-EPI equation for individuals ≥ 18 years or the 2021 CKD-U25 equation for those 1-25 years with CKD. These equations may result in different eGFR values at 18 years and older, leading to uncertainty in level of GFR.

Methods: We compared the CKD-EPI, CKD-U25, and European Kidney Function Consortium (EKFC) equations in young adults (aged 18 to 40 years) in an independent dataset from which all three equations were developed (1491 participants from 21 studies). Performance compared to measured GFR was assessed as bias (median difference between mgFR and eGFR) and percentage of eGFR within 30% of mgFR (%P30).

Results: Mean (SD) age was 31.7 (6.0) years and mgFR was 92.7 (32.7) mL/min/1.73m2. The equations provided similar estimates for participants with eGFR less than 60 mL/min/1.73m2. At eGFR a 60, CKD-EPI yielded higher eGFR (Figure). For the CKD-EPI equation, there was minimal bias between mgFR and eGFR overall ([–0.5 (95%CI -1.5 to 0.7) mL/min/1.73m2], with small variation by GFR. In contrast, the CKD-U25 equation moderately underestimated mgFR overall [7.2 (6.1, 8.3) mL/min/1.73m2], with larger bias at higher levels of eGFR. There was greater variation by age groups with CKD-U25 than CKD-EPI, with larger bias at younger adult ages for CKD-U25 (e.g. age 18-25 year, 12.0 (7.7, 15.5) for CKD-U25 vs -3.3 (-5.0, 0.0) for CKD-EPI) vs older age (e.g. age 35-40, 4.8 (2.8, 6.7) for CKD vs 1.0 (-0.3, 2.2) for CKD-EPI. Results for EKFC were similar to that of CKD-U25, with underestimation at higher levels of GFR and in the younger age group.

Conclusions: The results support use of the 2021 CKD-EPI equation for reporting of eGFR by clinical laboratories in individuals older than 18 years of age. For young adults with childhood CKD, our results support continuing use of the CKD-U25 equation, during the transition to adult services, to maintain consistency of eGFR. Additional research in young adults to resolve differences observed at high levels of GFR and refine recommendations for use of eGFR equations is needed.

Funding: NIDDK Support

SA-OR34
Discrepancy Between eGFR Cystatin C and eGFR Creatinine in Recently Hospitalized Adults
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Background: Having a lower estimated glomerular filtration rate using cystatin C (eGFRcys) than creatinine (eGFRcr) is associated with a higher risk of cardiac disease and death in the outpatient setting. However, the distribution of this discrepancy and its prognostic values in recently hospitalized adults are not well described.

Methods: In 1534 hospitalized adults enrolled in the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) cohort, we compared the difference between eGFRcys and eGFRcr at 3 months after discharge. We used survival analysis to determine the associations between differences in eGFRcys and eGFRcr and risk of end-stage kidney disease (ESKD), major adverse cardiac events (MACE), first heart failure hospitalization, and death after a median follow up of 4.7 years.

Results: The mean age of study participants was 64.5 years, 37.3% are female, and 50% had AKI during hospitalization. At 3 months after hospitalization, eGFRcys was lower than eGFRcr by a large margin (Table). The difference between eGFRcys and eGFRcr at 3 months was 4.4% (2.4%- 6.5%) and 7.1% (3.8%- 10.5%) larger in those with AKI and sepsis during hospitalization, respectively. Having a lower in eGFRcys than eGFRcr was further associated with a higher risk of MACE, heart failure, ESKD, and death (Table), and these associations are consistent in participants with and without AKI (p for interaction with AKI all > 0.1).

Conclusions: By systematically measuring eGFRcys and eGFRcr in a cohort of recently hospitalized adults, we found that having lower eGFRcys than eGFRcr is commonly observed and provides additional prognostication for adverse clinical events.

Funding: NIDDK Support
SA-OR35

Comprehensive Evaluation of CKD Heat Map


Background: The 2012 KDIGO heat map framework for CKD analyzed five outcomes in 1.2 million participants. We comprehensively evaluated this framework using new equations for eGFR using creatinine alone and in combination with cystatin C (eGFRcr and eGFRcr-cys; CKD-EPI 2021 and EKFC) and more categories of albuminuria, assessing their individual and combined associations with ten adverse outcomes, overall and by age, sex, diabetes, and cardiovascular disease.

Methods: Individual-level data analysis: 27,503,140 participants from 114 global cohorts (eGFRcr); 720,736 participants from 20 cohorts (eGFRcr-cys). Outcomes: kidney failure with replacement therapy, all-cause mortality, cardiovascular mortality, acute kidney injury, hospitalization, coronary heart disease, stroke, heart failure, atrial fibrillation, and peripheral artery disease.

Results: Mean participant eGFRcr was 90 ml/min/1.73 m$^2$ (SD, 22) and median ACR was 11 mg/g (interquartile range 8-16 mg/g). Lower eGFRcr and higher ACR were associated with higher risk of all ten adverse outcomes, including in the mildest categories of CKD (eGFR 45-59 ml/min/1.73 m$^2$ and ACR <30 mg/g, or ACR 30-299 mg/g) and within subgroups. Associations were generally stronger and with less U-shape in the higher range of eGFR for eGFRcr-cys compared with eGFRcr.

Conclusions: This comprehensive evaluation of the heatmap framework in >27 million people demonstrated that the framework holds for associations with previous endpoints as well as novel kidney and cardiovascular endpoints; across subgroups of age, sex, diabetes, and cardiovascular disease; and for different GFR equations, including those incorporating cystatin C.

Funding: NIDDK Support, Private Foundation Support

SA-OR36

Hospital Health Care Costs Following Incident CKD in Japan, Sweden, and the United States

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Background: Chronic kidney disease (CKD) affects an estimated 10% of the global population. It is associated with cardiorenal complications (e.g. end stage kidney disease and heart failure [HF]), premature mortality, and high healthcare burden and costs. Here we assess hospital healthcare costs following incident CKD.

Methods: This study uses secondary data from electronic health records or claims data sources from Japan, Sweden and the US. Adult patients with incident CKD (defined as having either: two estimated glomerular filtration rate [eGFR] measurements ≥90 days apart of ≤60 mL/min/1.73 m$^2$ or an eGFR measurement ≤60 mL/min/1.73 m$^2$ followed by a CKD diagnosis) were identified during 2016–2023. Cumulative costs per patient for hospitalizations associated with a main diagnosis of HF, CKD, myocardial infarction (MI), stroke or peripheral artery disease (PAD) were summarized for up to 5 years after index (date of second eGFR measurement or CKD diagnosis).

Results: Overall, 549,884 patients were included (Japan, 74,285; Sweden, 76,133; US, 399,466). In Japan, Sweden and the US, respectively: median ages were 81, 78 and 74 years; 54%, 48% and 37% were males; and across countries the majority (68%) of patients did not have type 2 diabetes. Median eGFR measurements were similar across countries. Hospital healthcare costs associated with cardio renal events (CKD and HF) were high (Figure). Atherosclerotic cardiovascular disease (MI, stroke and PAD) contributed less to hospital healthcare costs.

Conclusions: Hospital healthcare costs were high and largely driven by cardio renal events (CKD and HF) among patients with incident CKD. This was consistent across all three countries, despite differences in healthcare systems.

Funding: Commercial Support - AstraZeneca
SA-OR37
External Validation of the Klinrisk Model in US Commercial, Medicare Advantage, and Medicaid Populations
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Background: Chronic kidney disease (CKD) is typically undiagnosed till the majority of kidney function (eGFR) is lost. Accurate risk prediction tools for progressive CKD can enable early intervention for high risk individuals. The Klinrisk machine learning model accurately predicts progressive CKD using routinely collected laboratory data. We aimed to validate this model in US commercial, Medicare Advantage, and Medicaid populations.

Methods: The Klinrisk random survival forest model predicts progressive CKD (40% decline in eGFR or kidney failure) using the values of age, sex, and 20 laboratory variables, including results from complete blood cell counts, chemistry panels, comprehensive metabolic panels, and urinalysis. We assessed model performance at 2- and 5-years post-index (first available serum creatinine result) in patients with/without urinalysis results available (albumin-to-creatinine ratio, protein-to-creatinine-ratio, and serum quantitative dipstick) in a large representative US population. Performance was assessed with discrimination (area under the receiver operating characteristic curve), Brier scores, and calibration plots.

Results: A total of 4,410,131 patients were evaluated with commercial insurance, 341,666 with Medicare Advantage, and 93,056 patients with Medicaid coverage. Discrimination was excellent across all forms of payor and with or without the results of urinalysis. In all cohorts, for prediction of the progression, AUCs ranged between 0.80 to 0.83 at 2 years, and 0.78 to 0.83 at 5 years. When urinalysis data were available, AUCs ranged between 0.81 to 0.87 at 2 years, and 0.80 to 0.87 at 5 years (Table). Brier scores were below 0.071 (0.068 to 0.075) for each combination of urinalysis availability and insurer type.

Conclusions: A machine model trained on routine laboratory data can predict progression of CKD in a large representative US population of adults with or at risk for kidney disease. Implementation of the Klinrisk model can help identify patients who benefit from early intervention to delay CKD progression and reduce health care costs.

SA-OR38
The Effect of Thiazide Diuretics on Urinary Prostaglandin E2 Excretion and Serum Sodium in the General Population

Background: Recent data suggest that thiazide-induced hyponatremia (THI) is induced by prostaglandin E2 (PGE2)-mediated water reabsorption and that people with a single nucleotide polymorphism (SNP) in SLC2A1 are more susceptible for THI. Here, we hypothesize that higher urinary PGE2 excretion is also associated with lower serum sodium in the general population and that this association is stronger in thiazide users. Methods: PGE2 and its metabolite PGEM were measured in spot urine from the population-based Rotterdam Study cohort and expressed as ratio with creatinine. The association between PGE2 and serum sodium and its interaction with thiazide use was analyzed using regression analysis with adjustments for potential confounders (sex, age, BMI, baseline eGFR, smoking status, systolic blood pressure, ACE-inhibitor use). A propensity score-match cohort was generated by matching on the same confounders in addition to serum potassium and diabetes status. The contribution of SNPs was analyzed using genome wide association studies (GWAS).

Results: 2178 patients were included in the analysis (65% female, age 64 ± 8 years). Thiazide users (n=190) had a significantly lower serum sodium compared to non-thiazide users (140.9 vs. 141.3 mmol/l, p=0.007) but had similar urinary PGE2 (101.7 vs. 101.5 pg/mmol, p=0.7) and PGEM (55.6 vs. 56.3 pg/mmol, p=0.6) excretions. Urinary PGE2 and PGEM excretions were negatively associated with serum sodium in the multivariable analysis (PGE2: p=0.002, PGEM: p=0.001) and this association was stronger in thiazide users (Figure 1). Similar findings were observed in the propensity score matched cohort. The GWAS data is currently being analyzed.

Conclusions: Urinary PGE2 and PGEM excretions are higher in people with lower serum sodium and this association is stronger in thiazide users. Our findings provide further evidence for the role of PGE2 in renal water handling, even within the normal range of serum sodium, and its potential contribution to hyponatremia and THI.

SA-OR39
The Plasma Metabolome and Risk of Incident Kidney Stones
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Background: The pathogenesis of kidney stone disease is not completely understood. Information on metabolomic profiles in kidney stone formers is limited, with most studies focusing on urine metabolomics or on pediatric populations using cross-sectional designs. To examine independent associations between plasma metabolomic profiles and the risk of incident, symptomatic kidney stones in adults, we conducted prospective nested case-control studies in two large cohorts.

Methods: We performed plasma metabolomics on 1,758 participants, including 879 stone formers (346 from the Health Professionals Follow-up [HPFS] cohort, 533 from the Nurses’ Health Study [NHS] II cohort) and 879 non-stone formers (346 from HPFS, 533 from NHS II) matched for age, race, time of blood collection, fasting status and (for NHS II) menopausal status and luteal day of menstrual cycle for premenopausal participants. Conditional logistic regression models were used to estimate the odds ratio of kidney stones corresponding to a one standard deviation increase in metabolite levels, adjusted for covariates. A plasma metabolite based score reflecting risk of incident kidney stones was developed in each cohort in a conditional logistic regression model with a lasso penalty. The scores derived in the HPFS (‘KMS_HPFS’) and the NHS II (‘KMS_NHS’) were each tested for its association with kidney stone risk in the other cohort.

Results: In each cohort, a variety of individual metabolites were associated with incident kidney stone formation at prespecified levels of metabolome-wide statistical significance. We identified three novel metabolites associated with kidney stones in both HPFS and NHS II, all with inverse associations with kidney stones risk: beta-cryptoxanthin, sphingomyelin (d18:2/24:1, d18:1/24:2), and sphingomyelin (d18:2/24:2). The standardized KMS_HPFS yielded an OR for stones in the NHS II cohort of 1.23 (95% CI 1.05, 1.44; p-value = 0.008). The standardized KMS_NHS was in the expected direction but did not reach statistical significance in HPFS (OR 1.16, 95% CI 0.97, 1.39; p-value = 0.10).
Conclusions: The findings of specific metabolites associated with kidney stone status in two cohorts as well as a plasma metabolomic signature in stone formers offers a novel approach to characterize stone formers and to elucidate the pathogenesis of stone formation with the future potential to personalize therapeutic approaches.

Funding: NIDDK Support

SA-OR40
Dietary Potassium and Potassium Supplementation Differentially Affect Plasma Potassium in Patients with CKD
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Background: Guidelines advise increased potassium (K⁺) intake to prevent hypertension and cardiovascular disease, but whether patients with chronic kidney disease (CKD) can safely increase K⁺ intake is unknown.

Methods: We performed a systematic review and meta-analyses of intervention studies that assessed the acute or short- to long-term effects of increased K⁺ intake on plasma K⁺ in patients with CKD. Studies were eligible if they studied the effects of specified amounts of dietary K⁺, K⁺ supplementation, or K⁺-enriched salt substitution in patients with CKD and provided plasma K⁺ at baseline and end of study (for pre-post intervention studies) or at end of study in control and intervention groups (for randomized trials).

Results: Fourteen eligible studies were identified (2 randomized, 12 pre-post intervention studies). K⁺ supplementation for five to days to two years increased plasma K⁺ by on average 0.7 (95% confidence interval, 0.2-1.1) mmol/L and caused hyperkalemia in 4.3% (3 studies, 370 participants). In contrast, increased dietary K⁺ intake for two weeks to three years did not significantly increase plasma K⁺ (7 studies, 275 participants). One study reported two hyperkalemia occurrences on the high K⁺ diet, another study reported lower hyperkalemia incidence on the high K⁺ than on the low K⁺ diet, and five studies reported that no hyperkalemia occurred. These results suggest that increased dietary K⁺ intake may be safer than K⁺ supplementation (Table). However, they do not rule-out the risk of postprandial hyperkalemia, i.e. hyperkalemia occurring after a K⁺-rich meal. Unfortunately, no studies assessed the acute effects of a K⁺-rich meal on plasma K⁺ in CKD patients. K⁺ supplementation increased plasma K⁺ by 1.2 (95% confidence interval, 0.9-1.6) mmol/L (4 studies, 35 participants). We found no studies that assessed the safety of K⁺-enriched salt substitution in CKD.

Conclusions: In the short- to long-term, K⁺ supplementation increases plasma K⁺ and the risk of hyperkalemia, although the majority maintains normokalemia. Conversely, increased dietary K⁺ intake does not increase plasma K⁺ in the short- to long-term. Whether a K⁺-rich meal causes postprandial hyperkalemia is unknown.

SA-OR41
HARMONIZE ASIA: A Phase 3 Study to Investigate the Safety and Efficacy of Sodium Zirconium Cyclodextrin in Patients with Hyperkalemia in China
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Background: Sodium zirconium cyclodextrin (SZC) is an oral potassium (K⁺)-lowering therapy for adults with hyperkalemia (HK). HARMONIZE ASIA (NCT03528681) evaluated SZC safety and efficacy in patients (pts) with HK in China.

Methods: This Phase 3, randomized, double-blind, placebo (PBO)-controlled study recruited pts with serum K⁺ (sK⁺) ≥5.1 mmol/L at 35 sites in China. Pts received SZC 5 g, 10 g, or 20 g (0.04 mmol of SZC) or PBO once daily for 7 days. The primary endpoint was the increase in sodium levels from baseline to end of study (for pre-post intervention studies) or at end of study in control and intervention groups (for randomized trials). We performed a systematic review and meta-analyses of intervention studies that assessed the acute or short- to long-term effects of increased K⁺ intake on plasma K⁺ in patients with CKD. Studies were eligible if they studied the effects of specified amounts of dietary K⁺, K⁺ supplementation, or K⁺-enriched salt substitution in patients with CKD and provided plasma K⁺ at baseline and end of study (for pre-post intervention studies) or at end of study in control and intervention groups (for randomized trials).

Results: Results: Seventeen patients were included (14 females, median age 68 [61, 79]). After 7 days of 90 g daily protein supplementation (n = 17), plasma sodium levels increased by a median of 3 mmol/L [0, 5], plasma urea by 5 mmol/L [1.7, 4.9] and urinary urea corrected for urine creatinine by 21.2 mmol/mmol [6.2, 29.1]. After 7 days of oral urea (n = 10), sodium levels increased by a median of 2 mmol/L [1, 3], plasma urea by 5.8 mmol/L [2.7, 9.2] and urinary urea corrected for urine creatinine by 31.0 mmol/mmol [18.7, 45.1].

Conclusions: Our findings suggest that a high-protein supplementation with placebo increases plasma sodium levels in patients with chronic HK through protein-induced urea reabsorption and osmotic diuresis. The effects are comparable to oral urea intake.

Funding: Commercial Support - OMANDA AG (provided study material, i.e., protein powder, but not any financial support), Private Foundation Support, Government Support - Non-U.S.

SA-OR42
Effect of Protein Supplementation on Plasma Sodium Levels and Urinary Urea Excretion in Patients with Chronic Syndrome of Inappropriate Antidiuresis (SIAD): A Monocentric Open-Label Proof-of-Concept Study
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Background: The syndrome of inappropriate antidiuresis (SIAD) can be treated with oral urea. We hypothesized that dietary proteins could increase free-water clearance through urea-induced osmotic diuresis and aimed to investigate the effect of a high-protein supplementation on plasma sodium levels in chronic SIAD.

Methods: This is a monocentric open-label proof-of-concept trial conducted at the University Hospital of Basel, Switzerland, between 10/2021 and 02/2023. Adult outpatients with chronic SIAD received 90 g protein daily for 7 days in the form of protein powder. After a wash-out period of at least a week, patients received 30 g of oral urea daily for 7 days. The primary endpoint was the increase in sodium levels from baseline to the end of the 7-day protein supplementation.

Results: Seventeen patients were included (14 females, median age 68 [61, 79]). After 7 days of 90 g daily protein supplementation (n = 17), plasma sodium levels increased by a median of 3 mmol/L [0, 5], plasma urea by 5 mmol/L [1.7, 4.9] and urinary urea corrected for urine creatinine by 21.2 mmol/mmol [6.2, 29.1]. After 7 days of oral urea (n = 10), sodium levels increased by a median of 2 mmol/L [1, 3], plasma urea by 5.8 mmol/L [2.7, 9.2] and urinary urea corrected for urine creatinine by 31.0 mmol/mmol [18.7, 45.1].

Conclusions: Our findings suggest that a high-protein supplementation with placebo increases plasma sodium levels in patients with chronic SIAD through protein-induced urea reabsorption and osmotic diuresis. The effects are comparable to oral urea intake.
SA-OR43
Safety and Efficacy of Proactive vs. Reactive Administration of DDAVP in Severe Symptomatic Hyponatremia: A Randomized Controlled Trial
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**Background:** DDAVP is effective in preventing and reversing overcorrection of hyponatremia. However, the recommended strategy for its use remains unclear and is based on retrospective data. This study aims to compare the safety and efficacy of proactive and reactive DDAVP strategies in severe symptomatic hyponatremia.

**Methods:** This randomized controlled trial included patients with severe symptomatic hyponatremia (serum sodium < 125 mmol/L) from June 20, 2022, to February 20, 2023. Patients were assigned to either the proactive group, which received DDAVP immediately after diagnosis, or the reactive group, which received DDAVP only if the serum sodium level tended to overcorrect. The primary outcome was the incidence of overcorrection between the two groups.

**Results:** The study enrolled 49 patients, with 24 in the proactive group and 25 in the reactive group. There was no significant difference in the incidence of overcorrection between the two groups (16.7% vs. 28.8%, P = 0.54), nor in the change of serum sodium levels at 1, 6, 12, and 24 hours. However, at 48 hours, the proactive group had a higher change in serum sodium levels than the reactive group (10.3 ± 3.6 vs. 7.7 ± 3.6, P = 0.013), but it remained within the safety range. The time to symptom improvement, total amount of intravenous fluid administered, dose of DDAVP, urine volume, length of hospital stay, incidence of ODS, and 28-day mortality did not differ significantly between the two groups.

**Conclusions:** This study found no significant difference in the incidence of overcorrection between the proactive and reactive strategies for treating severe symptomatic hyponatremia. However, future large studies are needed.

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SA-OR44
Monitoring Serum Potassium Concentration in Patients with Severe Hyperkalemia: The Role of Bloodless Artificial Intelligence (AI)-Assisted Electrocardiography
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**Background:** Severe hyperkalemia is a potentially life-threatening emergency requiring prompt recognition with rapid management and surveillance. Although bloodless artificial intelligence (AI)-enabled electrocardiography (EGG) provides real-time detection of severe hyperkalemia, its application to monitor blood potassium (K⁺) levels during management has not been evaluated. This study aimed to determine the value of Al-enabled ECG (AI-ECG) for blood K⁺ monitoring in patients with severe hyperkalemia.

**Methods:** This retrospective cohort study was performed at an emergency department (ED) of a single academic medical center over 2.5 years. Patients with true severe hyperkalemia defined as Lab-K⁺ ≥ 6.3 mmol/L with matched Al-ECG K⁺ ≥ 5.1 mmol/L were included. AI-ECG K⁺ was quantified by ECG12Net as developed previously. The ΔAG and Lab-K⁺ and Al-ECG K⁺ were measured almost simultaneously during or after K⁺-lowering therapy at least 2 times. Clinical characteristics, therapeutic intervention, and pertinent laboratory data were analyzed.

**Results:** Seventy-eight patients fulfilled the enrolled criteria. Most of them had acute on chronic kidney injury, advanced CKD not yet on dialysis, and dialysis-dependent renal failure. Their initial Lab-K⁺ and Al-ECG K⁺ were 7.2 ± 0.7 and 6.6 ± 0.5 mmol/L, respectively. During and after K⁺-lowering therapy, both Lab-K⁺ and Al-ECG K⁺ were significantly declined in parallel in the patients both treated medically (n=37) and with hemodialysis group (n=41). Of note, six patients showing persistent ECG-K⁺-hyperkalemia despite the normalized Lab-K⁺ levels.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
SA-OR47

Minimizing Hypoglycemia After Intravenous Insulin Regular Therapy for Hyperkalemia
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Background: Intravenous (IV) insulin regular is utilized for the management of hyperkalemia. There is data demonstrating that weight-based (0.1 unit/kg) insulin results in less hypoglycemia while maintaining equivalent efficacy. The objective of this project was to evaluate if weight-based IV insulin regular dosing would minimize rates of hypoglycemia at our institution.

Methods: This single-center, pre-post design project included adult patients with hyperkalemia (potassium > 5 mEq/L) treated with IV insulin regular in the emergency department at a large tertiary care medical center. Historical management utilized fixed-dose 10 units of insulin regular (pre-intervention group). Exclusion criteria were patients who received insulin products for indications other than hyperkalemia, treated with hemodialysis, or received uncontrollable dextrose fluids. The hyperkalemia order set was updated to 0.1 unit/kg IV insulin regular (maximum 10 units) and expanded point-of-care (POC) glucose monitoring from one hour to a total of four hours (post-intervention group). The primary outcomes were rates of hypoglycemia (blood glucose < 70 mg/dL) and severe hypoglycemia (blood glucose < 50 mg/dL). Secondary outcomes were reduction in potassium levels, administration of additional potassium lowering agents, and compliance to weight-based dosing and expanded POC monitoring.

Results: A total of 68 patients were included in the pre-intervention group and 58 patients in the post-intervention group. Hypoglycemia was more frequent in the pre-intervention group compared to the post-intervention group (26.5% versus 17.2%). Similar results were seen with severe hypoglycemia (7.3% versus 1.7%). The median reduction in potassium levels in the pre-intervention group was 0.95 mEq/L and 0.85 mEq/L in the post-intervention group. For patients who received insulin regular only and with no concomitant potassium lowering agent, the median reduction in potassium in the pre-intervention group was 0.7 mEq/L (IQR 0.5-1.55) compared to 0.85 mEq/L (0.35-1.33). There was 36.2% compliance with weight-based insulin regular dosing and 0% compliance in the post-intervention group.

Conclusions: This project found that using weight-based insulin regular dosing may lead to a reduction in hypoglycemia, especially severe hypoglycemia, without needing additional potassium lowering agents.

SA-OR48

Role of Midodrine in Prevention of Intradialytic Hypotension: A Randomized Cross-Over Controlled Trial
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Background: Intradialytic hypotension (IDH) is one of the most common complications in hemodialysis (HD) patients. It is associated with reduced quality of life as well as an increased risk of myocardial infarction and mortality. Although midodrine, an α-1 adrenergic receptor agonist, has been proposed as a potential benefit in the prevention of IDH and has demonstrated efficacy in some studies, its long-term use with normal dialysate calcium has not yet been established.

Methods: This cross-over, placebo-controlled trial recruited adult patients who received thrice-weekly HD and had frequent IDH during the past 3 months. Participants were randomized to receive either oral 10-mg midodrine or placebo pills. The administration of the drugs took place 30 minutes prior to each dialysis session over a duration of 2 months (24 sessions) in each phase, with a one-week washout period between phases. All patients were prescribed a dialysate calcium concentration of 2.5 mEq/L. The trial protocol for this study was registered at clinicaltrials.gov (NCT0251197003).

Results: In the midodrine treatment group, the incidence rate of IDH was significantly lower compared to the placebo group (8.5 vs. 16.0 events per 100 HD sessions, p = 0.004). Furthermore, the midodrine group demonstrated significantly reduced incidence rates of dizziness (7.7 vs 16.2 events per 100 HD sessions, p < 0.001) and headache (0 vs 1.3 events per 100 HD sessions, p = 0.04). However, there were no significant differences observed between the midodrine and placebo groups in terms of nadir systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR). Regarding safety, there were no significant differences in the incidence of adverse events between the two treatment groups.

Conclusions: Midodrine demonstrates safety and efficacy as a prophylactic intervention for IDH while also effectively mitigating symptoms of dizziness and headache in patients undergoing hemodialysis with a normal dialysate calcium concentration.

Funding: Commercial Support - Cosma trading Ltd, Government Support - Non-U.S.

SA-OR49

Association of Calcium Channel Blocker Use with Intradialytic Hypotension
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Background: Calcium channel blockers (CCBs) are commonly used as anti-hypertensive agents among patients receiving maintenance hemodialysis (HD). Despite this, little is known regarding the association of CCBs with intra-dialytic hypotension (IDH), an important adverse outcome that is associated with cardiovascular morbidity and mortality.

Methods: Using detailed data from kinetic modeling sessions of the Hemodialysis Study, random-effects regression models were fit to assess the association of CCB use versus not with IDH (defined as systolic blood pressure (SBP) <90 mm Hg if pre-HD SBP <160 mm Hg or <100 mm Hg if pre-HD SBP >160 mm Hg). Models were adjusted for age, sex, race, K/V assignment, flux assignment, heart failure, ischemic heart disease, peripheral vascular disease, diabetes mellitus, BUN, ultrafiltration rate, access type (catheter, fistula, graft), pre-HD SBP, and other anti-hypertensive use.

Results: Data was available for 1,838 patients and 64,538 sessions; at baseline 49% of patients were prescribed CCBs. The overall frequency of IDH was 14% with a mean decline from pre- to nadir-SBP of 33 ± 15 mmHg. CCB use was associated with a lower adjusted odds of IDH, compared with no use (OR 0.81; 95%CI 0.75, 0.87). The association was most pronounced for those with (OR 0.77; 95%CI 0.69, 0.86) versus without (OR 0.87; 95%CI 0.78, 0.98) a history of HF at baseline (P-interaction=0.05).

Conclusions: Among patients receiving thrice-weekly HD in the Hemodialysis study, CCB use was associated with a lower risk of developing IDH, independent of pre-HD SBP and other anti-hypertensive use. Mechanistic studies are needed to better understand the effects of CCB and other anti-hypertensive drugs on peri-dialytic blood pressure parameters among patients receiving maintenance HD.
**SA-OR50**

**Association Between Extended Ultrafiltration Rates and All-Cause Death in Patients Undergoing Extended-Hours Hemodialysis Using Time-Fixed and Time-Dependent Models: The LIBERTY Cohort**

Takahiro Imaizumi,1 Masaki Okazaki,2 Shoichi Matsumiya,1 Nagoya Daiyoku, Nagoya, Japan;1 University of California Irvine School of Medicine, Irvine, CA.

**Background:** Overhydration or excessive fluid removal during dialysis sessions is a risk factor for acute heart failure (CHF) death and death for dialysis patients, as evidence shows that the ultrafiltration rate (UFR) was associated with CHF and all-cause death. Studies have shown that extended-hours hemodialysis (EHDI, >18 h/w) improves various dialysis-related parameters such as hemoglobin, phosphate, and left ventricular hypertrophy as well as survival. Although EHDI may prevent congestion, the appropriate range of UFR in patients undergoing EHD is unknown.

**Methods:** Using data from 636 patients undergoing EHD in the LIBeralized diet Extende-houRs hemodialysis Therapy (LIBERTY) cohort, we examined the association between UFR and cause death in time fixed or time-dependent multivariable Cox models adjusted for dialysis conditions and laboratory data. UFR was calculated by fluid removal (mL) per hour divided by dry weight (kg) and averaged in a week (mL/h/kg).

UFR and covariates at baseline (within 6 months from EHD initiation) were used in the time-fixed model, while the mean values of UFR and covariates every 3 months in a time-updated manner were used in the time-dependent model.

**Results:** The mean age was 62 years and male participants comprised 65%. Median UFR was 7.0 mL/kg/h. The median time since starting dialysis was 1.8 [IQR, 0.1–5.6] years. During a median of 6.4 [IQR, 3.4–10.3] years, 230 patients died. Overall survival at 5 years from the baseline showed 75% of baseline UFR was not associated with all-cause death (Log-rank test P=0.091, Figure A). In the multivariable-adjusted models, baseline UFR was not associated with the outcome, while low or high time-updated UFR was associated with the outcome (Figures B and C).

**Conclusions:** UFR at the start of EHD was not associated with all-cause mortality, while time-updated UFR <7 mL/kg/h, which may represent reduced dietary intake, was associated with short-term prognosis.

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

**SA-OR51**

**Impact of ESRD on Stroke Risk in Atrial Fibrillation Patients**

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**Background:** Patients with end-stage renal disease (ESRD) are at higher risk of atrial fibrillation (Afib) due to multiple underlying factors. However, the impact of concomitant Afib and ESRD on stroke risk is now well established. The purpose of this study is to evaluate the impact of concomitant Afib and ESRD on stroke risk compared to individuals with Afib alone.

**Methods:** The national inpatient sample (NIS) database 2016-2018 was used to identify individuals with Afib using ICD-10 codes. Patients with age less than 18 or those with history of stroke were excluded. 1:1 propensity matching was used to match patients with ESRD to those without ESRD on different comorbidities. Univariate analysis pre- and post-match were performed. Binary logistic regression was performed after matching to assess whether ESRD was independently associated with stroke risk. A p-value of <0.05 was considered statistically significant.

**Results:** A total of 1,749,172 patients were included in the study with 89,741 being ESRD. ESRD patients were younger and had higher prevalence of baseline comorbidities except for COPD, CAD, and smoking. Oral anticoagulation use and aspirin use was less in ESRD patients. On univariate analysis, ESRD patients had significantly lower ischemic stroke (1.8% vs 2.9%), hemorrhagic stroke (0.3% vs 0.6%), transient ischemic attack (TIA) (0.4% vs 0.7%). However, mortality was higher in ESRD group (8.1% vs 4.8%). Post-match analysis showed that ESRD patients had significantly lower ischemic stroke [OR: 0.59], hemorrhagic stroke [OR: 0.37] and TIA [OR: 0.76] along with higher mortality [OR: 1.95].

**Conclusions:** Concomitant presence of Afib and ESRD was associated with a lower stroke rates compared to Afib alone. The platelet dysfunction associated with ESRD along with time-updated UFR <7 mL/kg/h, which may represent reduced dietary intake, was associated with short-term prognosis.

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

**SA-OR52**

**Use and Association of Rate Control and Anti-Arrhythmic Medications with Risk of Subsequent Stroke and Mortality Among Hemodialysis Patients with Atrial Fibrillation**

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**Background:** Atrial fibrillation (AF) is highly prevalent amongst patients with kidney failure on maintenance dialysis and is associated with poor clinical outcomes. Treatment of AF in this population is particularly challenging, as associations of the core AF management strategies of antithrombotic and rate-control medications with clinical outcomes in dialysis patients is unknown.

**Methods:** We evaluated patients with kidney failure on maintenance dialysis and incident AF from Kaiser Permanente Northern and Southern California. We evaluated associations between time-updated use of rate-control medications alone, antiarrhythmic medications alone, use of both medications, and use of neither medication (referent group) with the composite outcome of ischemic stroke and all-cause mortality using Cox regression models, with adjustment for multiple covariates.

**Results:** Among a total of 2,100 patients, 44.0% were newly initiated on rate-control medications alone, 6.6% on antiarrhythmic medications alone, 8.5% on both, and 42.9% were on neither medication within 12 months of incident AF diagnosis. Over a median (IQR) follow-up of 1.66 (0.45, 3.39) years, we observed 1,406 composite events. Use of antiarrhythmic medications alone (adjusted HR 0.73, 95% CI 0.57–0.93), or both medications (adjusted HR 0.70, 95% CI 0.56–0.88) was associated with lower ischemic stroke or death compared to neither medication use (Table). Use of rate-control medications alone was not associated with decreased risk for the composite outcome.

**Conclusions:** While the use of antiarrhythmic medications was low in AF patients on maintenance dialysis, antiarrhythmic medication use alone or with rate-control medications was associated with decreased risk of ischemic stroke or all-cause mortality. Future trials are needed to confirm the efficacy and safety of antiarrhythmic medications in dialysis patients.

**Funding:** NIDDK Support, Other NIH Support - NHLBE: R01 HL142384, Private Foundation Support

**SA-OR53**

**Hemoglobin Stability in the ASCEND-TD Trial**

Anjali Acharva,1 Anjay Rastogi,2 Vivekanand Jha,3 Ajay K. Singh,4 Amy M. Meadowcroft,5 Purav R. Bhatt,6 Angela R. Leon-Jones,6 Jennifer Shannon,7 Jaebin El Sayegh.1 1University of California Los Angeles, Los Angeles, CA; 2George Institute for Global Health, New Delhi, India; 3Kaiser Permanente Northern California, Oakland, CA; 4Brigham and Women's Hospital and Harvard Medical School, Boston, MA; 5GlaxoSmithKline, Collegeville, PA.

**Background:** Daprodestat (Dapro), a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI), has been investigated as a treatment for anemia of chronic kidney disease (CKD) in the ASCEND program. Maintaining hemoglobin (Hb) levels in the target range per clinical guidelines for patients (pts) with CKD is complex. Primary efficacy results for daprodustat administered three times weekly (TW) are reported (Coyne DW, CJASN 2022). Here we examine additional Hb stability data of Dapro dosed TW, compared to epoetin alfa (EPO) or darboepoetin alfa (Dapro) dosed TH.

**Methods:** ASCEND-TD (NCT03400033) was a randomized, double-blind, double-dummy, active comparator study evaluating the efficacy and safety of Dapro dosed over 52 weeks compared with epoetin alfa (EPO) in pts receiving hemodialysis. Various Hb stability measures were assessed in a pre-specified manner. Responders were defined as pts with mean Hb within the Hb analysis range (10–11.5 g/dL) during the evaluation period (EP, Weeks 28–52).

**Results:** 322/407 (79%) pts had evaluable Hb during the EP. The difference in response rate (daprodustat-EPO) was 0.1645 (95% CI [0.06, 0.27]) and demonstrated nominal superiority. Median time Hb was in the analysis range [% interquartile range] was higher in pts administered Dapro compared with pts administered EPO (70.83 [50.98; 91.07] and 61.76 [29.69; 85.19], respectively). The Hodges-Lehmann estimate of the median treatment difference (daprodustat-EPO) of 11.18% met non-inferiority. Dapro TW was also nominally superior to EPO for percentage of time Hb was within the analysis range [% interquartile range] according to the van Elteren test (P=0.0034; Table). The proportion of pts with evaluable Hb <7.5 g/dL and ≥12 g/dL during the EP and the proportion of time Hb ≥12 g/dL during the EP was lower in pts administered Dapro compared with pts administered EPO.

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

Underline represents presenting author.
Conclusions: In ASCEND-TD, Dapro TIW demonstrated a potential benefit in maintaining stable Hb compared with EPO. Further analysis is required to understand this effect and to provide conclusive evidence of better Hb stability for Dapro compared with EPO.

Funding: Commercial Support - The study and this analysis were funded by GSK.

Table 1. Analyzed results within the analysis range during the EPO vs. Dapro group analyses

<table>
<thead>
<tr>
<th>Group</th>
<th>Dependent (n=275)</th>
<th>EPO (n=277)</th>
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<tbody>
<tr>
<td>Hb</td>
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<td>Pre-dialysis</td>
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<td>Post-dialysis</td>
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Methods: A total of 372 hemodialysis patients were enrolled from a prospective multicenter cohort study. We measured four plasma ECM-associated proteins: matrix metalloproteinase (MMP-2, MMP-9, laminin-C, and thrombospondin-2. The primary outcome was set as a composite of cardiac and noncardiac vascular events.

Results: Plasma MMP-2 levels were significantly higher in patients with future CV events than in those without (p = 0.003), while the others were not. All the measured molecules had significant correlations with NT-proBNP levels, but the correlation coefficient was most strong with plasma MMP-2 (Rho = 0.317, p < 0.001). In logistic regression analysis, elevated plasma MMP-2 levels were independently associated with LV diastolic dysfunction (adjusted OR [OR] per standard deviation, 1.48; 95% confidence interval [CI], 1.05 – 2.08; p = 0.024). Cox regression analysis showed that plasma MMP-2 levels were associated with a 1.30-fold risk for the composite of CV events (per a standard deviation increase; 95% CI, 1.04 – 1.63; p = 0.022) after modelled adjustments.

Conclusions: Plasma MMP-2 levels were independently associated with an increased risk of LV diastolic dysfunction and adverse CV outcomes in hemodialysis patients. Our results suggest that MMP-2 levels can be a useful biomarker in identifying hemodialysis patients at high risk of future CV events.

SA-OR54

Depletion of Plasma Aromatic Amino Acids During Hemodialysis Is Associated with Fatigue
Subrata Baek,1 Jose M. Garcia, Niklesh Akula, Kumar Sharma, Carlos Lorenzo. The University of Texas Health Science Center at San Antonio, San Antonio, TX.

Background: The etiology of fatigue in hemodialysis (HD) patients remains elusive. Aromatic amino acids (AAA – tyrosine, phenylalanine, and tyrosine), the precursors of neurotransmitters serotonin, dopamine, and norepinephrine, are implicated in the pathogenesis of fatigue. A significant amount of AAA is lost during a dialysis. We examined the association of changes in AAA during a dialysis session with fatigue.

Methods: 114 adult HD patients self-reported fatigue on a dialysis day using validated Fatigue Inventory. Pre- and post-dialysis plasma AAA levels were measured by HPLC-mass spectrometry. Spearman correlation was used to assess the relationship between AAA levels and fatigue.

Results: Post-dialysis plasma levels of phenylalanine and tyrosine decreased significantly compared to the baseline pre-dialysis levels except for tryptophan (p < 0.0001, 0.04, and 0.62, respectively). None of the pre-dialysis plasma levels of amino acids were associated with fatigue (p > 0.05 for all correlations). Post-dialysis plasma levels of phenylalanine, tryptophan, and AAA correlated inversely with fatigue score (p < 0.05 for all correlations). The relative decline (post – pre/pre values) in phenylalanine, tyrosine, and AAA levels during dialysis was positively correlated with fatigue score (p < 0.05 for all correlations). Compared to the HD patients in the lowest tertile of fatigue score, those in the highest tertile had greater relative decline in plasma AAA levels between pre- and post-dialysis (p = 0.045) (Figure).

Conclusions: Plasma AAA depletion during a dialysis session is associated with fatigue, suggesting possible neurotransmitters imbalance as a contributory factor. Future studies are warranted to explore the role of neurotransmitters to the pathogenesis of HD fatigue using functional MRI.

SA-OR55

Association Between Circulating Extracellular Matrix (ECM)-Associated Molecules and Cardiovascular Outcomes in Hemodialysis Patients Jihyun Back,1 Yu ho Lee,1 So-young Lee,1 Hyeeyun Jeong,1 Jin sug Kim,2 Hyeon Seok Hwang,2 CHA Bundang Medical Center, Seongnam, Gyeonggi-do, Republic of Korea; 3Kyung Hee University, Seoul, Republic of Korea.

Background: The extracellular matrix (ECM) is a complex network of non-cellular components that provide structural support for the tissues. Circulating ECM-associated molecules are increased during cardiovascular (CV) remodeling process and can be potential biomarkers of adverse CV outcomes. However, their clinical significance in hemodialysis patients is unclear.

Methods: We conducted a cross-sectional study including patients receiving hemodialysis in three hospitals in Shanghai. All patients completed the Montreal Cognitive Assessment Basic (MoCA-B). To evaluate the effectiveness of MoCA-B score for screening MCI, a subset group underwent neuropsychological batteries. Serum proteomes were compared in patients with normal cognitive function and dementia undergoing HD. Plasma Aβ40/Aβ42 and total tau were measured using a single molecule array.

Results: A total of 311 patients undergoing hemodialysis were enrolled (mean age, 63 years; 55% male). The best cut-off score of MoCA-B for differentiating MCI and normal cognition was 24 with an area under the curve of 0.84. Serum proteomics revealed that neurodegenerative pathways related to Alzheimer’s disease were enriched in patients with dementia undergoing hemodialysis. The plasma Aβ40/Aβ42 ratio was significantly reduced in patients with MCI and dementia. The plasma Aβ42/Aβ40 ratio was independently associated with cognitive function after adjusting for age, sex, and educational levels.

Conclusions: We demonstrated that MoCA-B as an optimal cognitive function screening instrument for MCI in patients undergoing hemodialysis. The plasma Aβ42/Aβ40 ratio was a potential biomarker in distinguishing normal cognition, MCI, and dementia in populations undergoing hemodialysis.

Funding: Government Support - Non-U.S.

SA-OR56

Plasma Aβ42/Aβ40 Ratio as a Biomarker for Cognitive Impairment in Patients Undergoing Hemodialysis: A Multicenter Study Xujiao Chen, Fudan University Huashan Hospital Department of Nephrology, Shanghai, China.

Background: Mild cognitive impairment (MCI) and dementia, are more prevalent in patients undergoing hemodialysis. Although the cerebrospinal fluid amyloid beta (Aβ) and tau have proven to be valid biomarkers for the diagnosis of Alzheimer’s disease in the general population, the roles of plasma Aβ and tau for the diagnosis of cognitive impairment in patients undergoing hemodialysis remain unknown.

Methods: We conducted a cross-sectional study including patients receiving hemodialysis in three hospitals in Shanghai. All patients completed the Montreal Cognitive Assessment Basic (MoCA-B). To validate the effectiveness of MoCA-B score for screening MCI, a subset group underwent neuropsychological batteries. Serum proteomes were compared in patients with normal cognitive function and dementia undergoing HD. Plasma Aβ40/Aβ42 and total tau were measured using a single molecule array.

Results: A total of 311 patients undergoing hemodialysis were enrolled (mean age, 63 years; 55% male). The best cut-off score of MoCA-B for differentiating MCI and normal cognition was 24 with an area under the curve of 0.84. Serum proteomics revealed that neurodegenerative pathways related to Alzheimer’s disease were enriched in patients with dementia undergoing hemodialysis. The plasma Aβ42/Aβ40 ratio was significantly reduced in patients with MCI and dementia. The plasma Aβ42/Aβ40 ratio was independently associated with cognitive function after adjusting for age, sex, and educational levels.

Conclusions: We demonstrated that MoCA-B as an optimal cognitive function screening instrument for MCI in patients undergoing hemodialysis. The plasma Aβ42/Aβ40 ratio was a potential biomarker in distinguishing normal cognition, MCI, and dementia in populations undergoing hemodialysis.

Funding: Government Support - Non-U.S.
Background: Kidney transplant recipients (KTRs) with BK virus infection are at risk of nephropathy & graft loss. Posoceleuc (PSL) is an off-the-shelf allogeneic multivirus-specific T cell therapy targeting BKV.

Methods: In this phase 2 double-blind study (NCT04605484), KTRs with BK viremia were randomized 1:1:1 to receive PSL cells wkly for 3 wks then q4 (PSL1) or q8 d (PSL2), or placebo (PBO) for 12 wks. Patients (pts) were followed for 12 wks after treatment. Primary objective was safety; secondary was plasma BK viral load (VL) reduction.

Results: Baseline (BL) characteristics of 61 dosed pts were similar across groups. No deaths, GVHD, or cytokine release syndrome were seen. 3 pts in PSL groups had graft rejection but none deemed treatment-related. 1 pt had history of rejection, 1 had renal TB, and 1 had rejection 68 d after last PSL dose. eGFR was stable in all groups. Table shows VL changes in 52 pts with stable immunosuppression (IS) in the 30 d before randomization who completed study. Superior antiviral effects were seen in both PSL groups vs PBO. Greater effect on BL VL was at wk 24 in PSL1 pts with BK VL ≥ 10,000 cp/mL at screening: 75% (6/8) had a ≥ 1 log2, cp/mL decrease from BL (median -1.4 log) vs 25% (1/4) of PBO (-0.4 log). At BL most pts with high BK VL had no BK-specific T cell immunity. Over the 6 months after PSL infusion, circulating frequency of BK-reactive T cells increased vs PBO, more so in PSL1 group, coincident with VL reduction. PSL presence & persistence were confirmed by TCRVb deep sequencing, with higher levels in pts with high BL VL.

Conclusions: PSL was generally safe & well tolerated. Clinically meaningful BK VL reductions & increases in BK-reactive T cells were seen in PSL pts, particularly those with high BL VL who are at highest risk for renal impairment.

Results at Wk 24 in Patients with Stable IS* before Randomization

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BL VL ≥ 10,000 cp/mL</th>
<th>≥ 1 log2 decrease</th>
<th>≥ 2 log2 decrease</th>
<th>≥ 3 log2 decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSL1</td>
<td>10/30 (33.3%)</td>
<td>3/7 (42.9%)</td>
<td>2/7 (28.6%)</td>
<td></td>
</tr>
<tr>
<td>PSL2</td>
<td>7/28 (25%)</td>
<td>0/11 (0%)</td>
<td>1/11 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>PBO</td>
<td>0/22 (0%)</td>
<td>0/11 (0%)</td>
<td>0/11 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

SA-OR59

A Phase 1/2a Trial of Autologous Regulatory T Cell Therapy Together with Donor Bone Marrow Infusion in Kidney Transplantation

Rainer Oberbauer, Moritz Muckenhaber, Jasmin Mucha, Roman Reindl-Schwarzhofer, Andreas Heinzel, Gabriela Berlakovik, Michael Wolz, Thomas Lion, Nina Worel, Thomas Wekerle. Medizinische Universität Wien, Wien, Austria.

Background: In preclinical models combining Treg therapy with donor bone marrow transplantation leads to reduced hematopoietic chimerism and tolerance without myelosuppressive recipient conditioning, avoiding the adverse effects of irradiation or cytotoxic drugs.

Methods: A single center, controlled, first-in-human phase I/IIa trial is conducted in HLA-mismatched living donor kidney transplant recipients. In vitro expanded polyclonal recipient Tregs and MNC-separated donor bone marrow cells are administered within 3 days after transplant, tocilizumab is injected s.c. for the first 3 weeks. No irradiation or cytotoxic drugs are given. Immunosuppression (IS) consists of thymoglobulin, belatacept, sirolimus and steroids. Starting at 6 months, sirolimus and steroids are gradually withdrawn in stable study group patients. A parallel control group receives the same IS, but no Tregs, bone marrow or tocilizumab. Total leukocyte donor chimerism and safety are co-primary endpoints. Immune monitoring accompanying the trial includes NGS of the TCR repertoire (of the recipient and Treg cell product), flow cytometric leukocyte subset analysis, scRNAseq and protocol biopsies (at 6, 12, 24, 36 and 60 months) including transcriptomic analysis.

Results: Ten patients have been enrolled and treated so far. One additional patient was enrolled but not treated as Treg manufacturing failed. Treg (1-1.5×10^7 cells/kg) and bone marrow cell (0.7-1.9×10^8 nucleated cells/kg) infusions were well tolerated. The study group developed low levels of total leukocyte donor chimerism (<1%) in the first weeks post-transplant, whereas no chimerism was detectable in the control group. The study group shows a favorable clinical course, with GFRs of 50-82 ml/min/1.72m2 at latest follow-up (median follow-up 23 months) and no safety signals were observed. IS reduction has been completed in three patients currently maintained on belatacept monotherapy q6 weeks and is in progress in all other patients. Protocol biopsies at 12 months were clear.

Conclusions: Combined Treg therapy and bone marrow transplantation is safe and feasible in living donor kidney transplantation and induces low-level chimerism.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

SA-OR60

Reduction of Renal Graft Fibrosis with Valganciclovir Prophylaxis for Cytomegalovirus Prevention Compared to Preemptive Therapy: Long-Term Outcomes of Randomized Controlled Trial (OVERT Study)

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Background: Prevention of cytomegalovirus (CMV) infection including CMV indirect effects is essential in kidney transplantation. The 12-month results of OVERT Study showed less subclinical rejection and a trend toward lower incidence of acute rejection in recipients receiving valganciclovir prophylaxis compared to preemptive therapy. Here we report long-term results of OVERT Study.

Methods: This was an open-label, single-center, randomized clinical trial of valganciclovir prophylaxis vs preemptive therapy in 140 kidney transplant recipients recruited between June 2013 and May 2018. CMV-seronegative recipients with negative donors (D-R-) were excluded. Patients were randomized 1:1 to receive either valganciclovir prophylaxis for 3 months (or 6 months in D+R-) (n=70) or preemptive valganciclovir for donors (D-R-) were excluded. Patients were randomized 1:1 to receive either valganciclovir prophylaxis for 3 months (or 6 months in D+R-) (n=70) or preemptive valganclovir for 3 months (or 6 months in D+R-) (n=70) or preemptive valganclovir for significant CMV DNAemia detected in predefined assessments through month 24 (n=70).

The primary outcome was the incidence of moderate to severe interstitial fibrosis and tubular atrophy (IFTA) in protocol biopsy at 3 years. Key secondary outcomes included acute rejection, CMV disease and DNAemia, patient and graft survival.

Results: Among the 127 patients who had a protocol biopsy specimen available at 3 years, 8 (6%) of 66 patients in the prophylaxis group and 14 (23%) of 61 patients in the preemptive group had moderate to severe IFTA (P=0.015). At 3 years the incidence of acute rejection was lower with valganclovir prophylaxis (13% vs 36%, P=0.052). In spite of 9% (77%) additional patients with CMV DNAemia after month 12 in the prophylaxis group in contrast to none in the preemptive group (P=0.025) the cumulative incidence at 2 years remained lower with prophylaxis (51% vs 75%, P=0.001). Both regimens prevented CMV disease (6% vs 4%, P=0.733). While the 4-year graft survival was comparable (90% vs 93%, P=0.460) patient survival was improved in the prophylaxis group (100% vs 94%, P=0.042).

Conclusions: Among kidney transplant recipients, the use of valganclovir prophylaxis, compared with preemptive therapy, led to less severe IFTA at 3 years after transplantation.
SA-OR61

Outcomes Associated with Sodium-Glucose Cotransporter-2 Inhibitors in Kidney Transplant Recipients: A Real-World Analysis Using a Global Federated Database
Nageen Awan,1 Elin Davies,2 Mark A. Devonald,3 Gregory Y. Lip,2,3 Garry Medcalf,4 Anirudh Rao,2,3 1Liverpool University Hospitals NHS Foundation Trust, Liverpool, United Kingdom; 2University of Liverpool Faculty of Health and Life Sciences, Liverpool, United Kingdom; 3Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, United Kingdom; 4Liverpool John Moores University, Liverpool, United Kingdom.

Background: Several trials have shown the effectiveness of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in cardiovascular events and its nephroprotective effects on patients with native kidney disease, but little is known about the safety and efficacy of SGLT2i in the kidney transplant setting. The study aimed to investigate the benefits of SGLT2i in kidney transplant recipients.

Methods: A retrospective cohort study was performed of adult renal transplant recipients (≥ 18 years) using electronic medical records from a TriNetX database searched on 19th May 2023. Cohorts were grouped by receipt of SGLT2i and 1:1 propensity-score matched for demographics (age, gender, & ethnicity), baseline co-morbidities (cardiovascular disease, diabetes mellitus & smoking status), laboratory data (estimated glomerular filtration rate & proteinuria) and immunosuppression. Logistic regression produced odds ratios with 95%CI for incident 3-year graft failure, rejection, major adverse cardiac events (MACE), all-cause mortality, and genitourinary infections. All statistical analyses were performed on the TriNetX online platform.

Results: The propensity score matching identified 3,450 patients (Mean age 59.4 ± 16.1 years, 65% Male), each in the SGLT2i and non-SGLT2i treated renal transplant cohorts. The table shows the outcomes, odds ratio (OR), and 95% confidence interval (CI) for the SGLT2i and non-SGLT2i treated renal transplant patients 3 years post-index event.

Conclusions: Kidney transplant patients treated with SGLT2i demonstrated a significant reduction in graft failure, rejection, MACE, all-cause mortality, and genitourinary infections. This data call for a Randomized Control Trial to evaluate the long-term kidney and cardiovascular outcomes of SGLT2i therapy in the renal transplant setting.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SGLT2i (n=1725)</th>
<th>Non-SGLT2i (n=1725)</th>
<th>OR (95% CI) P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney Transplant Failure</td>
<td>274</td>
<td>277</td>
<td>0.85 (0.80-0.90) 0.0002</td>
</tr>
<tr>
<td>Kidney Transplant Rejection</td>
<td>689</td>
<td>697</td>
<td>0.99 (0.95-1.03) 0.34</td>
</tr>
<tr>
<td>Major Adverse Cardiac Events</td>
<td>160</td>
<td>165</td>
<td>0.82 (0.69-0.99) 0.04</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>133</td>
<td>137</td>
<td>0.88 (0.68-1.12) 0.29</td>
</tr>
<tr>
<td>Genitourinary Infections</td>
<td>179</td>
<td>181</td>
<td>1.03 (0.85-1.26) 0.75</td>
</tr>
</tbody>
</table>

SA-OR62

Deceased Donor Kidney Function Is Determined by Branch Chained Amino Acid Metabolism During Ex Vivo Normothermic Perfusion

Background: Current kidney perfusion protocols are not optimized for addressing ex vivo physiological and metabolic needs of the kidney. We studied kidney function parameters and their link with metabolic competence during a 12-hour ex vivo normothermic perfusion (EVNP).

Methods: Eight human kidneys from deceased donors deemed unsuitable for transplantation were preserved using 12 hours of EVNP during which markers of function and injury were monitored. Kidneys were grouped into good and poor performers based on their functional parameters. Metabolic profile from kidney cortex samples were obtained throughout the perfusion.

Results: The mean age of the deceased kidney donors was 43 ± 16 yrs with a mean cold ischemia time of 37 ± 12 hrs. Hemodynamics parameters such as urine output (mean=99.5 ml/h) and creatinine clearance (mean=32.6 ml/min) progressively increased and peaked at 8 hrs post perfusion among good performers (Figure 1). Urinary neutrophil gelatinase-associated lipocalin was also significantly different at 8 hours post perfusion among good performers (Figure 1).

Conclusions: We identified impaired BCAA metabolism at 6 hours of EVNP as the metabolic phenotype distinguishing poor and good performing kidneys. Future studies with larger sample sizes are needed to validate the association of impaired BCAA metabolism with kidney functional decline.

Funding: NIDDK Support

SA-OR63

The Association Between V-Set Ig Domain-Containing 4 (VSIG4) Expression and Chronicity in Transplant Kidneys
Sang Youb Han,1 Heungman Jun,2 Han Seong Kim,1 1Inje University Ilson Paik Hospital, Goyang, Republic of Korea; 2Korea University Anam Hospital, Seoul, Republic of Korea.

Background: A Banff-based chronicity index is associated with graft outcomes in patients with a kidney transplant. Recent studies have highlighted the association of V-set Ig domain-containing 4 (VSIG4) with epithelial-mesenchymal transition in various diseases, including chronic kidney disease. However, its role in kidney transplantation remains unclear. This study aimed to assess the significance of serum and urinary VSIG4 levels in kidney transplant patients who underwent biopsy.

Methods: A total of 44 patients (24 males, 20 females, average age 50.9 ± 12.8 years) were categorized into three groups based on their chronicity index (1-4, 5-8, and 9-12) as per the 2019 Banff classification. The chronicity index, with a maximum score of 15, represents the sum of scores for interstitial fibrosis, tubular atrophy, chronic vasculopathy, and chronic glomerulopathy. Serum and urinary VSIG4 levels were measured using ELISA, with urinary levels adjusted for urine creatinine levels.

Results: The mean serum creatinine was 1.92 ± 0.88 mg/dL, and eGFR was 41.2 ± 16.1 ml/min/1.73m². The mean number of HLA mismatches was 3.44 ± 1.40. The mean activity index and chronicity index were 2.07 ± 0.67 and 6.27 ± 2.34, respectively. Significant differences in both serum and urinary VSIG4 levels were observed among the three groups using the Kruskal-Wallis test: serum VSIG4 (ng/mL) - lower group median (IQR): 2.14 (1.46, 3.37); middle group: 6.66 (5.53, 8.40); higher group: 12.85 (9.90, 17.83), p = 0.013. Spearman’s rank test revealed positive correlations between serum VSIG4 levels and the total chronicity index (r = 0.391, p = 0.069), age (r = 0.377, p = 0.013), and BUN (r = 0.439, p = 0.003). Urinary VSIG4 levels showed a negative correlation with eGFR (r = -0.367, p = 0.009). However, both serum and urinary VSIG4 levels did not differ significantly based on the total activity score.

Conclusions: This study concludes that serum and urinary VSIG4 levels are associated with chronic changes in patients with kidney transplantation. Given the relationship between the chronicity index and allograft loss, these levels may serve as markers for graft outcomes.

Funding: Government Support - Non-U.S.

SA-OR64

Overlapping Pathologic Findings in the Kidney Allograft Biopsy: Pitfalls for the Molecular Microscope Diagnostics System (MMDx)

Background: The Molecular Microscope Diagnostic System (MMDx) has been suggested to add diagnostic value in cases suspicious of antibody-mediated (ABMR) and T cell-mediated rejection (TCMR). Other overlapping pathologies, however, have the potential to mimic molecular rejection.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: In this single-center cohort of 326 indication kidney transplant biopsies assessed by histology and MMMDx at the University Hospital Zurich, we analyzed 66 cases with overlapping pathologic findings by histology: by histology: SC-TCMR, 5 cases with pyelonephritis, 21 cases with BK nephropathy (BKVN), 5 cases with acute interstitial nephritis (AIN), and 28 cases with recurrent de novo glomerulonephritis (GN).

Results: Peckedplot: 5 of 15 cases (33%) with pyelonephritis showed minor molecular findings (normal rejection score but abnormal ABMR and/or TCMR score or vice versa), which were diagnosed in only 1 of 260 (0.7%) cases without overlapping pathologies (p=0.004). 8 of 15 cases (53%) with pyelonephritis showed a TCMR phenotype score (R2) ≥0.20. BKVN: 4 of 21 cases (19%) with BKVN showed minor molecular findings, whereas 3 (14%), 3 (14%), and 6 (29%) of 21 cases showed ABMR, TCMR, and ABMR/TCMR, respectively. 11/21 cases (52%) with BKVN showed an all ABMR rejection phenotype score (sum of R4, R5, and R6) ≥0.20, none of which had proven ABMR by histology. AIN: 3 of 5 cases (60%) with AIN showed molecular TCMR, of which 2 cases showed mixed ABMR/TCMR in the absence of any antibody-mediated changes by histology. GN: 21 of 28 cases (75%) with GN showed no molecular ABMR/TCMR, whereas 2 of 28 cases (7%) showed minor molecular findings, and 5 of 28 cases (18%) showed ABMR. Surprisingly, 16 of 28 cases (57%) showed an all ABMR rejection phenotype score ≥0.20, and 8 of 28 cases (29%) showed a late-stage ABMR score ≥0.20.

Conclusions: Minor molecular findings should always suggest the presence of any overlapping pathology. Cases of pyelonephritis, BKVN, and AIN mostly mimic molecular rejection and might be misleading in their interpretation. Although GN does not show molecular rejection in most cases, the elevated ABMR scores suggest a GN-associated phenomenon.

Funding: Private Foundation Support

SA-OR65
The Impact of Subclinical T Cell-Mediated Rejection on Subsequent Rejections and Allograft Survival in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis
Takayuki Yamada,1 Shota Obata,2 Arjun L. Kalaria,1 Michele Molinari,1 Rajil B. Mehta.1 UPMC, Pittsburgh, PA; 2Mount Sinai Beth Israel Hospital, New York, NY.

Background: Subclinical T cell mediated rejection (SC-TCMR) refers to the presence of histological features of acute rejection on renal biopsy without a decline in renal function. Although single centers have reported an adverse impact of SC-TCMR on allograft outcomes, there is a dearth of data on this subject.

Methods: We conducted a comprehensive systematic search on PubMed, EMBASE, and the Cochrane Library from inception to May 16th, 2023. We included studies involving adult patients (>18 years old) who underwent kidney transplants and exhibited SC-TCMR detected through surveillance biopsy. Studies involving non-human subjects or lacking adult patients (>18 years old) who underwent kidney transplants and exhibited SC-TCMR were excluded. The primary outcome measure was death-censored allograft loss, while the secondary outcome was subsequent rejection. A random-effects model was used to determine the risk.

Results: A total of nine studies were selected, encompassing a pooled population of 2,423 patients. SC-TCMR was found to be associated with an increased risk of death-censored graft loss (Risk ratio (RR) 1.78, 95% confidence interval (CI) 1.03 to 3.07), although heterogeneity was high (I2 69%). Furthermore, SC-TCMR was also associated with a higher risk of subsequent rejection (RR 2.66, 95% CI 1.96 to 3.61, I2 9%).

Conclusions: SC-TCMR diagnosed through surveillance biopsy was found to be linked with an elevated risk of subsequent rejection and death-censored graft loss.

Forest plot of the association between Subclinical T cell mediated rejection (SC-TCMR) and death-censored graft loss

SA-OR66
Cell Subtypes and Cell-Specific Pathways Associated with Acute-to-Chronic Injury Transition in Posttransplant AKI
Enver Akalin,1 Shaqquat Azim,2 Amol C. Shetty,2 Thomas Rousselle,2 Haseeb Zubair,3 Valeria R. Mas.1 2Montefiore Medical Center, New York, NY; 3University of Maryland School of Medicine, Baltimore, MD.

Background: Kidney transplants (KT) offer a unique opportunity to evaluate molecular pathways involved in development and response to acute kidney injury (AKI). This study of transplanted kidneys with AKI aims to identify cells involved in injury or impaired reparation.

Methods: A total of 14 kidney samples (normal donor kidneys, n=5, normal allografts, n=4, and samples from patients with post-KT AKI, n=4 (<6 weeks post-KT)) were evaluated using single nuclear (sn) RNA-seq.

Results: The analyses of 49,787 combined nuclei showed increased fibroblasts in post-KT AKI samples. Fibroblasts in post-KT AKI compared to normal allografts showed increased expression of genes enriched in extracellular matrix (ECM) organization, proteoglycans, collagen formation, and response to wounding. The analyses of these fibroblasts in 3 sex-mismatched cases using an XY-gene expression signature showed both donor- and recipient-derived fibroblasts (Fig 1A) not observed in normal allografts.

Up-regulated genes in recipient fibroblasts were enriched in laminn interactions, ECM organization, and cellular response to TGF-β stimulus. Increased macrophages (MΦ) proportions in AKI samples, and 3 MΦ subsets were identified, including: MΦ1 (MRC1, LGMN, STAB1) and MΦ2 (FCN1, LYN1, KYNU1, RTN11), and the MΦ2 (CSF3R, LUCAT1, NCF1, LMK2) (Fig 1B-C) characterized by markers of myofibroblasts/fibroblast-like (COL18A1, COL4A3, COL4A4, VCAN, AB3BP, FGL2, GAS6, THSD4). Resident and infiltrating MΦ present a pro-inflammatory profile and enriched in immunoregulatory response signaling pathways.

Conclusions: These novel data emphasize the critical role of resident MΦ in responding to injury transform into MΦ with fibroblast-like markers and a transcriptomic phenotype leading to impaired repair.

Funding: Other NIH Support - R01DK109581-01 and R01DK122682-01
Suitability to Donate and Attitude Toward Living Kidney Donation in Older Adults: Results from the BIS Study
Cédric Villain,1,2 John S. Gill,3 Nina Mielle,1 Tim Bothe,4 Muhammad Barghouthi,1 Anna Pohlmann,1 Anne-Katrin Fietz,1 Natalie Ebert,1 Elke Schaeffner,1 Charité – Universitätsmedizin Berlin corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; 2Normandie Univ UNICAEN, CHU de Caen, Caen, France; 3Division of Nephrology, St. Paul’s Hospital, University of British Columbia, Vancouver, BC, Canada.

Background: Guidelines differ regarding thresholds of glomerular filtration rate (GFR) and albuminuria (ACR) to accept living kidney donation (LKD). We aimed to assess the proportion of community-dwelling older adults suitable to LKD according to different GFR and ACR thresholds, and their attitude toward LKD.

Methods: We used data from the BIS-study, a cohort of adults aged ≥70 years. Kidney-related contraindications to LKD were defined using KDIGO (high and low GFR thresholds of 90 and 60/ml/min/1.73m2 using the EFK equation based on creatinine and cystatin C, respectively; LKD can be discussed between these thresholds) and British Transplantation Society (BTS; age and sex-specific GFR thresholds) guidelines. The ACR thresholds were 30mg/g (low threshold for both guidelines), 100mg/g (high KDIGO threshold), and 300mg/g (high BTS threshold). Participants’ attitude toward LKD was asked at the first follow-up visit.

Results: Among the 209 participants (median age 80 years, 55% women, median estimated GFR 63ml/min/1.73m2), none had an estimated GFR above the high KDIGO threshold at baseline. Combining the consideration of other GFR and ACR thresholds, prevalence of renal contraindication to LKD ranged from 38 to 54%. Ninety-three percent of participants presented a non kidney-related contraindication to LKD, among which heart failure, coronary artery disease, and cancer were the most frequent. Prevalence of suitability to LKD ranged from 0 to 6%, depending on combinations of thresholds of GFR and ACR. After an 8-year follow-up period, 11 to 16% of participants suitable to LKD at baseline maintained their suitability criteria, 6 to 11% switched, and none of them developed CKD stage 4-5. Overall, 73% of all participants agreed to donate a kidney to a relative, but this percentage rose to 85 to 87% in participants suitable to LKD.

Conclusions: Most older adults were theoretically willing to donate a kidney to a relative. Regardless of the low percentage of participants without any contraindication to LKD, their absolute sample size could be an opportunity to increase the number of kidney donors at the population level. To this purpose, the choice of GFR and ACR thresholds may be crucial.

Funding: Government Support - Non-U.S.

SA-OR68
The Association Between Potassium Intake and Risk of CKD
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Background: High dietary potassium intake is associated with lower risk of cardiovascular disease. However, the association between potassium intake and chronic kidney disease (CKD) development in the general population is uncertain.

Methods: From UK biobank cohort, we included 317,162 participants without CKD between 2006-2010. The main predictor was spot urine potassium-to-creatinine ratio (K/CR) as a surrogate of potassium intake. The primary outcome was incident CKD defined by ICD-10 and OPCS-4 codes. In secondary analyses, we examined dietary potassium intake as an additional predictor in 141,180 participants who completed 24-h dietary recall questionnaires.

Results: At baseline, individuals with higher KCR had lower levels of blood pressure, BMI, and inflammation were less likely to have diabetes and hypertension vs. those with lower KCR. During a median follow-up of 11.9 years, the primary outcome occurred in 15,225 (4.8%) participants. In cause-specific models, the adjusted hazard ratio (aHR) per 1-SD increase in KCR for incident CKD was 0.90 (95% confidence interval [CI], 0.89–0.92). In addition, compared with quartile (Q1) of KCR, the aHRs (95% CIs) for Q2, Q3, and Q4 were 0.98 (0.94–1.02), 0.90 (0.86–0.95), and 0.80 (0.76–0.84), respectively. In secondary analyses, higher potassium consumption was also inversely associated with risk of CKD. Compared with Q1 of dietary potassium intake, the corresponding aHRs (95% CIs) for each Q were 0.85 (0.78-0.92), 0.73 (0.67–0.81), and 0.67 (0.60–0.75), respectively.

Conclusions: In this large-scale population-based cohort study, higher urinary potassium excretion and dietary potassium intake were significantly associated with a lower risk of CKD. Compared with Q1 of dietary potassium intake, the corresponding aHRs and Q4 were 0.98 (0.94–1.02), 0.90 (0.86–0.95), and 0.80 (0.76–0.84), respectively. In a 1-SD increase in KCR for incident CKD was 0.90 (95% confidence interval [CI], 0.89–0.92), and none of them developed CKD stage 4-5. Overall, 73% of all participants agreed to donate a kidney to a relative, but this percentage rose to 85 to 87% in participants suitable to LKD.

SA-OR69
Estimated Potassium Intake in Patients with CKD Is Associated with CKD Progression: The Fukuoka Kidney Disease Registry (FKR) Study
Tatsuya Suenaga,1 Shigeru Tanaka,1 Hirotsuka Kitamura,2 Kazuhiko Tsuchiya,2 Kiyotaka Kitamoto,1 Toshiaki Nakano.1 1Kyushu Daigaku Iikagaku Daigakuk Iikuke Gakasu Iikagaku Iikaku Kenkyuu, Fukuoka, Japan; 2Nara Kenritsu Ika Daigaku, Kashihi, Japan.

Background: Higher potassium intake is associated with a lower odds ratio of chronic kidney disease (CKD) prevalence among the general population. On the other hand, because of the limited evidence examining the benefits and risks of encouraging potassium intake or restricting potassium in patients with CKD, the Kidney Disease Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative guidelines only recommend potassium restriction in hyperkalemic patients with CKD, without making any recommendations regarding potassium intake.

Methods: A total of 4,092 patients aged 18 years or older in Japan were prospectively followed for 5 years using data from the Fukuoka Kidney Disease Registry (FKR) Study. Patients were divided into quartiles according to estimated potassium intake (EPI). In addition to the AKI threshold, three percent of participants presented ≥1 non-kidney-related contraindication to LKD, prevalence of renal contraindication to LKD ranged from 38 to 54%. Ninety-three percent of participants presented a non-kidney-related contraindication to LKD, among which heart failure, coronary artery disease, and cancer were the most frequent. Prevalence of suitability to LKD ranged from 0 to 6%, depending on combinations of thresholds of GFR and ACR. After an 8-year follow-up period, 11 to 16% of participants suitable to LKD at baseline maintained their suitability criteria, 6 to 11% switched, and none of them developed CKD stage 4-5. Overall, 73% of all participants agreed to donate a kidney to a relative, but this percentage rose to 85 to 87% in participants suitable to LKD.

Conclusions: Most older adults were theoretically willing to donate a kidney to a relative. Regardless of the low percentage of participants without any contraindication to LKD, their absolute sample size could be an opportunity to increase the number of kidney donors at the population level. To this purpose, the choice of GFR and ACR thresholds may be crucial.

Funding: Government Support - Non-U.S.

SA-OR70
Association of Dietary Potassium and Fiber Intake with Death Risk in a Prospective Hemodialysis Cohort
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Background: In ESKD patients, guidelines recommend dietary potassium (K) restriction given concerns about potential hyperkalemia leading to malignant arrhythmias and mortality. Yet there are sparse data informing recommendations for dietary K intake in this population. We examined the relationship between dietary K intake and death risk in a prospective HD cohort.

Methods: In a 687 hemodialysis patients from the multi-center NIH MADRAD cohort recruited from 16 outpatient dialysis clinics, dietary K intake data were obtained using protocolized Food Frequency Questionnaires (FFQs) administered over 10/2011-9/2022. We examined associations of dietary K intake categorized as tertiles (subdistribution HR [95% CI], 1.29 [1.08–1.55], p <0.05). Similarly, patients in Q1 had a significantly higher subdistribution HR for the progression of CKD than those in Q4 in the multivariable-adjusted Cox proportional hazards models (multivariable-adjusted HR [95% confidence interval [CI], 1.29 [1.08–1.55], p <0.05). In this population. We examined the relationship between dietary K intake and death risk in a prospective HD cohort.

The association between dietary K intake and death risk in a prospective HD cohort.
Results: In expanded case–mix analyses, the lowest dietary K intake was associated with higher mortality (ref: highest tertile) HR (95% CI) 1.58 (1.07, 2.33) (Fig A). After further adjustment for laboratory+nutritional covariates, associations showed greater magnitude of risk: HR (95% CI) 1.66 (1.11, 2.49). In adjusted analyses of dietary K/fiber pairings, patients with low K/low fiber intake and those with high K/fiber intake had worse survival vs. those with high K/high fiber intake: HRs (95% CIs) 1.45 (1.04, 2.00) and 1.51 (1.03, 2.28), respectively (Fig B).

Conclusions: In a prospective HD cohort, lower dietary K intake was associated with higher mortality. When examined in combination with fiber intake, both low K/fiber and high K/fiber intake were associated with worse survival. These findings suggest excessive dietary K restriction as well as high K intake from foods with lower fiber content (animal-based sources) may be deleterious in HD patients. Further studies are needed to determine the optimal amount and sources of dietary K intake in ESKD.

Funding: NIDDK Support

SA-OR71
Effects of a Whole-Food, Plant-Based Nutrition Education Program on Blood Pressure and Potassium Levels in CKD
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Background: Evidence suggests adoption of a predominately whole food plant-based diet (WFPBD) may be beneficial in management of CKD. Concerns over adherence and the potential for hyperkalemia may limit enthusiasm for this approach. This pilot trial tested the hypothesis that individuals with CKD 3 or 4 who attend an education program (known as Jumpstart [JS])- designed to foster lifestyle changes including adoption of a WFPBD via a combination of lectures, support systems and food demonstrations - would achieve lower blood pressure (BP) without an increased risk of hyperkalemia.

Methods: 40 subjects with CKD 3 or 4, with HTN but without proteinuria or hyperkalemia, were randomized to attend the JS education program or not (controls). Participants had vital signs, laboratory studies, and food diaries done before and at the completion of the 15 day JS program (or equivalent times for the controls). At the end of the trial, t-tests were use to compare values between the intervention and control groups.

Results: JS participants (n = 20) saw a greater decrease in systolic BP from baseline to day 15 compared with controls (n = 20) but this did not reach statistical significance (-8 vs 2.8 mm Hg, p=0.12). Potassium changed by -0.01 mEq/L in the JS group and to day 15 compared with controls (n = 20) but this did not reach statistical significance.

Conclusions: Subjects with CKD 3 or 4 attending the 15-day JS program emphasizing a WFPBD had no-significant reductions in systolic BP without increased risk of hyperkalemia. JS attendees achieved greater reduction in weight, BMI and most cholesterol values, without adverse effects on albumin and phosphorus. Larger trials are warranted to investigate potential long-term benefits of this approach.

Funding: Clinical Revenue Support

SA-OR72
Effect of Dietary Acid Reduction with Fruits and Vegetables vs. Oral NaHCO3 on Parameters of Cardiovascular Health in Stage 1 CKD: A 5-Year Randomized Trial
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Background: Patients with macroalbuminuric (urine albumin-to-creatinine ratio [ACR] > 200 mg/g cr) chronic kidney disease (CKD) have increased cardiovascular disease (CVD) risk. As high-acid-producing diets are associated with increased CVD risk, we compared effects of base-producing fruits and vegetables (F+V) vs. oral NaHCO3 on cardiouvascular health and on indices of CVD risk in participants with normal eGFR (> 90 ml/min/1.73 m2 or stage G1).

Methods: One hundred fifty-three macroalbuminuric, non-diabetic G1 participants on ACE inhibitors were randomized to receive F+V (n=51) in amounts to reduce dietary potential acid intake 50%, oral NaHCO3 (HCO3, n=51) 0.4 meq/kg bw/day) or no additional intervention (Usual Care, n=51). They were followed annually for 5 years, measuring systolic blood pressure (SBP), eGFR, isoprostane 8-iso prostaglandin F2α (8-iso), BMI, ACR, and Lp(a). Mixed linear regressions with random person intercepts tested differential group trajectories, p-values from the relevant interaction terms are included below.

Results: We highlight group differences at year-5 for brevity and provide p-values from the full model. At 5 years, SBP and BMI were lower in F+V than HCO3 and UC (SBP [mean (SE)], F+V[124.9 (0.70)], HCO3 [135.0 (0.73)], UC [134.6 (0.62)], mm Hg, ps<0.001); BMI; F+V [27.0 (0.25)], HCO3 [28.4 (0.26)], UC [28.0 (0.30)], ps<0.001). For both F+V & HCO3 relative to UC, 5-year eGFR was higher (eGFR, F+V [96.5(0.79)], HCO3 [95.9 (0.96)] vs. UC [92.1 (1.23), ml/min/1.73 m2, ps<0.001]) and 8-iso was lower (8-iso, F+V [1.08 (0.02)], HCO3 [1.06 (0.02)] vs. UC [1.27 (0.03), mg/g cr, ps<0.001]). Five-year Lp(a) was lower in F+V than HCO3 and UC (7.9a [1.4]), UC [60.8 (1.5), mg/dl, ps<0.001]). Furthermore, 5-year ACR was lower for F+V and HCO3 than UC (F+V [306 (8.5)], HCO3 [308 (8.4)] vs. UC [416 (15), mg/g cr, ps<0.001]).

Conclusions: Dietary acid reduction with either F+V or NaHCO3 over 5 years yielded similar eGFR preservation, systemic oxidative stress reduction, and lower ACR benefits. Dietary acid reduction with F+V compared to NaHCO3 and UC yielded better SBP control, lower BMI and lower Lp(a) and yielded better overall CVD protection in macroalbuminuric patients with initially normal eGFR.

SA-OR73
Food Insecurity, Dietary Intake, and Mortality Among Adults with CKD
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Background: Food insecurity in adults has been associated with a higher risk of diabetes, hypertension, chronic kidney disease (CKD), and mortality. We sought to examine the role of dietary intake in mortality risk due to food insecurity in adults with CKD.

Methods: We used data from the National Health and Nutrition Examination Survey (1999–2018) to assess differences in demographics, comorbidities, socioeconomic status (SES), and dietary intake in food secure versus food insecure adults with CKD (N=8935). Marginal, low, or very low household food security defined food insecurity. Using publicly available mortality-linked data, we explored mortality related to food insecurity, food intake, and other risk factors using Cox regression.

Results: Approximately 22% of adults with CKD reported food insecurity. These adults were younger, had lower SES and rates of health insurance, were more likely to be from a racial minority group, and had higher prevalence of obesity and diabetes. Food insecure adults had overall higher calorie intake, but fiber and potassium intake were lower, while carbohydrate and sodium intake were higher. Adjusting for demographics only, food insecure adults had a higher mortality rate (HR=1.46, P<0.001). Risk decreased when comorbidity, income, and education were considered (HR=1.22, P=0.006). Dietary intake did not further reduce this association.

Conclusions: Differing nutrient intake was seen in adults with CKD and food insecurity, yet these differences did not attenuate food insecure-related mortality risk; therefore, food insecurity plays a potential role in inducing comorbidities, which is not captured in existing studies. Future work may consider the higher risk of comorbidities in food insecure adults with CKD to improve health outcomes.

Funding: Other U.S. Government Support
SA-OR74

Dietary Inflammatory Potential and Kidney Function in the Hispanic Community Health Study/Study of Latinos

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Background: Inflammation is implicated in the pathogenesis and progression of CKD. Diet modulates chronic inflammation and possibly kidney health. We evaluated the association of diet-related inflammation and kidney function among US Hispanic/Latino adults.

Methods: Data were from participants in the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a population-based study of Hispanic/Latino adults 18-74 years old from 4 US communities, who were examined at visit 1 (V1) (2008-2011) and visit 2 (V2) (2014-2017) and had data on dietary intake and serum creatinine. Dietary inflammatory potential was assessed using the dietary inflammatory index (DII®); Scores were adjusted for total energy intake (E-DII®) and categorized into tertiles: having the lowest dietary inflammatory potential, and T3 having the highest (most pro-inflammatory). Creatinine-based eGFR was calculated using the 2021 CKD-Epi equation. Primary outcomes were incident CKD (eGFR <60 ml/min/1.73m2) at V2 and ≥30% decline in eGFR from V1 to V2 and rapid kidney function decline (RKFD) (≥30% decline in eGFR from V1 to V2). We excluded participants with eGFR <15 ml/min/1.73m2, and for incident CKD, those with eGFR <60 ml/min/1.73m2 at V1. Logistic regression models adjusting for study center and baseline socio-demographics, comorbidities, behavioral factors, medications, anthropometric measures, eGFR and albuminuria were used to compare E-DII® tertiles and determine odds ratio for incident CKD and RKFID.

Results: Of 10,574 participants, median age was 49 years, 22% had diabetes, 46% had hypertension. Median eGFR was 101.7 ml/min/1.73m2. Median E-DII® was 0.18 (IQR -1.06 to 1.30). Over a mean follow-up of 6 years, 122 incident CKD and 196 RKFID events occurred. Participants with the most pro-inflammatory dietary patterns compared to the lowest had 2.2-fold higher odds of incident CKD (95% CI: 1.14 – 4.31) after adjusting for covariates. The E-DII® was not significantly associated with RKFID.

Conclusions: A pro-inflammatory dietary pattern is associated with a higher likelihood of incident CKD among US Hispanic/Latino adults. To prevent kidney disease, US Hispanic/Latino adults may opt to reduce intake of foods with higher pro-inflammatory potential (e.g., processed or fried foods, red meat, sweetened beverages).

Funding: NIDDK, Support, Other U.S. Government Support

SA-OR75

Personalized Patient Education on Lifestyle Modification and Nutrition Management in CKD Using ChatGPT

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Background: Lifestyle modifications are critical for managing CKD. Patients struggle to access reliable information on modifying lifestyle. AI-based natural language processing technology, like ChatGPT, has the potential to provide information on lifestyle modification and nutrition. This study aimed to evaluate the effectiveness of ChatGPT in providing education by addressing questions related to lifestyle modification and nutrition in CKD.

Methods: 15 frequently asked questions were generated using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines “CKD evaluation and management 2012”, “Diabetes in CKD 2022”, and “Lipids in CKD 2013”. The questions were categorized into 4 levels to evaluate the versatility of ChatGPT in generating responses. ChatGPT (March 23 Version) provided responses were evaluated by nephrologists and compared to KDIGO guidelines.

Results: Overall the response to addressing patient queries for original questions, paraphrased questions with different interrogative adverbs, paraphrased questions with incomplete sentences, and paraphrased questions with misspelled words were similar. ChatGPT provided accurate responses to 13 out of 15 FAQs across various complexity levels and paraphrasing variations. In 2 questions some statements made by ChatGPT could have been misleading to patients, such as “medications like erythropoietin stimulating agents and phosphate binders may affect the patient’s ability to engage in physical activity.” Statements such as “high protein intake can result in accumulation of metabolites like ammonia in tubular cells” and “excessive protein intake can activate renal angiotensin aldosterone system” could be confusing to providers when these statements are not used consistently in human studies. Consultation with nephrologist was encouraged by ChatGPT in all the questions.

Conclusions: This research highlights the potential of ChatGPT as an effective tool for providing patient education. ChatGPT’s response in addressing patient queries was comparable to the assessments provided by the KDIGO guidelines. Rare statements though made by ChatGPT could be misleading. Further advancements are necessary to enhance ChatGPT’s performance in addressing more intricate aspects of lifestyle modification and nutrition management.

SA-OR76

Intradialytic Cycling Exercise Improves Arterial Stiffness in Hemodialysis Patients

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Background: Cardiovascular diseases are the main causes of death and morbidity in hemodialysis patients. Arterial stiffness is an essential predictor of cardiovascular mortality. Exercise has been shown to contribute vascular and physical benefits in healthy populations. Physical function would affect the quality of life in hemodialysis patients. Intradialytic cycling exercises provide regular exercise with good supervision. We conducted this randomized controlled trial to examine the vascular and physical effects of intradialytic exercise in hemodialysis patients.

Methods: One hundred and fourteen hemodialysis patients were randomly assigned to exercise or control group for a 12 months period. We compared the effect of intradialytic cycling on arterial function (arterio-femoral pulse wave velocity, cfPWV) as primary endpoint and physical performance (gait speed and 5 times sit to stand) as secondary evaluations in these participants.

Results: Among 114 participants, 89 and 82 participants completed the tests at 6 and 12 months, respectively. We observed a significantly decrease in cfPWV in the exercise group compared to the control group (95% confidence interval (CI): (-5.71, -2.90), p < 0.001). With further evaluation with GEE analysis, there was a significant difference on group-by-time interaction of cfPWV (p < 0.001 both after 6 and 12 months). In the secondary outcomes, we observed a significantly faster gait speed in the exercise group compared with the control group (95% confidence interval (CI): (0.03, 0.30), p = 0.019). However, the difference in group-by-time interaction of gait speed between the two groups was not observed during further evaluation. There was no difference in arterial health and physical performance in the exercise group. Therefore, intradialytic cycling is an effective exercise to achieve arterial health and physical performance in the hemodialysis population.

SA-OR77

Oxygen Consumption Recovery is Delayed After the Long Interdialytic Period

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Background: Prolonged interdialytic periods leading to accumulation of uremic toxins and volume changes would be associated with alterations in ventilatory response to exercise. O2 uptake (VO2) kinetics during the early recovery period on cardiopulmonary exercise testing (CPET) have strong prognostic value in patients with heart failure and have the advantage of being independent of achieving maximal volitional effort. In this study, we sought to examine the effects of the long interdialytic interval on VO2 kinetics.

Methods: We analyzed data from the ongoing. “Effects of long interdialytic intervals on Cardiovascular Functional Capacity (ECON)” study, a randomized crossover trial of patients on conventional HD. CPET was performed on three study visits: post-HD (baseline), and at the end of a 2-day and the 3-day interdialytic intervals. VO2 recovery (% was calculated using the following formula: (VO2 peak–VO2 at minute 1 of recovery)/VO2 peak.

Results: A total of 30 patients (n=19 men, mean [SD] age=54 [11] years, dialysis vintage=71.1 [63] months) were included in this analysis. No differences between visits were observed in VO2 Peak (BL=1.00 [IQR: 0.84-1.14] L/min; 2-day=0.96 [0.83-1.22] L/min; 3-day=0.99 [0.87-1.20] L/min; p=0.71) nor in VO2 at ventilatory threshold (BL=0.67 [0.51] L/min; 2-day=0.67 [0.51] L/min; 3-day=0.68 [0.14] L/min; p=0.9). However, post-HD fatigue limited the patients’ effort during the BL CPET, as reflected by a lower peak respiratory exchange ratio compared to non dialysis day visits (p=0.014). VO2 Recovery was lower during the 3-day interval (20 [%] compared to BL (23 [8 %]; p=0.013), while differences were observed between the 2-day interval (22 [11 %]) and BL (p=0.11). Additionally, heart rate (p=0.044) and minute ventilation (p=0.025) after 1 minute of recovery were higher during the 3-day interval compared to BL.

Conclusions: The long interdialytic period may be associated with slowed repletion of energy stores in peripheral muscles as reflected by the delay in VO2 and ventilation recovery following maximal exercise. VO2 Peak assessment the same day following HD may be confounded by post-HD fatigue, therefore exercise recovery kinetics may provide incremental prognostic data and unveil subclinical pathophysiological alterations occurring during interdialytic intervals.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.
SA-OR78

Liddle Syndrome Caused by Loss-of-Function Mutations in the Ubiquitin Ligase NEDD4L

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Background: Liddle Syndrome (Pseudohypertension) is an autosomal dominant form of hereditary hypertension characterized by early-onset hypertension, hypokalemia, low blood aldosterone and renin levels, and metabolic alkalosis. In most patients it is caused by a pathogenic variant in the PY motifs (PXXY) of the β (SCNN1B) or γ (SCNN1G) subunits of the amiloride-sensitive Epithelial Na+ Channel, ENaC. Mutant ENaC exhibits increased retention and function at the plasma membrane in the distal nephron, increased reabsorption of luminal Na+, increased circulating blood volume and hypertension. These ENaC variants impair its binding to NEDD4L, an E3 ubiquitin ligase comprised of C2-WW(4)-HECT domain architecture. Impaired NEDD4L binding to ENaC leads to reduced cell surface ENaC ubiquitination, impaired channel endocytosis and degradation, thus explaining the increased retention of ENaC at the plasma membrane.

Methods: Targeted exome sequencing was used, which included SCNN1A, SCNN1B, SCNN1G and NEDD4L. The patient’s variants on either allele of NEDD4L were generated by site-directed mutagenesis and tested for self-ubiquitination in vitro, substrate ubiquitination against a model substrate and against cell-surface αETαENaC in kidney Hek293T cells. Cell surface ENaC stability was analyzed in parallel.

Results: Unlike most Liddle syndrome patients with pathogenic ENaC variants, a subset of patients have normal ENaC. Here we describe the discovery of novel compound heterozygous pathogenic variants in the NEDD4L gene in a patient with Liddle syndrome and normal ENaC genes. Both parents are unaffected carriers. The maternal allele is a frameshift variant that yields a truncated NEDD4L protein devoid of the entire catalytic HECT domain. The paternal allele is a missense variant in the HECT domain that exhibits a severe loss of its enzymatic activity. This results in a dramatic reduction in ENaC ubiquitination, thereby increasing the stability of this channel at the plasma membrane.

Conclusions: This is the first demonstration of a novel recessive form of Liddle syndrome caused by loss of function of the ENaC suppressor NEDD4L. On this basis, it will be important to include NEDD4L in commercial hypertension gene panels to facilitate diagnosis of other Liddle syndrome patients with normal SCNN1A (ENaC) genes.

Funding: Government Support - Non-U.S.

SA-OR79

Recessive Variants in MYO1C as a Potential Novel Cause of Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. The identification of monogenic causes of SRNS has revealed ~60 single-gene etiologies. While in 12-30% of patients it is caused by a pathogenic variant in the PY motifs (PPxY) of the b (β) and γ (γ) subunits of the amiloride-sensitive Epithelial Na+ Channel, ENaC. Mutant ENaC leads to reduced cell surface ENaC ubiquitination, impaired channel endocytosis and degradation, thus explaining the increased retention of ENaC at the plasma membrane.

Methods: Targeted exome sequencing was used, which included SCNN1A, SCNN1B, SCNN1G and NEDD4L. The patient’s variants on either allele of NEDD4L were generated by site-directed mutagenesis and tested for self-ubiquitination in vitro, substrate ubiquitination against a model substrate and against cell-surface αETαENaC in kidney Hek293T cells. Cell surface ENaC stability was analyzed in parallel.

Results: Unlike most Liddle syndrome patients with pathogenic ENaC variants, a subset of patients have normal ENaC. Here we describe the discovery of novel compound heterozygous pathogenic variants in the NEDD4L gene in a patient with Liddle syndrome and normal ENaC genes. Both parents are unaffected carriers. The maternal allele is a frameshift variant that yields a truncated NEDD4L protein devoid of the entire catalytic HECT domain. The paternal allele is a missense variant in the HECT domain that exhibits a severe loss of its enzymatic activity. This results in a dramatic reduction in ENaC ubiquitination, thereby increasing the stability of this channel at the plasma membrane.

Conclusions: This is the first demonstration of a novel recessive form of Liddle syndrome caused by loss of function of the ENaC suppressor NEDD4L. On this basis, it will be important to include NEDD4L in commercial hypertension gene panels to facilitate diagnosis of other Liddle syndrome patients with normal SCNN1A (ENaC) genes.

Funding: Government Support - Non-U.S.

SA-OR80

Circulating Nephrin Autoantibodies Are Present in Almost 2/3 of Steroid-Naive Pediatric Idiopathic Nephrotic Syndrome

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Background: Children who present with idiopathic nephrotic syndrome (INS) are initially treated with corticosteroids (CS) and do not routinely require a renal biopsy unless they have atypical features or subsequent resistance to CS. We recently identified circulating nephrin autoantibodies in approximately 30% of children and adults with biopsy proven MCD. As the majority of these patients had already received CS prior to serum sampling we hypothesized that this likely underestimated the true prevalence of pediatric nephropathy.

Results: In this North American, multicenter, prospective study (via the Pediatric Nephrology Research consortium (PNRC)) we evaluated serum samples obtained from children at presentation and following GC monotherapy for nephropathies by indirect ELISA. A threshold for positivity was determined from a healthy control cohort in kidney disease.

Conclusions: The median age was 4 years (IQR 3-11years) and 45% male. Almost two thirds, 63% (n=12/19) of steroid naïve INS patients were positive for nephropathy autoantibodies at initial presentation and of those 75% (n=9/12) became negative following CS therapy. Including patients with minimal steroids prior to initial presentation revealed that 95% (n=17/18) were nephropathy autoantibody positive. In those children who were steroid naïve at initial presentation, 69% (n=9/13) with INS were nephropathy autoantibody positive compared with 50% (n=3/6) with SRNS. We found that just under 2/3 of children with INS who were steroid naïve at initial presentation were serologically positive for nephropathy autoantibodies. Furthermore, we identified nephrin autoantibodies in both INS and SRNS, and although the mechanism of GC in INS remains to be determined, B-cell targeted therapies are effective in treating some patients with SSNS and SRNS. This raises the possibility that nephrin autoantibodies may serve as an important biomarker to guide B cell targeted therapies in both INS and SRNS.

Funding: Private Foundation Support

SA-OR81

Unveiling the Disproportionate Impact of Rare Kidney Diseases on Kidney Failure: A Longitudinal Analysis Using the UK National Registry of Rare Kidney Diseases (RaDaR)

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Background: Patients with rare kidney diseases account for ~10% of people living with CKD, but make up 25% of prevalent patients on Renal Replacement Therapy (RRT). The history of rare kidney diseases are poorly described. Formed in 2010, RaDaR gathers longitudinal data from UK rare kidney disease patients. We used these data to study outcomes of death and RRT initiation for these conditions.

Methods: RaDaR recruited participants from 108 UK renal units. Incidence rates for mortality and ESKD were calculated and compared to those from unselected UK patients using population estimates of CKD and UK Renal Registry RRT incidence data. Cumulative incidence and Kaplan Meier survival estimates were calculated for a)Age at RRT start b) age at death c) time from RRT start to death d) time from diagnosis to eGFR thresholds allowing calculation of time from last eGFR ≥75 to first <30ml/min/1.73m2 (therapeutic window).

Results: 27,293 patients in 20 Rare Disease Groups (RDGs) were included. RaDaR patients had higher 5 year incidence rates of ESKD compared to 2.81 million patients with all causes CKD (28% vs 1%) and better survival rates (Standardised Mortality Ratio 0.45, 95% CI 0.37-0.54). There was heterogeneity in median age at RRT start between RDGs (Fig 1). Time in therapeutic window varied between 20 years in Retinopetal Fibrosis to 1.3 years in Monoclonal Gamopathy of Renal Significance.

Conclusions: Patients with rare kidney diseases differ from the general CKD population: they are more likely to reach ESKD and half as likely to die with CKD stages 3-5, so are disproportionately represent in the RRT population. Successfully addressing unmet need in rare diseases may therefore have a disproportionate effect on RRT demand long term.

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

Underline represents presenting author.
SA-OR83

Risk Factors and Impact of Peritoneal Podoplanin in Children on Chronic Peritoneal Dialysis
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Background: Diffuse, peritoneal podoplanin staining (DPS) positivity has been described with encapsulating peritoneal sclerosis (EPS) in patients on peritoneal dialysis (PD). The pathophysiological role in PD is uncertain.

Methods: Peritoneal tissues from 250 children (8.5, IQR 2.5, 13.2 years), with normal renal function (NRF), CKD5, and on chronic PD with fluids that contain low and high glucose degradation product (GDP) concentrations underwent digital histomorphometry and high-dimensional multiplexed imaging mass cytometry followed by deep learning-based segmentation and spatial single-cell and cellular neighborhood interaction analysis.

Results: Children with NRF and CKD5 exhibited no DPS, 21% of children on low-GDP PD and 46% on high-GDP PD were DPS positive, but without clinical, radiological or histological features of EPS. PD duration and peritonitis incidence were similar in DPS positive and as in non-DPS PD patients. DPS positive patients were younger, had higher diabetic glucose exposure and more arteriolar luminal narrowing. Dialytic glucose exposure, PD duration, lower body surface area (BSA) and epithelial-to-mesenchymal (EMT) transformed cell counts were independently associated with DPS. DPS and lower mesothelial surface coverage were independently associated with arteriolopathy. In subgroups matched for age, PD duration and dialytic glucose exposure, DPS positive children had higher submesothelial leukocyte (CD45+) and macrophage (CD68+) counts, and higher lipopolysaccharide and hyaluronan receptor CD44 abundance. DPS intensity was higher with history of peritonitis. Hierarchical clustering demonstrated highest similarity of DPS positive patients with CD68 positive areas, classified as M2 macrophages (CD68+CD163+), followed by fibroblastic cells (αSMA+PROX1-CD31-CD68-CD163+); DPS signals from M1 macrophages (CD68+CD163-) were low.

Conclusions: DPS is prevalent in children on PD devoid of EPS, and is independently associated with peritoneal arteriolopathy. Independent DPS risk factors are high dialytic glucose and GDP exposure, history of peritonitis, BSA and EMT. DPS cell invasion; M2 macrophages presumably play a key role.

Funding: Government Support - Non-U.S.

SA-OR84

Preliminary Findings from the Phase 2 EPPIK Study of Sparsentan in Pediatric Patients with Selected Proteinuric Glomerular Diseases
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Background: Sparsentan (SPAR) is a novel, non-immunosuppressive, single molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) approved by the US FDA for the treatment of adults with IgA nephropathy (IgAN) at risk of rapid disease progression and is being investigated for focal segmental glomerulosclerosis (FSGS).

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

SA-OR82

Contemporary Infant and Neonatal Dialysis (COINED) Study: Practice Patterns and Outcomes
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Background: Neonatal dialysis is technically challenging and rare. Prior neonatal dialysis research is primarily limited to medical claims/coding data. There are critical knowledge gaps specific to neonatal dialysis. Our objective was to describe contemporary neonatal dialysis demographics, access, modalities, complications, and outcomes.

Methods: This is a preliminary report from a multicenter retrospective cohort study of 14 centers in the Pediatric Nephrology Research Consortium. Neonates initiated on neonatal dialysis within the first 30 post-natal days between June 2017-May 2022 were enrolled. Neonates with a dialysis catheter placed post-cardiac surgery for fluid management without kidney dysfunction were excluded. Data were collected until initial hospital transfer/discharge.

Results: 183 neonates on dialysis were enrolled. 58% were diagnosed with acute kidney injury (AKI) and 30% with end-stage kidney disease (ESKD). The majority received some form of continuous kidney replacement therapy (CKRT) (71%). 25% experienced a change in dialysis modality, 52% died before hospital discharge, and 19% remained on dialysis at discharge/transfer on dialysis.

Conclusions: In this multicenter, cohort, a larger number of neonates received CKRT, many neonates changed dialysis modalities prior to discharge/transfer, and mortality rates are far greater than previously reported. Future research to inform development of evidence-based guidelines is needed to improve neonatal dialysis management and outcomes.

Funding: Private Foundation Support, Clinical Revenue Support
The ongoing Phase 2 EPPIK study is examining the safety and long-term antiproteinuric and nephroprotective potential of SPAR in pediatric patients with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS). Here we report preliminary findings.

Methods: This open-label, single-arm, multicenter trial is evaluating the safety, efficacy, and pharmacokinetics of SPAR in ~30 patients aged 1–18 years with FSGS and/or MCD (Population 1) and ~27 aged 2–18 years with IgAN, IgAV, or AS (Population 2) over 108 weeks with a 4-week safety follow-up. SPAR is administered once daily in a liquid formulation with dose adjusted to body weight. Patients receiving RAASi undergo a 2-week washout prior to study medication start (baseline). Primary endpoints include safety and efficacy (change in urine protein/creatinine ratio [UP/C] from baseline over 108 weeks).

Results: At data cutoff (4/5/23) 23 participants had received ≥1 dose of SPAR. Baseline characteristics are shown in Table. UP/C decreased over 12 weeks by 25% and 52% in Populations 1 and 2 and 35% overall (Figure). SPAR has been safe and generally well-tolerated.

Conclusions: SPAR treatment reduced proteinuria over the initial 12 weeks in pediatric patients with a range of proteinuric glomerular diseases. SPAR was safe and generally well-tolerated, consistent with findings from ongoing FSGS and adult IgAN trials.

Funding: Commercial Support - Travere Therapeutics, Inc.

SA-OR86

Molecular Pathways Associated with Early Vascular Calcification in Pediatric CKD

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Background: Children with advanced stages of chronic kidney disease (CKD) are at higher risk of cardiovascular disease (CVD) and vascular calcification (VC) may already occur during childhood. This study comprehensively investigated the molecular pathways underlying early VC in children with CKD stage 5.

Methods: Arteries from children with normal renal function and CKD5, (median age 8.9 and 8.8 years) were analyzed using digital quantitative histomorphometry, von Kossa staining and 18F-sodium autoradiography (18F-NaF) for calcium deposit quantification. Arteriolar microcalcifications were identified from Gene Ontology database. The identified key molecular mechanisms were validated in independent pediatric CKD5 cohorts (n=32) and healthy controls (n=20) using quantitative immunostaining.

Results: Von Kossa staining did not reveal calcium deposits, but 18F-NaF autoradiography demonstrated arteriolar microcalcifications in children with CKD5. Compared to children with normal renal function, the arteriolar lumen/vessel ratio was reduced (p<0.001), due to intima and media thickening (p=0.001/0.02), together with CD68+ macrophage infiltration in the subendothelial space (p=0.001/0.02). Multi-omics VC pathway analysis identified 50 pathways primarily associated with actin cytoskeleton, Wnt signaling, extracellular matrix (ECM) organization, complement activation, apoptosis, and ossification regulation. In independent age-matched cohorts, two components of the Wnt pathway, DKK3 and Wnt2b, were decreased (p=0.0004/0.009). Fibroentin-1, a major regulator of ECM, was identified as a hub gene in VC and showed reduced abundance in children with CKD5 (p<0.001). Arteriolar osteoglycin, involved in ectopic bone formation, was increased in CKD5 (p=0.001).

Conclusions: Arteriolar microcalcifications are already present in young children with CKD5. We provide a comprehensive analysis of underlying molecular pathways and identified processes involved in vascular remodeling which open new avenues for potential therapeutic targets.

SA-OR87

Prospective Validation of the PERSEVERE-II AKI Prediction Model in Pediatric Septic Shock

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Background: Treatment of sepsis-associated AKI (SA-AKI) is supportive, without effective therapies. Identification of patients at risk for severe SA-AKI could facilitate targeted kidney protection and enrich future trials. We derived the multi-biomarker PERSEVERE-II AKI Model that predicts Day 3 severe SA-AKI with strong test characteristics (AUC 0.95, 95%CI 0.92-0.98, sensitivity 92%, specificity 89%). We aimed to prospectively validate this tool.

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

Underline represents presenting author.
Methods: Secondary analysis of a prospective study of patients aged 0-25 admitted to 11 PICUs with septic shock from 3/19 to 12/22. D1 PERSEVERE biomarker values (C-C chemokine ligand 3, granzyme B [GZMB], heat shock protein 70 kDa [HSPA1B], IL-8 and MMP8) were combined with platelet count to assign a PERSEVERE-II mortality probability (PIT MP). D1 KDIGO Stage, PIT MP, GZMB, HSPA1B and IL-8 levels were used to assign a D3 severe AKI probability (Figure 1). Model performance was assessed and compared to D1 serum creatinine (SCr) elevation.

Results: Seventy-nine of 363 subjects (22%) had D3 severe AKI. The model predicted D3 severe AKI with an AUC 0.89 (95% CI 0.85-0.93), sensitivity 77% (95% CI 66-86) and specificity 85% (95% CI 84-92). Compared to subjects with D1 SCr-based AKI, those predicted to have severe AKI by the model (n=94) had more D3 severe SA-AKI (65% vs 45, p=0.003) and kidney replacement therapy use (40% vs 26%, p=0.021), and lower rates of renal recovery from early AKI (37% vs 53%, p=0.019) (Figure 2). Model performance was superior to D1 SCr elevation above baseline (p=0.004).

Conclusions: We have prospectively validated the PERSEVERE-II AKI Model for prediction of D3 severe AKI in pediatric septic shock. The next step to translating this tool to the bedside is timely biomarker availability.

Funding: Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health (KL2TR001426, PI: Natalie J. Stanski). The original study was funded by National Institute of General Medical Sciences (R35GM126943, PI: Hector R. Wong).

SA-OR89

Plasma Proteome Profiling for Remission Diagnosis in ANCA Vasculitis Ralph Kettritz,1,2 Uwe Jerke,1 Marielieuse Kirchner,1 Theda U. Bartolomaeus,1 Maximilian Ebert,1 Lovis Kling,1 Sofia K. Forslund,1 Philipp Meritis,1 Kai-Uwe Eckardt,2 Adrian Schreiber.1,2 Experimental and Clinical Research Center (ECRC) and Max Delbrück Center for Molecular Medicine (MDC) in the Helmholtz Association and Charité, Berlin, Germany; Nephrology and Medical Intensive Care, Charité, Berlin, Germany; Core Unit Proteomics, Berlin Institute of Health (BIH) at Charité and MDC, Berlin, Germany.

Background: Systemic anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) requires intensive immunosuppressive treatment that is desescalated once patients achieved remission. Thus, reliably diagnosing remission has therapeutic implications but remains challenging. We hypothesized that the plasma proteome harbors objective information that may assist clinicians in diagnosing AAV remission.

Methods: Plasma proteomes from 50 healthy controls (HC), 59 active, and 55 remission AAV patients were analyzed with LC-MS/MS based proteomics. For data analysis, a machine learning pipeline was established, containing confounder analysis, LASSO regression and Likelihood ratio test. After “leave-one-out” validation the final biomarker combination for ANCA disease status assignment was tested on the 20/80 data split.

Results: From 970 identified proteins, 605 passed the quality check for quantification and 523 were differently expressed. The principal component analysis showed excellent separation of active and remission AAV patients. Using machine learning, we identified a 5-protein biomarker combination with the potential to separate active AAV from remission patients, namely leucine-rich alpha-2-glycoprotein 1, beta-2-microglobulin, insulin-like growth factor-binding protein 3, lamin X, and alpha-2-HS-glycoprotein. Assessing all AAV patients, the 5-protein panel showed an AUC of 0.94 with a negative predictive value (NPV) of 87.5% and performed better than ANCA titer (AUC 0.75, NPV 63.6%) or c-reactive protein (CRP) (AUC 0.91, NPV 73.3%) using a binary logistic regression model of remission diagnosis. In challenging remission patients with positive ANCA, the panel was the better classifier compared to CRP (AUC 0.96, NPV 85.7% versus AUC 0.92, NPV 75.0%), and better than ANCA in challenging remission patients with increased CRP (AUC 0.82, NPV 83.3% versus AUC 0.68 without any value in diagnosing remission).

Conclusions: Using proteomics combined with machine learning, we identified a protein signature that may assist clinicians in diagnosing AAV remission and guiding immunosuppressive treatment.
SA-OR90
Development of Novel Selective DDR1 Inhibitors with the Potential to Treat CKD

Background: Discoidin domain receptors (DDRs) are collagen-activated receptor tyrosine kinases which have been shown to have increased expression in many fibrotic diseases. Inhibition or knockdown of DDR1 has previously been shown to decrease fibrosis and protect kidney function in multiple preclinical mouse models of kidney fibrosis. However, to date there are no approved selective inhibitors of DDR1 in the clinic. In this study, the protective role of REDX-DDR1, a novel and selective orally bioavailable small molecule inhibitor of DDR1 was investigated in a mouse unilateral ureteral obstruction (UUO) model.

Methods: For therapeutic intervention, mice were subjected to UUO and subsequently from day 5 to treatment with vehicle, REDX-DDR1 or oral gavage. Animals were sacrificed at day 10 and kidneys were collected and processed for histological analysis of collagen deposition and myofibroblast transformation in stained tissue sections.

Results: REDX-DDR1 exhibits nanomolar potency in cells and target engagement in the kidney as measured by suppression of phospho-DDR1. REDX-DDR1 is highly selective when tested against a panel of 468 kinases. REDX-DDR1 has a favourable in vitro and in vivo ADME profile including good in vivo exposure across species and low potential for drug-drug interactions. Early safety pharmacology assessment showed no findings in standard ion channel panels. In vitro genetic toxicology showed no genotoxic findings in 5-strain Ames test. The favourable selectivity and pharmacokinetic profiles of REDX-DDR1 allow for selective inhibition of DDR1 in mouse models of chronic kidney disease. Animals treated with REDX-DDR1 had a significant reduction in histological markers of inflammation and fibrosis in the therapeutic mouse UUO model. REDX-DDR1 suppressed inflammation and fibrosis as measured by F4/80, α-SMA and PPAR-γ respectively. In addition REDX-DDR1 suppressed a number of pro-fibrotic genes.

Conclusions: These data show that selective inhibition of the DDR1 receptor via REDX-DDR1 results in anti-fibrotic efficacy in the UUO model. Selective inhibition of DDR1 represents an attractive approach for further investigation towards the development of new treatments for CKD.

Funding: Commercial Support - Redx Pharma Plc

SA-OR91
Spatial Metabolomics Identifies Novel Glomerular Metabolite Signatures of Normal and Diabetic Kidneys
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Background: The Zucker Diabetic Fatty (ZDF) rat is a model of type 2 diabetes as it develops pathologic changes in the glomerulus similar to human disease. Untargeted matrix-assisted laser desorption/ionization (MALDI) - mass spectrometry imaging (MSI) can be a powerful platform to identify metabolic pathways linked to pathologic features. However, quantification of metabolites from specific regions of interest in an unbiased manner via MALDI-MSI is challenging. MSI-DeepPath is a new computational platform that enables spatial quantitation of metabolites.

Methods: Control and ZDF male rats (age 6 mo, n=3/group) were used for the current study. Spatial metabolomic analysis of glomeruli in Control and ZDF rat kidneys was performed using MALDI-MSI at 20 μm spatial resolution from replicate samples per animal. Metabolites were detected at mass accuracy <2 ppm using Q-Exactive orbitrap MS followed by annotations using METASPACE. SygnaMap’s MSI-DeepPath computational platform was used to register each glomerulus in a section to the corresponding MSI pixel and then quantify the annotated metabolites per glomerular pixel.

Results: Of 1600 metabolites annotated at m/z range 70-500 Da the top features were selected by ranking individual metabolite intensity per pixel in the normal and the diabetic groups. The top metabolite in normal glomeruli was L-glutamic acid and in diabetic glomeruli was D-glucose. Based on the top 20 enriched metabolites, the most prominent pathway in the normal glomeruli was Arginine biosynthesis whereas the most prominent pathway in the diabetic glomeruli was Glyoxylate and dicarboxylate metabolism.

Conclusions: For the first time, MSI-DeepPath enables quantification of spatial metabolomics of glomeruli using untargeted MALDI-MSI data. With MSI-DeepPath-based analysis of kidney sections from the ZDF rat, we identified that Glyoxylate-dicarboxylate metabolism was the most prominent pathway in the diabetic glomeruli. As glyoxylate is a highly reactive aldehyde and can be nephrotoxic via conversion to oxalate, further studies on glomerular glyoxylate-dicarboxylate metabolism will shed new light on its potential role in diabetic glomerular disease.

Funding: NIDDK, Support, Other U.S. Government Support

SA-OR92
Single-Nucleus Transcriptome Profiling of the Kidney Glomerulus Identifies Cell-Specific Responses in an Autoimmune Mouse Model of Membranous Nephropathy
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Background: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. However, the pathogenic mechanisms remain poorly understood due to a missing comprehensive characterization of cell-specific changes during disease progression.

Methods: We developed a novel pipeline involving the gentle enrichment of glomeruli followed by single-nucleus RNA-sequencing (snRNA-seq). We applied this technique to mice with experimental autoimmune ThSD7A-associated MN at different time points.

Results: We generated a transcriptomic landscape involving 91,114 single-nuclei, with >95% deriving from glomerular cells, i.e. podocytes, mesangial cells and endothelial cells (ECs). This procedure provided a high-quality dataset with only minimal technical perturbations such as stress gene activation during the single cell dissociation process. Distinct changes in gene expression specific to podocytes were identified in MN model mice. A side-by-side comparison with other snRNA-seq datasets revealed both an MN-specific gene expression profile as well as transcriptomic alterations observed also in other glomerular nephropathies. Pathways enriched in MN model mice included regulation of focal adhesion, actin cytoskeleton, cell migration, and changes in kinase activities in podocytes. We further found increased infiltration of immune cells with disease progression and a cluster of proliferating/repairing cells mainly consisting of mesangial cells and ECs in MN model mice. Interestingly, mesangial cells and ECs were identified to participate in modulation of leukocyte transendothelial migration, cytokine signaling, and cell-cell/cell-matrix interactions, indicating the involvement of various glomerular cell types in the pathogenesis of MN.

Conclusions: Our study identifies cellular pathways underlying podocyte injury in experimental MN and provides important novel molecular insights into the pathogenesis of MN.

SA-OR93
Lymphangiogenesis Regulates the Differentiation and Function of Th1 Cells in Experimental Anti-Glomerular Basement Membrane (GBM) Crescentic Glomerulonephritis (cGN)
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Background: Increasing evidence has shown the critical role of Th1 cells in the pathogenesis of anti-GBM cGN, however, the underlying mechanism is unclear. Our previous study has reported lymphangiogenesis regulate the activation and polarization of T cells in chronic kidney diseases. However, whether lymphatic vessel endothelial cells (LECs) controls the differentiation of Th1 cells in anti-GBM cGN remains unknown.

Methods: To address this question, we established the selective proliferating lymphatic vessel knockout mice for experimental autoimmune THSD7A-associated MN model. Single-cell RNA sequencing, Bulk RNA sequencing and histological methods were used to investigate the immunopathological features of various renal T cells in anti-GBM cGN. Intra-renal LECs were obtained through multicolor flow cytometry and smart sequencing technology was applied to analyze the transcriptional signature of LECs.

Results: We found lymphangiogenesis is actively involved in anti-GBM cGN. Depletion of proliferated LECs protects against anti-GBM cGN. Most significantly, the proportion of Th1 cells in the LECs knockout mice decreased with a significantly down-regulated interferon response. Smart sequencing analysis on LECs revealed that the expression of IFNγ which promotes Th1 differentiation increased significantly in anti-GBM cGN group, but decreased in LECs knockout group. At the same time, the expression of cDC1, the main effector cell to induce Th1 differentiation, changes from pro-inflammatory activation to regulation of tolerance. In addition, the transcriptional expression profiles of T cells enriching the signal pathways related to Th1, Th2 and Th17 cell differentiation were inhibited after LECs knockout. It is further demonstrated that LECs also produce chemokines CCL5 and XCL1 to recruit cDC1, which was reversed by LECs knockout in anti-GBM cGN.

Conclusions: Our studies reveal functionally crosstalk between LECs and T cells in anti-GBM cGN, LECs directly or indirectly involved in the chemotaxis, differentiation and activation of Th1 cells. In conclusion, the findings presented a new unidentified role for lymphangiogenesis in progressive immune-mediated kidney disease, implying that LECs-Th1 cell axis can be a novel and effective immunotherapy target for anti-GBM cGN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-OR94
Bub1 Is a Potential Mediator of TGFβ-Induced Renal Fibrosis
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Background: Bub1 is a conserved eukaryotic kinase and mouse Bub1 gene-deficient mice are embryonic lethal. Bub1 has long been recognized to localize to the centromere in mitosis as a component of the spindle checkpoint complex and to regulate chromosome segregation. Meanwhile, on siRNA screening targeting human kinases against cancer cell lines, it has been suggested that Bub1 may co-express with TGFβ receptors to regulate Smad3 phosphorylation. Since TGFβ-SMAD pathway is a major pathway in fibrosis, it is assumed that Bub1 may be involved in development of fibrosis as a novel mediator of the TGFβ-SMAD pathway. These findings are limited to cancer cell lines, therefore, it remains unknown whether similar events will be identified in the kidney.

Methods: The expression and localization of Bub1 was confirmed in the kidney of wild type (BL6) mice. To generate conditional Bub1 knockout mice, the Bub1+/− mice were crossed with eGFP-Cre mice or Fsp1-Cre mice. Renal fibrosis was induced in 8-10 week old male conditional Bub1 knockout mice by unilateral ureteral obstruction (UUO) model. In vitro, human renal proximal tubular epithelial cells (HK-2) were cultured, then Bub1 knockout was performed by siRNA transfection.

Results: In wild-type mice, Bub1 was expressed in renal tubular epithelial cells by immunofluorescence staining with LTA. The Bub1 staining was diminished in conditional Bub1 renal knockout mice. Renal fibrosis and the expression of aSmA induced by UUO were attenuated in the mice with Bub1 proximal tubular cells (PTCs) knockout compared to wild type mice. On the other hand, the renal fibrosis induced by UUO in the mice with Bub1 fibroblasts knockout was not changed compared to wild type mice. Furthermore, knockdown of Bub1 in HK-2 cells attenuated the phosphorylation of Smad3 by TGFβ stimulation.

Conclusions: These results uncovered that Bub1 deficiency of renal proximal tubular cells plays a protective role in renal fibrosis triggered by UUO via TGFβ-SMAD pathway. Further studies are needed to clarify the role of Bub1 in renal diseases.

Funding: Government Support - Non-U.S.

SA-OR95
Protective Role of RBPjk in HIV-Related CKD
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Background: The Notch signaling is activated in HIV-associated Nephropathy. The Notch signaling is initiated when a ligand binds to a Notch receptor and leads to cleavage and translocation of the Notch intracellular domain (NICD) into the nucleus. NICD binds to RBPjk and converts it into a transcriptional activator from a repressor and leads to activation of Notch downstream targets. The HIV-LTR promoter contains two RBPjk binding sites. It is thought that RBPjk is a repressor of HIV-LTR. This would imply counterintuitive roles of Notch and RBPjk in HIV-related diseases. Here we investigate for the first time the in vivo roles of RBPjk in regulating the podocyte and myeloid-specific HIV gene expression.

Methods: The Tg26 mice harbor the active HIV-LTR promoter in many cells/tissues. Tg26 mice were bred with floxed RBPjk mice. The resulting mice were further bred with mice harboring podocin-cre or lysM-cre promoters to drive the RBPjk deletion in podocytes or myeloid precursors, respectively. The resulting mice, Tg26: RBPjkKO-Pod or Tg26:RBPjkKO-LysM were compared with normal or Tg26 mice. Renal disease severity was assessed by histology, renal function and inflammation assessment. Nef gene expression served as a measure of HIV-LTR activity.

Results: Deletion of RBPjk alone in podocytes led to disease aggravation and early lethality in Tg26 mice. Compared to Tg26 mice, Tg26:RBPjkKO-Pod mice exhibited increased collapsing glomerular phenotype, focal segmental glomerulosclerosis, blood urea nitrogen, tubular dilations and fibrosis. There was an increase in inflammatory markers IL6 and MMP10. NFκB (p65) was drastically elevated in the glomerular and tubular compartments. RBPjk deletion in podocytes of Tg26 mice did not affect Nef expression. Moreover, a significant increase in the nef expression was observed. Similarly Tg26:RBPjkKO-LysM mice had increased disease severity compared to Tg26 mice but less than Tg26:RBjpkKO-Pod mice.

Conclusions: RBPjk deletion in podocytes may be sufficient to activate the HIV-LTR promoter which increases expression of HIV genes leading to inflammation and disease aggravation. This indicates a non-canonical Notch signaling activation and Notch-independent roles of RBPjk in HIV-related diseases. Eliciting these mechanisms are important for treatment development and add to our understanding of the latency caused by HIV in people treated with antiretroviral therapy.

Funding: NIDDK Support, Other NIH Support - NIGMS NIH P20 GM103418

SA-OR96
Changes in Gene Expression in Fatty Acid Metabolism and De Novo Lipogenesis Are Conserved in Human CKD and Animal Models
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Background: Lipid accumulation has been consistently observed in kidneys of patients with various kidney diseases. Altered fatty acid oxidation (FAO) and de novo lipogenesis (DNL) signaling are proposed to drive the fatty kidney’s transition to kidney disease. However, changes in lipid composition and mechanisms of lipid accumulation that specifically drive alterations in FAO, DNL, and lipid uptake have not yet been characterized in unbiased manner.

Methods: We collected control (healthy) and diseased (diabetic and hypertensive kidney disease) human kidney samples from surgical nephrectomies. Demographics, clinical information, and estimated Glomerular Filtration Rate (eGFR) were collected, and histological analysis was performed by our renal pathologist. We analyzed gene expression changes in 405 microdissected human kidney tubule samples by RNA sequencing (RNA-seq). Bulk RNA-seq data from 3 mouse induced CKD models–unilateral ureteral obstruction (UUO), n=3, folic-acid induced nephropathy (FAN, n=3), and tubule-specific deletion of mitochondrial transcription factor A (TFAM, Ksp/Cre/ Tam1loxP, n=3)–was generated. Furthermore, an unbiased metabolomics analysis was performed on both human and mouse kidney samples using the Metabolon platform.

Results: Kidney metabolobolism data indicated complex changes in lipid levels. We observed accumulation of glycerophospholipids in diseased kidney samples. Transcripts related to FABP (ACOX1, ACOT1, ACOX2, ACOX3, CPT2, ESRAF, HADHFB, HADHB, PGC1a, PPARa, SLC25A20) were lower in kidneys of mouse CKD models. Their expression levels positively correlated with kidney fibrosis and negatively correlated with eGFR. Genes associated with DNL genes (ACSS2, ChREBP, SCD, FABP4, FASL, FASN) showed higher expression in mouse kidney disease models; their expression levels negatively correlated with fibrosis and slightly positively correlated with eGFR.

Conclusions: Unbiased metabolomics and gene expression analysis of human and mouse kidneys indicated increased lipid accumulation in diseased kidneys. Decrease in FAO and to some degree an increase in DNL likely contribute to lipid accumulation.

Funding: NIDDK Support, Commercial Support - Regeneron, Gilead, Novo Nordisk, Genentech, Novartis Boehringer Ingelheim, Bayer, Ventus, Variant Bio, Maze
serum Gd-IgA1 absolute value and relative proportion to IgA1 increased 4 times in IGHA1+/−LCWE mice. We quantitatively analyzed the glycosyltransferases of human IgA1 hinge region (HR) using LC-MS analysis and found HR from IGHA1+/−LCWE mice showed hypo-galactosylation than IGHA1+/−PBS mice. IGHA1+/−LCWE mice showed a continuous and stable human IgA1 (positive rate: 100%) kidney mesangial deposition with C3 co-deposits (positive rate: 81.25%) until 8 months old. Histology demonstrated a significant rise in mesangial expansion and hypercellularity. Electron microscopy showed typical mesangial electron-dense deposits in IGHA1+/−LCWE mice.

**Conclusions:** We established a novel serum Gd-IgA1 elevated mouse model presenting typical pathological characteristics of IgAN, which will be used to further explore the mechanisms and new therapeutic strategies.

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

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**TH-PO002**

**Assessing Drug Interactions with Tacrolimus: Evaluating ChatGPT as a Promising Resource for Drug Interactions with Tacrolimus**


**Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN.**

**Background:** Tacrolimus is the most common immunosuppressant in kidney transplantation recipients. However, its blood concentration can be affected by other medications and thus, assessing drug interactions is essential to optimize its efficacy and minimize toxicity. ChatGPT is a high-capacity language model proficient in natural language processing tasks. This study aims to evaluate the accuracy of ChatGPT in assessing drug interactions involving tacrolimus.

**Methods:** We used the Micromedex Drug Interactions and Lexicomp databases to evaluate ChatGPT’s ability to correctly assess if a drug interaction with Tacrolimus was present and in what direction should the tacrolimus dose be adjusted. A total of 79 drugs were chosen based on the risk rating of D (consider therapy modification) or X (avoid combination). Each question was executed twice using ChatGPT (03/2023, OpenAI), and we determined the concordance between the 2 runs, conducted 2 weeks apart. An additional assessment was conducted using ChatGPT to draw a conclusion from our study.

**Results:** The overall accuracy of ChatGPT in assessing the presence of drug interactions with tacrolimus was found to be 96% on the 1st run and 98% on the 2nd run. The direction of adjustment was correct in 87% on both runs. The concordance in correct answers was 96% for the need of adjustment and 86% on the direction. ChatGPT itself acknowledged these results, emphasizing that while it exhibits promising accuracy, it should not be the sole source of information for clinical decision-making. Comprehensive and reliable assessment of drug interactions and dosing adjustments should involve consultation with additional resources and healthcare professionals.

**Conclusions:** ChatGPT demonstrated an accuracy exceeding 96% regarding the presence of drug interactions involving tacrolimus. However, when asked about the adjustment direction, the accuracy dropped to 87%. The integration of ChatGPT in clinical practice should be accompanied by caution and should not replace consultation with healthcare professionals or the utilization of comprehensive resources. Future steps should focus on refining ChatGPT’s capabilities to ensure its safe and effective use in assessing drug interactions involving tacrolimus.

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**TH-PO004**

**Unraveling ChatGPT's Performance in Addressing ESKD: Implications for Artificial Intelligence (AI)-Assisted Healthcare**


**Mayo Clinic Rochester, Rochester, MN.**

**Background:** ChatGPT is an AI-powered cutting-edge language model that has demonstrated outstanding capabilities in numerous natural language processing tasks, such as generating responses resembling those crafted by human beings. While there has been growing discussion about ChatGPT’s potential to serve as a replacement for physicians in clinical contexts, its proficiency in nephrology, specifically chronic kidney disease, remains unclear. The objective of this study is to evaluate ChatGPT’s accuracy in answering essential questions related to chronic kidney disease, such as diagnosis, treatment, and management.

**Methods:** We evaluated ChatGPT’s performance using the Nephrology Self-Assessment Program (NephSAP) and Kidney Self-Assessment Program (KSAP) question banks (57 questions). We used the Micromedex Drug Interactions and Lexicomp databases to evaluate ChatGPT’s ability to correctly assess if a drug interaction with Tacrolimus was present and in what direction should the tacrolimus dose be adjusted. A total of 79 drugs were chosen based on the risk rating of D (consider therapy modification) or X (avoid combination).

**Results:** ChatGPT’s performance in chronic kidney disease fell below the minimum passing threshold of 75% set by the ASN for nephrologists. On the NephSAP question banks, ChatGPT achieved accuracies of 58.3% and 53.8% on the 1st and 2nd runs, respectively, with an overall concordance of 86.7%. Similarly, on the KSAP question banks (57 questions), the accuracy of ChatGPT was 47.4% and 42.1% on the 1st and 2nd runs, respectively, with a concordance of 68.4%. The overall concordance between the two runs was 77.8%. The concordance in correct answers was found to be higher than that of incorrect answers (43.6 vs 34.2%).

**Conclusions:** Upon evaluating ChatGPT’s performance in answering questions related to kidney transplantation, we found that its accuracy was below the passing threshold set by the ASN for both NephSAP and KSAP. Excluding questions with clinical images, the overall accuracy of ChatGPT (NephSAP + KSAP) was found to be 53% on the 1st try and 50.4% on the 2nd one. From this we conclude that the current version of ChatGPT is not yet a reliable medical education tool for training nephrologists, and requires further development.

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**TH-PO003**

**The Performance of ChatGPT in CKD: An Assessment Using NephSAP and KSAP**

Pajaree Krisanapan,1,2 Supawat Tangpanthicide,1 Oscar A. Garcia Valencia,1 Jing Miao,1 Charat Thongprayoon,1 Wisit Cheungpasitporn.1,3 Mayo Clinic Minnesota, Rochester, MN; 4Thammasat University Hospital, Klong Nueng, Thailand.

**Background:** ChatGPT is an AI-powered cutting-edge language model that has demonstrated outstanding capabilities in numerous natural language processing tasks, such as generating responses that closely resemble those created by human beings. While there has been growing discussion about ChatGPT’s potential to serve as a replacement for physicians in clinical contexts, its proficiency in nephrology, specifically chronic kidney disease, remains unclear. The objective of this study is to evaluate ChatGPT’s accuracy in answering essential questions related to chronic kidney disease, such as diagnosis, treatment, and management.

**Methods:** We evaluated ChatGPT’s performance using the Nephrology Self-Assessment Program (NephSAP) and Kidney Self-Assessment Program (KSAP) question banks (from 2020-2023) of the ASN. Questions containing images were excluded. A total of 323 questions were included, with 205 from NephSAP and 103 from KSAP. Each question bank was executed twice using ChatGPT, and agreement between the initial and subsequent runs was determined.

**Results:** ChatGPT’s performance in chronic kidney disease fell below the minimum passing threshold of 75% set by the ASN for nephrologists. On the NephSAP question banks, ChatGPT achieved accuracies of 53.2% and 55.6% on the first and second runs, respectively, with an overall agreement of 78.1%. On the KSAP question banks, ChatGPT’s accuracy was 48.5% and 44.7% on the first and second runs, respectively, with an overall agreement of 74.5%. ChatGPT’s level of agreement between initial and subsequent runs was higher for correct answers compared to incorrect ones.

**Conclusions:** Based on these results, it can be concluded that the current version of ChatGPT is not yet a fully reliable and useful medical education tool for clinical physicians, medical students, and nephrologists, and requires further development.
about the potential of ChatGPT as a substitute for physicians, its abilities in the field of nephrology, particularly in ESKD including dialysis, remains uncertain. The objective of this study is to assess the performance of ChatGPT in addressing fundamental inquiries pertaining to ESKD.

**Methods:** We conducted an evaluation of ChatGPT’s accuracy in answering questions related to CKD, ESKD, including hemodialysis, and peritoneal dialysis, using the ASN eLEARNING CENTER (nephSAP and Dialysis Core Curriculum 2021). There were 95 questions included. Each question set was executed twice using ChatGPT (Mar 14 version, OpenAI), and the level of agreement between the initial and subsequent run, conducted two weeks apart, was determined. Also, an assessment was performed using ChatGPT using the query, “Based on these findings, what is ChatGPT’s performance, and is ChatGPT ready to provide answers pertaining to ESKD?”

**Results:** In our study evaluating ChatGPT’s performance in answering questions related to CKD and ESKD, we found that on the two different question banks combined, ChatGPT achieved accuracies of 54% and 57% on the first and second runs, respectively. The overall agreement between the two runs was 71%. The study revealed that the level of agreement between the initial and subsequent runs of ChatGPT was higher for correct answers compared to incorrect ones, concordance of 46% vs 24%, respectively. Among the 28 instances where ChatGPT provided different responses, it changed from incorrect to correct in 10 questions (36%), from correct to incorrect 7 times (25%). ChatGPT acknowledged these results, further highlighting its limitations in accurately addressing questions related to ESKD.

**Conclusions:** The current study demonstrates that ChatGPT’s accuracy in answering questions related to ESKD is below the minimum passing threshold of 75% set by the ASN for nephrologists, with an accuracy of 55% (average of the two runs), indicating the need for further development and training to improve its accuracy and consistency.

**TH-PO006**

**ChatGPT vs. a First-Year Nephrology Fellow in Electrolyte and Acid-Based Disorders**

*Poemlarp Mekraksakit, Pajaree Krisanapan, Jasmina Craici, Kambiz Kalantari, Charat Thongprayoon, Wisit Cheungpasitporn. Mayo Clinic Minnesota, Rochester, MN.

**Background:** ChatGPT is a leading natural language processing model known for its artificial intelligence ability to generate human-like responses in various tasks. This study aims to assess ChatGPT’s proficiency in addressing electrolyte and acid-base disorders in Nephrology.

**Methods:** In our study, we used nephSAP and KSAP, provided by the American Society of Nephrology (ASN), to assess ChatGPT’s accuracy in answering basic questions about electrolyte and acid-base disorders. Questions with images were excluded as ChatGPT cannot process images. We evaluated a total of 152 questions, with 122 from KSAP and 30 from nephSAP. ChatGPT was tested twice, with the initial and subsequent runs conducted 1 to 2 weeks apart. To compare scores, we considered the performance of a first-year Nephrology fellow who extensively studied this topic. The complete set of questions can be found at https://education.asn-online.org/.

**Results:** In the 122 KSAP question banks, ChatGPT achieved accuracies of 32.8% and 37.7% on the first and second runs, respectively. In comparison, a first-year Nephrology fellow achieved an accuracy of 76.2%. On the nephSAP question banks, consisting of 30 questions, ChatGPT demonstrated an accuracy of 50% on the initial run and 53.3% on subsequent runs. The first-year Nephrology fellow correctly answered 83% of the questions. Notably, ChatGPT changed its answers on the second run for 56 out of 152 questions (36.8%). Out of these 56 questions, ChatGPT corrected its answers from incorrect to correct in 18 cases, but also changed its answers from correct to incorrect in 10 instances.

**Conclusions:** ChatGPT’s proficiency in addressing electrolyte and acid-base disorders in nephrology is limited. It did not achieve the minimum passing threshold of 75% set by the ASN for nephrologists. Its accuracies were lower compared to a dedicated first-year Nephrology fellow. ChatGPT’s responses were inconsistent across different runs. Therefore, ChatGPT is not a suitable replacement for human clinicians in this clinical setting.

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

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**TH-PO007**

**The Accuracy of Artificial Intelligence in Identifying Potentially Harmful Non-Prescription Medications and Dietary Supplements in Patients with Kidney Diseases**


**Background:** Search engines are commonly used to obtain health-related information, including information about drug safety. Non-prescription medications and supplements are generally perceived as safe; however, may be harmful to patients with kidney diseases. ChatGPT is a cutting-edge language model that has gained attention for its potential to improve clinical decision making. Its ability to serve as a drug information resource for patients with kidney disease has not been determined. This study aimed to evaluate ChatGPT’s accuracy in discerning the safety of medications in patients with kidney diseases when compared to Micromedex, a widely used tertiary drug information reference.

**Methods:** One hundred twenty-four commonly used non-prescription medications and supplements were evaluated in ChatGPT using the query “Is X potentially harmful in people with kidney disease?” The resultant output was evaluated and categorized into one of three categories: “generally safe”, “potentially harmful”, or “unknown” level of harm. Safety of the non-prescription medications and supplements was also evaluated in Micromedex and categorized similarly. Concordance between the two resources was summarized.

**Results:** Micromedex identified 68(55%) medications as safe, 52(42%) as potentially harmful, and 4(3%) as unknown. ChatGPT identified 74(60%) medications as safe, 26(21%) as potentially harmful, and 24(19%) as unknown. The overall agreement between Micromedex and ChatGPT was 65% with ChatGPT identifying only 46% of potentially harmful medications. Supplements as a subclass had the lowest concordance between ChatGPT and Micromedex, with a rate of 56%. Among the 24 medications identified as unknown by ChatGPT, 21(87%) were supplements.

**Conclusions:** ChatGPT’s accuracy to identify the safety of non-prescription medications, particularly supplements, was modest in patients with kidney disease when compared to a contemporary drug information resource. The findings suggest that ChatGPT neither be considered nor recommended as a drug information resource for patients with kidney disease or their healthcare professionals. Further development would be necessary to improve its accuracy and reliability in this domain.
TH-PO008
Application of Large Language Models such as ChatGPT to Support Nutritional Recommendations for Dialysis Patients
Lin-Chun Wang,1 Hanjie Zhang,1 Nancy Ginsberg,2 Peter Kotanko.1,3 Renal Research Institute, New York, NY; 2Fresenius Kidney Care, Waltham, MA; 3Icahn School of Medicine at Mount Sinai, New York, NY.

Background: The diversity of food preferences has increased over the past years and provides challenges to dietitians working in dialysis clinics. We explored the use of Large Language Models (LLM), such as ChatGPT, to support nutritional advice given to patients.

Methods: We applied a simple LLM syntax that allows us to consider a variety of factors that determine personalized dietary recommendations/menus options. The syntax integrates several domains, such as patient demographics (e.g., age, sex, dialysis vintage) and food preferences (e.g., vegetarian, Indian, Mediterranean, etc.), laboratory data (e.g., levels of phosphate, potassium), and clinical characteristics (e.g., weight, BMI, blood pressure). We deployed these characteristics as queries to ChatGPT (ChatGPT (openai.com)). The resulting dietary recommendation were reviewed by an experienced renal dietitian.

Results: The ChatGPT command line allowed simple input of inquiries. We were able to narrow down and personalize requests in a short dialogue with the bot, for example: “John is a hemodialysis patient aged 63, with diabetes, CHF and fluid overload, his weight is 95 Kg, BMI is 32, his albumin is 3.5 g/dl, potassium is 4.8 mmol/L, phosphorua is 3.3 mg/dl. John likes Mediterranean food. Could you develop a few recipes for him?” We created multiple requests for several imagined patients. The review of the bot’s dietary recommendations by a renal dietitian was in general satisfactory. However, while the amount of phosphate was targeted, phosphate additives were not considered by the LMM. We also explored the use of ChatGPT to create personalized dietary recommendations/ menu options in different languages, such as Mandarin. The translations, as judged by native speakers, were reliable.

Conclusion: While we identified some gaps, LLMs such as ChatGPT hold promise to provide personalized nutritional guidance to diverse populations of hemodialysis patients. As a next step, exploring their application in clinical practice will be important.

Funding: Commercial Support - Renal Research Institute

TH-PO009
Artificial Intelligence Language Processing Models in Literature Reviews for Nephrology
Supawadee Supadungsook,1,2 Pajaree Krisapanan,1,2 Supawat Tapanathanrude,2 Oscar A. Garcia Valencia,1 Charat Thongprayoon,1 Kianoush Kashani,2 Wiwat Chungsapitisorn1,3 Mayo Clinic Minnesota, Rochester, MN; 1Chakri Naruobudsed Medical Institute, Bang Phli, Thailand; 3Thammasat University, Bangkok, Thailand.

Background: Literature reviews are a valuable tool for summarizing and evaluating the available evidence in various medical fields, including Nephrology. However, identifying and selecting relevant literature can be time-consuming for clinicians and researchers. ChatGPT is a novel artificial intelligence (AI) language model renowned for its exceptional ability to generate human-like responses across various tasks. However, whether ChatGPT can effectively assist medical professionals in identifying relevant literature is unclear. Therefore, this study aimed to assess the effectiveness of ChatGPT in identifying references to literature reviews in Nephrology.

Methods: We keyed the prompt “What are the references to literature reviews in Nephrology, with subgroup analysis in specific areas?” into ChatGPT (03/23 Version). We selected all provided results by ChatGPT and assessed them for existence, relevance, and author/link correctness. We recorded each resource’s citations, references, authors’ names, and links. The relevance of each resource was assessed by its citation index on Google Scholar.

Results: Of the total 511 references in Nephrology literature, only 319 (62.43%) of the references provided by ChatGPT existed, while 30.3% did not exist, and in 7.3% of recommendations, they were negative. To improve the nephrology workforce, we must address the concerns of trainees identified here.

Funding: NIDDK Support

TH-PO011
Kidney Outcome Comparisons of Clinician Evaluated Electronic AKI Alerts
Abinet M. Aklilu, Kyle D. O’Connor, Francis P. Wilson. Yale School of Medicine, New Haven, CT.

Background: The personalized recommendations for hospitalized patients with Acute Kidney Injury (AKI) using a Kidney Action Team (KAT-AKI) trial is an ongoing multicenter randomized clinical trial evaluating early recommendations for AKI. It is unknown whether clinician adjudication of an electronic alert for AKI can improve AKI diagnosis.

Methods: We used data from KAT-AKI trial that utilizes an EHR alert for real-time diagnosis of AKI in hospitalized patients. The alert implements the KDIGO serum creatinine(sCr) based AKI criteria (a50% ↑ or 3.0 mg/dl ↑) in 7day and 48hour windows. A trained team of a physician and pharmacist receives an InBasket EHR alert. The team independently reviews sCr trend to adjudicate the AKI diagnosis then select agree or disagree. Patients with eGFR ≤59 mL/min/1.73m², end-stage kidney disease or admission sCr ≥4mg/dl were excluded. We compared the distribution of ΔsCr72 (a difference between sCr at AKI and the maximum sCr in the subsequent 72hrs), ΔsCr95 (difference between AKI sCr and max sCr in the next hospital days), 14-day progression to a higher AKI stage, length of stay(LOS) between alerts flagged as AKI− and AKI+. We used Wilcoxon-Rank Sum test to compare continuous variables and χ² test for categorical variables.

Results: Between November 2021 and April 2023, 2414 alerts were screened. The team disagreed with 431 (17.9%) of EHR alerts. Baseline sCr and AKI sCr were lower in the AKI− group(Table1). Median(sCr) ΔsCr72 = 0.02[0.00,0.35]mg/dl (AKI−), while ΔsCr72 was 0.02[0.00,0.35]mg/dl respectively. 14-day AKI progression was 12.6%(AKI+1) vs 9.7%(AKI−), p=0.099. There was no difference in LOS.

Conclusion: Real-time clinician adjudication of an AKI alert did not improve AKI diagnosis as measured by prediction of AKI persistence or progression.

Funding: Other U.S. Government Support

Table1

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<td>baseline sCr median (IQR)</td>
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<td>1.10 (1.01,1.19)</td>
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<td>KDIGO AKI stage (n, %)</td>
<td>2 (1.0)</td>
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Disclosures: Underline represents presenting author.
Noninvasive Artificial Intelligence (AI)-Enhanced Electrocardiographic Detection of Hyperkalemia in the Emergency Department (ED) and ICU
John J. Dillon, Kan Liu, Jennifer Dugan, Jacob Jentzer, Zachi I. Attia, Paul Friedman, David M. Harmon. Nephrology/Cardiology. Mayo Foundation for Medical Education and Research, Rochester, MN.

Background: We have previously trained a convolutional neural network using an all-patient cohort to produce an AI algorithm that can detect hyperkalemia from the surface ECG. In this validation study, we assessed the network’s performance among ED and ICU patients.

Methods: We included adult patients presenting to the ED at all Mayo Clinic sites between February and August 2021 (ED cohort) and patients admitted to the ICU at Mayo Clinic Rochester, MN between August 2017 and February 2018 (ICU cohort) if they provided research authorization, had a standard 12-lead supine ECG and had a blood K value within 4 hours of the ECG. The network analyzed leads I and II of the 12-lead ECG to calculate the probability of hyperkalemia, defined as K>6 mEq/L. The ED and ICU cohorts were analyzed separately. Exploratory subgroup analyses were performed for patients with eGFR<45 ml/min and eGFR<30 ml/min.

Results: 40,128 ED patients and 2636 ICU patients were included. The prevalence of hyperkalemia was 0.9% in the ED cohort and 3.3% in the ICU cohort. The AI-ECG had AUCs of 0.88 in both cohorts with sensitivities and specificities of 80%. Negative predictive values (NPVs) were >99% in both cohorts. Although positive AI-ECGs quadrupled the probability of hyperkalemia, positive predictive values (PPVs) were relatively low: 3.3% in the ED and 14% in the ICU in part due to low hyperkalemia prevalences. Low eGFR subgroups had higher hyperkalemia prevalences and higher PPVs as shown in the Table.

Conclusions: The AI-ECG demonstrated excellent discrimination with AUCs of 0.88 in both cohorts. It was highly effective at ruling out hyperkalemia with NPVs>99% in both cohorts, but with much lower PPVs, suggesting that it is most useful as a screening test to exclude hyperkalemia. One method by which PPVs can be increased is by limiting testing to high-risk populations, such as those with reduced eGFR.

Funding: Clinical Revenue Support

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TH-PO013

Machine Learning Algorithm in Predicting Non-Diabetic Kidney Disease in Type 2 Diabetes Mellitus: Development and Validation of a Noninvasive Predictor Scoring Model
Vamsidhar Veenanki, Narayan Prasad, Jeyakumar Meyyappan, Nephrology-SGPGI, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.

Background: Identifying non-diabetic kidney disease (NDKD) is essential in retarding the progression of chronic kidney disease among patients with type-2 diabetes mellitus (T2DM). Renal biopsy, despite being the gold standard in detecting the presence of NDKD, has an inherent risk of life-threatening complications. The current study aims to develop a non-invasive scoring model to predict the presence of NDKD using clinical and laboratory parameters.

Methods: Patients with T2DM who underwent biopsy for various indications were included and were divided into derivational and validation cohorts. Using the variables significantly associated with presence of NDKD on univariate analysis, a model was developed using multivariate logistic-regression based machine learning algorithm. The model was then run on the derivational (internal validation) and validation cohort (temporal validation) and the performance was assessed by receiver operating characteristic (ROC) curve.

Results: A total of 538 patients with T2DM were included in the study analysis; 376 in derivational cohort and 162 in validation cohort. The final model consists- diabetes mellitus duration < 5 years, absence of coronary artery disease, absence of diabetic retinopathy, presence of oliguria, acute rise in creatinine, & low serum complement-C3 level significantly predicted presence of NDKD on renal-biopsy. The model performed robustly with AUC-ROC of 0.869(95% CI:0.805-0.933) in validation cohort.

Conclusions: The clinical and laboratory parameter-based prediction model robustly predicted the NDKD among T2DM patients, and a cut-off total score of ≥ 6 has a high sensitivity & specificity of 86% & 80% in predicting NDKD.

TH-PO014

The Renal Prognosis Prediction Model of Diabetes Nephropathy Based on Machine Learning
Chuanpeng Wang,1 Peng Xia,1 Ze Zhao,2 Yubing Wen,1 Limeng Chen,1
1Department of Nephrology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China;
2Institute of Computing Technology, Chinese Academy of Sciences, Beijing, China.

Background: Diabetes nephropathy (DN) has become one of the most common causes of chronic kidney disease (CKD). This study is to establish a prognosis prediction model of DN using machine learning methods.

Methods: This retrospective cohort study enrolled 247 DN patients diagnosed by renal biopsy at Peking Union Medical College Hospital from December 2012 to September 2021 and collected clinical data from the EMR system. The primary endpoint
was all-cause mortality, end-stage renal diseases (ESRD) requiring dialysis and kidney transplantation. We used maximum likelihood estimation to complete the missing data and principal component analysis to standardize the data. K-means, hierarchical, and SOM clustering were compiled in Python to classify the data set. The weight of each variable in the clustering model was measured by several model misjudgments after removing the variable. The weight Analysis was to find the potential risk factors for poor prognosis.

Results: About 57.5% of patients had renal insufficiency, and 62% with massive proteinuria. A total of 100 of them reached the primary endpoint with a median renal survival time of 2 years. Multivariate Cox regression showed that the independent risk factors for renal survival included proteinuria (OR = 1.13, 95%CI (1.07, 1.20), P<0.001), grade 3 hypertension (OR = 2.55, 95%CI (1.09, 5.99), P<0.031) and low eGFR (OR = 1.02, 95%CI (1.00, 1.03), P=0.043). By cluster analysis, two groups of patients had significant difference in renal survival at six months (OR=3.06, 95%CI (1.05, 8.92)) 12 months (OR=4.00, 95%CI (1.65, 9.70)), and 24 months (OR=2.46, 95%CI (1.78, 3.40)), as well as 24hUP (p<0.001), urinary red blood cells (p<0.001), hemoglobin (p=0.003), and albumin (p<0.001). 3. The machine learning models using LR, xgboost, and AdaBoost have the highest accuracy of prediction results in the test set, with an accuracy of up to 87.8% and auc = 0.87; The ten characteristics with the highest weight in this model were blood chloride, hypertension grade, creatinine, EGFR, gender, diabetes retinopathy, age since the onset of diabetes, free triiodothyronine, urinary red cells, and plasma proteins.

Conclusions: Machine learning models combined with patient history and laboratory examination are a potentially powerful method for predicting the DN prognosis.

Funding: Government Support - Non-U.S.

TH-PO015
Impact of Retinal Photography-Based Deep Learning System on Risk Stratification for CKD Progression
Young Soo Jou,1,2 Hye Byung Koh,1,2 Tyler H. Rim,1 Shin-Wook Kang,1,2 Jung Tak Park.1,2 Yonsei University Institute of Kidney Disease, Seodaemun-gu, Seoul, Republic of Korea; 1Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; 2Medihwaie, Seoul, Republic of Korea.

Background: We had previously developed a deep-learning-based risk evaluation system from retinal photographs, Reti-CKD, for stratifying chronic kidney disease development risk in kidney function preserved people. This study aims to evaluate whether Reti-CKD can improve risk assessment of kidney disease progression in diabetic patients with prevalent CKD.

Methods: Total of 5348 diabetic patients from two tertiary hospitals in Korea were evaluated. Patients with estimated glomerular filtration rate (eGFR) <90 ml/min/1.73m2 or albuminuria were included. Those with missing data for retinal photograph, serum creatinine, or albuminuria were excluded. Patients were categorized into low-risk, moderate-risk, and high-risk groups according to the KDIGO criteria for progression of CKD. The KDIGO groups were additionally dichotomized based on Reti-CKD score (Reti-CKD <20 and ≥20). CKD progression was compared between the categories using Cox regression models. Primary outcome was CKD progression, defined as incremental progression to a higher NKF-KDOQI CKD stage.

Results: The mean age of the patients was 62.4 ± 11.4 years and 60.6% were male. Mean eGFR was 86.6 ± 15.3 ml/min/1.73 m2 and albuminuria was present in 46.9%. During a median follow-up of 5.0 (interquartile range, 2.5-7.8) years, primary outcome incidence rate gradually increased with higher KDIGO and Reti-CKD combined risk categories. The risk for CKD progression progressively increased in KDIGO moderate-risk and high-risk groups compared to low-risk. When Reti-CKD was incorporated to the KDIGO categories, significant stratification of CKD progression risk was noted in the KDIGO low-risk and moderate-risk groups. Additionally, the combination of KDIGO and Reti-CKD classification showed better discrimination power compared to the KDIGO only classification (delta c-statistics, 0.03; 95% CI 0.02 to 0.040).

Conclusions: Retinal photography-based deep learning system (Reti-CKD) further stratifies the risk of CKD progression and improves predictability in diabetic patients with reduced renal function.

TH-PO016
Computed Tomography Radiomics Analysis for Discrimination and Severity Assessment of Diabetic Kidney: A Retrospective Machine Learning Study
Seung Hye Choo, Soyeon Kim, Hyunjin Noh, Soon hyo Kwon. Soonchunhyang University Hospital, Seoul, Republic of Korea.

Background: Kidney radiomics has been evaluated for the development of accurate diagnostics tools for renal tumors. However, there is a scarcity of radiomics studies focusing on diabetic kidney disease (DKD). In this study, we aimed to investigate whether computed tomography (CT) radiomics features can differentiate DKD from normal kidneys and assess the severity of DKD.

Methods: We analyzed type 2 diabetes mellitus (T2DM) patients and healthy controls (HCs) who underwent abdominal CT scans between November 2014 and November 2022. CT volumetric data of both kidneys were extracted using a deep-learning model, enabling radiomics feature extraction. T2DM patients were categorized into risk groups based on estimated glomerular filtration rate (eGFR) and degree of albuminuria. Machine learning (ML) models were used to differentiate DKD patients from HCs and classify DKD risk groups. The models were trained and evaluated on separate patient data sets, with performance metrics such as sensitivity, specificity, accuracy, and area under the curve (AUC).

Results: The study included 462 T2DM patients and 90 HCs, who were randomly assigned to a training set (n=586; mean age a standard deviation, 60.9 years ± 16.2; 239 men or a test set (n=166; mean age, 60.7 years ± 15.7; 91 men). A total of 1,219 radiomics features were extracted. The random forest model showed excellent performance in differentiating between HCs and patients with low-risk DKD, with an AUC of 1.00 and an accuracy of 100% in the training set and an AUC of 0.84 and an accuracy of 80.6% in the test set. It also showed a good performance in discriminating between DKD groups based on eGFR (AUCs, 0.99-1.00, in the training set, AUCs, 0.67-0.94, in the test set) (Table1).

Conclusions: CT-derived radiomics analysis of the kidneys can effectively differentiate diabetic kidneys from normal kidneys and assess the severity of DKD. These findings suggest that radiomics data capture pathological changes in the kidneys associated with diabetes.

Funding: Government Support - Non-U.S.

TH-PO017
Machine Learning Classification of Kidney Biopsy Smartphone Images for Adequacy Assessment

Background: Kidney biopsy is the gold standard for diagnosis of medical renal diseases. A biopsy that yields predominantly medulla or not enough renal cortex is an unsatisfactory result. There has been a significant increase in the rate of inadequate kidney biopsies. Unfortunately, not all centers have access to trained professionals who can assess biopsy adequacy in real time. Therefore, we aim to create a machine-learning model capable of classifying smartphone images of kidney biopsy tissue as adequate or inadequate.

Methods: 747 kidney biopsy cores and corresponding smartphone macro images were obtained from unused deceased donor kidneys. Each core was imaged, formalin fixed, sectioned and stained with Periodic acid–Schiff (PAS). A photo of the fresh unfixed core was taken using the macro camera on an iPhone 13 Pro. The amount of cortex in each core (percent cortex), was determined by two renal pathologists review of the PAS sections. Biopsies with less than 30% cortex were labelled as inadequate. Biopsies with 30% or more cortex were labeled as adequate. The images were split into a training (n=643), validation (n=30), and test (n=74) sets. The preprocessing steps were converting from HEIC iPhone format to JPEG, normalizing, and detecting the renal tissue; a U-Net deep learning model was trained to segment renal tissue from the background. After preprocessing, a deep learning model was trained on the renal tissue region of interest and corresponding class label. See Figure 1.

Results: The deep learning model had an accuracy of 87% on the training data. On the test dataset, the model had an accuracy of 82%. For inadequate samples in the test dataset, the model had a sensitivity of 71%. The area under the receiver operating curve was 0.79.

Conclusions: We developed and tested a machine learning model to classify smartphone images of kidney biopsy as adequate or inadequate, based on the amount of cortex determined by a renal pathologist. With further work, such models can be deployed as a smartphone application to aid in real time assessment of renal biopsy adequacy.

Funding: Other NIH Support - SBIR Grant Number: 1R43DK134273-01

Figure 1. Methodology Overview

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO018

Machine Learning to Predict Unplanned Dialysis in Advanced CKD
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Background: Unplanned dialysis occurs when dialysis is initiated in the hospital setting and results in increased morbidity, mortality, and healthcare costs. Patients with advanced chronic kidney disease (CKD) are at higher risk for unplanned dialysis, but it is difficult to identify those who might benefit from targeted interventions. Machine learning was used to attempt to predict unplanned dialysis in a large CKD cohort.

Methods: A retrospective analysis of 15,424 patients in a large U.S. health system with stage 4 and 5 CKD between January 2018 to March 2023 was performed using the MDClone ADAMS Platform and a proprietary CKD temporal staging algorithm. Variables included age (71.4 ± 14.9 years), gender (Female, 55%), most recent eGFR (32.4 ± 16.7 ml/min/1.73m²), count of emergency department visits in two years prior (2.2 ± 3.3), count of all clinical encounters in two years prior (33.3 ± 35), BMI (30.2 ± 9.8), hypertension (78.3%), diabetes (58.6%), obstructive sleep apnea (34.1%), peripheral arterial disease (32.7%), and systolic blood pressure (134.4 ± 24.4 mmHg). XGBoost, a gradient boosting algorithm, was employed to predict unplanned dialysis events.

Results: The model’s performance predicting unplanned dialysis was evaluated using accuracy, precision, recall, and F1 score metrics. The model achieved accuracy of 90.5%, precision of 55.2%, and recall of 54.7%, resulting in a F1 score of 0.55. Discrimination was high with an AUC 0.89 (Figure 1).

Conclusions: The model developed using a XGBoost machine learning algorithm demonstrated high accuracy and discriminatory power to identify stage 4 and 5 CKD patients at risk for unplanned dialysis. This predictive model has potential to help guide targeted interventions to prevent these events in the advanced CKD population.

Figure 1. Model Receiver Operating Characteristic Curve.

TH-PO019

Machine Learning-Based Risk Prediction Model for ICU Survival After Continuous Renal Replacement Therapy Initiation: A WEBOCK Study
Shina Menou,1,2 Sameer Thadani,2 Katja M. Gist,3 Danielle E. Soranno,4 Danny T. Wu,5 WE-ROCK, 1University of Washington, Seattle, WA; 2Seattle Children’s Hospital, Seattle, WA; 3Cincinnati Children’s Hospital Medical Center; Cincinnati, OH; 4Indiana University School of Medicine, Indianapolis, IN; 5Baylor College of Medicine, Houston, TX.

Background: Continuous renal replacement therapy (CRRT) is preferred in critically ill pediatric patients with acute kidney injury (AKI) and/or fluid overload (FO). Prediction of clinical outcomes in patients on CRRT is challenging given heterogeneous clinical practices and study population. Our aim was to predict survival to intensive care unit (ICU) and hospital (HOSP) discharge using machine learning (ML) techniques.

Methods: The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) study is a retrospective international multicenter study (32 centers, 7 nations). Our methods have been published previously. We included 991 patients aged 0-25 years treated with CRRT for AKI and/or FO from 2008-2021. Candidate data elements were selected based on clinical practice and included age at the time of renal biopsy, gender, blood tests, and renal function tests. The data were split into training (85%) and test (15%) sets after data augmentation. Models constructed using IG contained 436 features versus 42 features using CFS. The top features included blood urea nitrogen, creatinine, platelets, Glasgow coma score, and fluid balance. NB model outperformed the other approaches. The NB with IG feature selection achieved area under the ROC curve (AUCROC) 0.925, area under the precision-recall curve (AUPRC) 0.813, accuracy 0.88, F1 score 0.88, whereas the NB model with CFS achieved comparable accuracy and F1-score but the performance was slightly better with 0.945 AUCROC, 0.890 AUPRC.

Results: We present a model that uses ML and leverages structured, time-series data to identify patients likely to need CRRT in the ICU. The study’s limitations include being conducted in a single institution and not considering unstructured data, which may improve the model’s performance.

TH-PO021

Machine Learning Models for IgA Nephropathy Diagnosis: A Retrospective Study on Predictive Performance and Influential Variables
Ryuonosuke Noda,1 Duusuke Ichikawa, Yuuga Shibagaki. 1St. Marianna University School of Medicine, Kawasaki, Japan.

Background: IgA nephropathy often requires therapeutic modalities associated with potential complications, such as steroids, and so requires definitive diagnosis by invasive renal biopsy rather than non-invasive clinical diagnostic measures. Although the efficacy of machine learning (ML) for diagnostic purposes has been underscored in recent years, its application in the context of nephrology remains unclear. In this study, we investigated the diagnostic performance of ML algorithms for IgA nephropathy.

Methods: We conducted a retrospective cohort study on 1,419 cases that underwent renal biopsy in our hospital from January 2006 to September 2022. Cases with indeterminate diagnoses and overfrequent diagnoses were excluded. The remaining cases were randomly divided into train and test datasets at an 8:2 ratio. We utilized a total of 33 clinical variables which included age at the time of renal biopsy, gender, blood tests, and urinalysis, as explanatory variables. Subsequently, multiple machine learning algorithms were evaluated, including K-nearest neighbor, support vector machines, random forest, extreme gradient boosting, and LightGBM, using Python. The model with the highest average Area Under the Curve was identified through stratified 5-fold cross-validation in the train set. Thereafter, we compared the AUC of this model in the test

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set to that of the logistic regression (LR) model in the test set. To interpret the predictive outcomes, we deployed the SHapley Additive exPlanations (SHAP) methodology.

**Results:** In the train set, LightGBM outperformed the other ML models, exhibiting the highest AUC of 0.92, which also mirrored its performance in the test set (LightGBM 0.92, LR 0.88). SHAP analysis unveiled that the variables contributing to prediction were, in descending order, urinary red blood cell count, serum albumin, IgA/C3 ratio, urinary protein/creatinine ratio, and age.

**Conclusions:** Our study indicated that ML, particularly the LightGBM model, could improve IgA nephropathy diagnostic performance beyond conventional logistic regression. The influential variables identified were consistent with those reported in the existing literature. This highlights the potential utility of ML in IgA nephropathy diagnosis, necessitating further validation for clinical use.

**Funding:** Private Foundation Support

**TH-PO022**

**Machine Learning Models for the Prediction of Kidney Stone Composition and Recurrence**

**Matteo Bargagli, Daniel G. Fuster. Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.**

**Background:** Kidney stones are prevalent and cause high patient morbidity and healthcare cost. Kidney stone treatment depends on stone type and recurrence risk. We hypothesized that machine learning (ML) methods provide higher accuracy compared to current approaches for stone type and recurrence risk prediction.

**Methods:** Data from three comprehensively phenotyped Swiss cohorts comprising 1505 kidney stone formers with demographic, anthropometric and clinical information, stone composition analysis, and 24-h urine measurements were included. Several supervised ML models, including logistic regression, parallel-tree boosting (XGBoost), random forests, and neural networks, were trained independently to predict the stone type and the 5-year recurrence risk.

**Results:** XGBoost performed with generally high specificity (>90%), except for calcium oxalate stones which demonstrated lower sensitivity. The algorithm achieved an accuracy of 85% when distinguishing between uric acid-containing and calcium phosphate-containing stones. Key features informing the model included age at first stone event, body mass index, 24-h urine calcium and pH. The 5-year recurrence risk predicted by the neural network ranged between 48% and 83%, closely aligning with observed recurrence risk (R² = 0.913).

**Conclusions:** The developed ML models demonstrated remarkable accuracy in predicting the risk of stone recurrence. These findings have the potential to address an unmet clinical need by assisting healthcare specialists in clinical decision-making, and ultimately enhancing patient outcomes and quality of life for those affected by recurrent kidney stone disease.
was to assess the correlation between the classification results generated by our aneurysm classification app and the independent clinical examination performed by physicians specializing in access care.

Methods: As described recently (Zhang, Clin Kidney J, 2022), AV accesses were photographed, and the images were transferred to the cloud, where they were classified as “Advanced” or “Not Advanced” by a convolutional neural network algorithm (Fig. 1A). We compared classifications made by physicians who were blinded to the app results (i.e., the ground truth) and those generated by our app.

Results: We studied 28 subjects (Fig. 1B). Twenty out of 22 aneurysms were accurately classified as “Not Advanced” and 5 out of 6 as “Advanced” (Fig. 1C), resulting in an accuracy of 89%, sensitivity of 83%, and specificity of 91%.

Conclusions: Our preliminary results show that an AI-powered app can classify AV aneurysms with actionable accuracy in a demographically diverse HD population. If these results are corroborated in a larger patient population, our tool has the potential to support the development of a robust aneurysm monitoring system, enabling timely detection, facilitating referrals, and avoiding emergency interventions associated with aneurysms.

### TH-PO025

**Derivation and Validation of Machine Learning Models for the Prevention of Unplanned Dialysis in Advanced CKD Patients**

Cedric A. Edwards, Bahak Rashidi, Ayub Akbari, Gregory L. Hunsicker, Carleton University, Ottawa, ON, Canada; University of Ottawa, Ottawa, ON, Canada.

Background: A short timeframe kidney failure risk prediction model may serve to prevent unplanned dialysis starts, a detrimental outcome associated with increased morbidity, mortality, and healthcare costs. To date, no such clinical tool exists.

Methods: We developed and externally validated models for prediction of kidney failure over short timeframes of 6 and 12 months. The models were fit in 2,432 consecutive advanced CKD patients from The Ottawa Hospital. Models were externally validated in two independent advanced CKD cohorts from the Kingston General Hospital (N=724), and the Sunnybrook Health Sciences Center (N=323). All hospitals are in Ontario, Canada. Patients lost to follow-up, under conservative care management, or with <12 months of follow-up were excluded. Random forest classifiers were used to predict the 6- and 12-month probability of kidney failure for each patient at each follow-up visit.

Results: Input features included age, sex, and commonly available laboratory measurements and features characterizing their trajectory. The percentage of patients detected within clinically actionable timeframes of 3-15 months were computed for both models.

Conclusions: Internally, upon presentation, patients had a mean±SD age 66±15 years, and eGFR 18±7 ml/min/1.73m², and median (IQR) ACR 164 (49, 333). Internal ROC-AUCs (95% CI) of 0.88 (0.87-0.88) and 0.86 (0.86-0.87) were achieved by the 6- and 12-month models, respectively. Models were well-calibrated. Internally, at 70% precision, patients requiring dialysis were correctly identified with at least 6 months advanced notice in 20% and 34% of cases using the 6- and 12-month models. Performance did not significantly differ from external site.

### TH-PO026

**Predictive Model of the Time to Renal Replacement Therapy Using Machine Learning**

Jun Okita, Takeshi Nakata, Hiroki Uchida, Akiko Kudo, Akihiro Fukuda, Hirotaka Shibata, Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan.

Background: In the treatment of chronic kidney disease, nephrologists are expected to prolong the renal prognosis for those at high risk for end-stage renal disease (ESRD). It is also important to estimate the time to renal replacement therapy (RRT) in patients at high risk of ESRD. In Japan, the “time-series data of estimated glomerular filtration rate (eGFR)” is used to estimate the time to RRT based on the annual decline rate. In this study, we used machine learning to predict the time to RRT from the “data obtained at a single time point.”

Methods: Patients who underwent hemodialysis at our hospital from April 2016 to March 2021 were included, and a data set, including 30 laboratory data items (BUN, creatinine [Cr], etc.), six patients’ background demographic background, and medications were extracted retrospectively from the electronic medical records. 75% of the data were randomly split for training and 25% for testing, and the predictive models were created with several algorithms: linear regression, ridge regression, least absolute shrinkage selection operator (LASSO) regression, elastic nets, random forests, and gradient boosting decision trees. We also predicted the time to RRT using “time-series data of eGFR” and compared the accuracy by the coefficient of determination (R²) and mean absolute error (MAE).

Results: A total of 13,323 data were extracted from 147 patients of which 99 were males, resulting in a total of 1,801 data groups with no missing data. The mean age at dialysis induction was 60.8 years, the most common etiology for ESRD was diabetic nephropathy (44%), the mean Cr was 7.6 ± 2.0 mg/dL, and the mean eGFR was 61 ± 1.7 ml/min/1.73 m². The prediction model based on LASSO was moderately accurate with R² of 0.62 and MAE 416, while the prediction based on the “time-series data of eGFR” was highly inaccurate with R² of -17.1 and of MAE 2466, indicating that the machine learning is superior in predicting the onset of dialysis.

Conclusions: The machine learning method was used to predict the time to RRT using “data obtained at a single time point,” and a moderately accurate prediction model was obtained. The ability to specify the time to RRT, even approximately, is useful not only for medical staff to make treatment decisions, but also for patients to motivate themselves to receive treatment and making long-term plans.

### TH-PO027

**Prediction of the Presence of Vesicoureteral Reflux Using Kidney Ultrasound Images with Deep Learning**

Yuichi Morimoto, Keisuke Sugimoto, Kohei Miyazaki, Kinki Daigaku, Higashiosaka, Japan.

Background: In previous studies, detection of vesicoureteral reflux (VUR) and renal scarring by ultrasonography has been attempted, but the results have not yet been satisfactory.

Methods: Patients who underwent ultrasonography and VCUG examinations in the course of a thorough examination for congenital renal urinary tract abnormalities at our hospital from January 1, 2010 to January 1, 2021 were included in the study. We used a deep learning image classification method to create a discriminant model of VUR using kidney echo images as training data and VCUG examination results as teacher data. After creating the model using the training and validation data, the sensitivity and specificity were evaluated using the test data. The model was then evaluated for sensitivity and specificity using the test data. The model was visualized using the Grad-cam to determine the explanatory power of the model.

Results: In this study, 46 VCUG cases (male cases [57%, median age 4.5 years [0 months to 10 years]) were included. 23 of the 46 cases had VUR, 12 were Grade I-III and 11 were Grade IV-V. 230 echo images (115 each) from the groups with and without VUR were used for transition learning For VUR detection, the deep learning model had a sensitivity of 58%, specificity of 87.5%, positive predictive value of 82.4%, negative predictive value of 67.7%, and accuracy of 71.7% (Figure 1).

Conclusions: It was suggested that the presence of VUR could be predicted from renal ultrasonic images and may contribute to the decision of VCUG indication. In addition, it has been reported that thickening of the renal pelvis wall due to reflux has been observed, and in the visualization of features performed with the model created in this study (Figure 1), similar areas may have contributed to the AI’s judgment. If the presence and severity of VUR can be determined with a certain degree of accuracy from renal echo images, the pain and radiation exposure caused by VCUG may be avoided.
Background: The single most important factor determining quality of dialysis is adequate access. This begins with the placement of an access that is optimized for the individual patient and may include a fistula, graft, or in some cases a catheter. Constant monitoring of the fistula or graft is needed to avoid future complications and with the EMR we can provide this in real time using the dialysis machine / EMR interface. We evaluated an AI approach to prediction venous stenosis at different locations with sufficient warning that an intervention can be performed prior to interruption of dialysis.

Methods: Data were obtained from the University of Louisville dialysis electronic medical record system and the Interventional Nephrology program for the years 2018 to 2020. Routinely collected information at the time of initiation as well as intradialytic data were obtained. Events were determined by direct examination within the interventional facility and segregated into inflow, outflow, central, and other stenosis. Event classification was performed using sequential vector of predictors consisting of target and achieved blood flow rate, arterial pressure, arterial resistance, venous pressure, venous resistance, and mean arterial pressure. Resistance was defined as the ratio of pressure to blood flow rate. Events were predicted 1 week in advance. Classification was performed using tree ensembles (AdaBoost) and Artificial Neural Network.

Results: Data set contained 2369 samples with 27 inflow, 133 outflow, 56 central, and 59 other stenosis events. Classifiers were trained using 10-fold cross-validation. AdaBoost [97] held 10% of the data out for testing. This allows comparisons of the classifier performance on the test data between the two methods.

Conclusions: Sufficient information exists during the dialysis procedure that can be leveraged using advanced mathematical techniques to adequately predict dialysis access complications. The methodology applied also allows for the explanation of the observations seen and can provide predictions through a mathematical model or an expert system in the form of a decision tree.

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TH-PO030
Deep Learning-Based Prediction of Postoperative AKI After Noncardiac Surgery Using Intraoperative Vital Sign Parameters in a Minute Scale Sehoon Park, Yong Chul Kim, Dong Ki Kim, Haejung Lee. Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.

Background: Certain models were used to predict the risk of PO-AKI mainly with preoperative characteristics; however, complex intraoperative vital sign information was difficult to be combined to such strategy although intraoperative hemodynamic alteration is one of the major factors affecting PO-AKI risks. We aimed to construct an externally validated deep learning-based prediction model for PO-AKI, including complex, real-time collected hemodynamic information.

Methods: We collected systolic and diastolic pressure values and heart rate information collected from the real-time intraoperative monitoring in a tertiary university hospital (N = 51,345). The test and the internal validation set was split as 8:2 manner, and additional external validation was performed in two additional tertiary university hospitals (N = 47,093 and 12,259). Total collected measured points of blood pressure values were 17,816,251 (systolic) and 17,793,025 (diastolic) and of heart rate was 17,505,759. Deep-learning model was constructed using the EfficientNet based CNN model. The outcome was PO-AKI and critical AKI events, and the critical AKI was defined as high stage AKI learning model was constructed using the EfficientNet based CNN model. The outcome was PO-AKI and critical AKI events, and the critical AKI was defined as high stage AKI or AKI associated with death or dialysis. We compared the model performances with AUC-ROC values, and the conventional SPARK classification was used as the reference model.

Results: The deep-learning model only including intraoperative variables showed moderate but tolerable discrimination power against PO-AKI [AUC-ROC 0.724 (development), 0.729 and 0.716 (validation)] events. When major PO-AKI risk factors were incorporated to the models, the powers outperformed the conventional SPARK model; for PO-AKI [0.765 (development), 0.716 and 0.761 (validation)] and for critical AKI [0.816 (development), 0.794 and 0.794 (validation)]. The model performances even improved in the ensemble model learning both preoperative tabular data and the intraoperative prediction models.

Conclusions: Complex intraoperative vital sign information, including blood pressure and heart rate, can be used to develop tolerable deep-learning based PO-AKI risk stratification model that can be used after non-cardiac surgeries.

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**TH-PO031**

**Ultrasound-Based Imaging Methods for the Assessment of Kidney Fibrosis on Artificial Intelligence**

Dan Zhao, Shanghai Tongji Hospital, Shanghai, China.

**Background:** Renal fibrosis is the common pathway leading to end-stage kidney disease, but the assessment of renal fibrosis remains limitations. Artificial intelligence (AI)-based ultrasound imaging has shown high specificity and sensitivity in disease diagnosis via imaging biomarkers. Hereby, we intend to use artificial intelligence technology to explore a new method for early non-invasive assessment of renal fibrosis through ultrasound images.

**Methods:** A retrospective cohort of patients receiving kidney biopsy was developed from our hospital between January 2018 and July 2022. All participant underwent kidney ultrasound within one week. The magnitude of renal interstitial fibrosis (RIF) was evaluated by two experienced pathologists according to Banff criteria. All ultrasound images were preprocessed, then randomly divided into training and test sets in a 7 to 3 ratio. Radiomic features extracted from selected regions of interest (ROI), including first-order, texture, and wavelet-transformed features. Two-sample t-test, LASSO, and Spearman correlation analysis were used to reduce feature dimension. Three machine learning models and one deep learning model were established to distinguish mild and moderate-severe fibrosis. The area under the curve (AUC) of the receiver operating characteristic curve was employed to assess the models’ performance.

**Results:** A total of 193 patients were enrolled in this study, including 100 with mild fibrosis and 93 with moderate-severe fibrosis. 837 radiomic features were extracted from gray scale ultrasound images. After feature dimension reduction, 10 features were retained, of which 9 were wavelet-transformed features. Based on 10 selected radiomic features, three machine learning models were established: LR, SVM, and RF. In test sets, the AUCs were 0.75, 0.80, and 0.89, respectively. The accuracy were 60%, 63.7%, and 65% respectively. RF achieved the best classification performance. Further visualization on LR prediction model was visualized as nomogram. In addition, based on full kidney ultrasound images, VGG16 network model was also established, with AUC of 0.76 (95% CI, 0.63-0.90) and the accuracy of 77%.

**Conclusions:** AI-assisted imaging analysis endows traditional ultrasound techniques with the promising potential for early diagnosis of renal fibrosis. Our study would provide new insights for the future exploration of noninvasive assessment methods.

**TH-PO032**

**Development of Artificial Intelligence Model for the Prediction of AKI, Acute Kidney Disease, and CKD After General Anesthesia Surgery**

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**Background:** After the occurrence of AKI, ongoing renal pathophysiologic process leads to acute kidney disease (AKD) or chronic kidney disease (CKD). Postoperative AKI is associated with increased mortality and morbidity in patients undergoing surgeries performed under general anesthesia. A machine learning-based prediction model for postoperative AKI, AKD, and CKD is needed.

**Methods:** In this retrospective cohort analysis, noncardiac surgeries performed between 2009 and 2019 at 7 university hospitals in South Korea were included. The between-study heterogeneity was assessed using I² test and random [for I² > 50%] and fixed effects model were used. The AUCs were tested: deep neural networks, decision tree, random forest, and light gradient boosting. A total of 193 patients were enrolled in this study, including 100 with mild AKI and 93 with moderate-severe AKI. The magnitude of renal interstitial fibrosis (RIF) was assessed using the Banff criteria. All ultrasound images were preprocessed, then randomly divided into training and test sets in a 7 to 3 ratio. Radiomic features extracted from selected regions of interest (ROI), including first-order, texture, and wavelet-transformed features. Two-sample t-test, LASSO, and Spearman correlation analysis were used to reduce feature dimension. Three machine learning models and one deep learning model were established to distinguish mild and moderate-severe fibrosis. The area under the curve (AUC) of the receiver operating characteristic curve was employed to assess the models’ performance.

**Results:** A total of 193 patients were enrolled in this study, including 100 with mild fibrosis and 93 with moderate-severe fibrosis. 837 radiomic features were extracted from gray scale ultrasound images. After feature dimension reduction, 10 features were retained, of which 9 were wavelet-transformed features. Based on 10 selected radiomic features, three machine learning models were established: LR, SVM, and RF. In test sets, the AUCs were 0.75, 0.80, and 0.89, respectively. The accuracy were 60%, 63.7%, and 65% respectively. RF achieved the best classification performance. Further visualization on LR prediction model was visualized as nomogram. In addition, based on full kidney ultrasound images, VGG16 network model was also established, with AUC of 0.76 (95% CI, 0.63-0.90) and the accuracy of 77%.

**Conclusions:** AI-assisted imaging analysis endows traditional ultrasound techniques with the promising potential for early diagnosis of renal fibrosis. Our study would provide new insights for the future exploration of noninvasive assessment methods.

**TH-PO033**

**Deep Learning-Based Quantitative Assessment of Renal Chronicity Indices in Lupus Nephritis**

Tianqi Yu, Ying Tan. Peking University First Hospital, Beijing, China.

**Background:** Lupus nephritis (LN) is a common condition in patients with SLE. Evaluating kidney chronicity indices (CI) is crucial for diagnosing LN and predicting outcomes. Deep learning (DL) has shown promise in improving the workflow of pathologists. In renal pathology, DL has demonstrated high accuracy in identifying various histopathologic lesions. However, existing studies have not adequately addressed the challenges of assessing CI in LN, such as integrating features at different levels and dealing with class imbalances among tissue compartments.

**Methods:** This study enrolled 141 patients from two distinct cohorts. Training of the CNN model involved annotating 22,410 images from 30 biopsy slides, which were subsequently tested on 111 slides. The evaluation process encompassed the segmentation of tissue compartments, correlation analysis with pathologists’ assessments, and investigating associations between CI outcomes utilizing CoxPH models.

**Results:**
1. The developed pipeline exhibited an accuracy of over 0.91 in identifying six tissue compartments and histopathologic lesions, surpassing previous segmentation performance benchmarks.
2. Consistent with the evaluations by expert pathologists, our pipeline exhibited an agreement of over 0.85 in assessing CI in both cohorts, highlighting its reliability and consistency.
3. The application of the CoxPH model to predict patients’ outcomes achieved a score of 0.82 and 0.78 in the two cohorts.

**Conclusions:** Our study showcases the state-of-the-art performance of our deep learning pipeline in identifying tissue compartments and histopathologic lesions in lupus nephritis. The pipeline demonstrates strong agreement with pathologists’ CI assessments and maintains the correlation between CI and patient outcomes. This automated approach has the potential to enhance pathological assessment and disease stratification in lupus nephritis.

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

**TH-PO034**

**Using Artificial Intelligence (AI) to Predict Mortality in AKI Patients: A Systematic Review and Meta-Analysis**

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**Background:** Acute kidney injury (AKI) is associated with increased morbidity and mortality. With the recent advent of artificial intelligence (AI), novel models for mortality prediction in AKI patients have been developed using machine learning (ML). We reviewed the performance of different ML models for evidence generation to support their applicability and implementation in the clinical setting.

**Methods:** A literature search was conducted through Pubmed, Embase, and Web of Science Databases. Performance metrics of the ML models to predict hospital mortality in adult AKI patients were extracted. The between-study heterogeneity was assessed using the I² test and random [for I² > 50%] and fixed effects model were used. The ABORC of two models were compared using DeLong’s test (p-value < 0.05 considered significant).

**Results:** A total of 8 studies [8 derivation and 6 validation cohorts] with 37,032 adult AKI patients were included. The hospital mortality was 18% in the derivation and 15.8% in the validation cohorts. The pooled AUC (95% CI) was observed to be highest for logistic regression [0.86 (0.80 - 0.93)] and lowest for proposed clinical [0.77 (0.72 - 0.81)] models used as reference. Despite substantial variability, the pooled AUC (95% CI) of logistic regression did not differ significantly from other models except proposed clinical model [DeLong’s test p < 0.022].

**Conclusions:** Our results show that logistic regression is equivalently effective as other ML models in predicting in-hospital mortality among AKI patients, with substantial variability across models. Studies investigating the features influencing mortality and their impact on different models are needed.
**TH-PO035**

A Systematic Review of Artificial Intelligence Algorithms for Predicting AKI

**Background:** Acute kidney injury increases mortality and costs in hospitalized patients. New methods for early AKI identification have been developed with targeted biomarkers and electronic health records (EHR) data analysis. Machine learning use in diagnostics and health data analysis has recently increased. We performed a systematic review to analyze the use of ML for AKI prediction in hospitalized adults.

**Methods:** PubMed, EMBASE, Cochrane, and Web of Science databases were searched until 31 March 2023. English-language studies using ML in adults for AKI prediction were included using predetermined eligibility search terms such as acute kidney injury, machine learning, and artificial intelligence. Two reviewers evaluated the publications’ titles, abstracts, and full texts separately and obtained appropriate data. The main outcome was an area under the curve result of at least 0.70.

**Results:** Ten studies in 102 articles were included including 242,251 patients. Deep learning (AUC >0.907 in critical care AKI; AUC 0.797 in hospitalized patients) had similar AUC.

**Conclusions:** AKI is multifactorial; however, ML performed well with different etiologies, such as cardiac-related AKI, drug-related AKI, and critical care patients. Overfitting data and constructing black box models are limitations that might jeopardize the generalization and comprehension of the results. Most studies were single-center, and three manuscripts used the same database with a predominantly Caucasian population resulting in a lack of diversity and reducing external generalization. In conclusion, ML could effectively predict AKI in hospitalized adults. Future directions rely on including a more diverse population and completing prospective and controlled trials.

**TH-PO036**

Predictive Modeling of Graft Failure Risk in Deceased Donor Kidney Transplants: Leveraging Machine Learning for Improved Outcomes and Data-Driven Insights

**Background:** Machine learning (ML) has shown its potential to improve patient care over the last decade. The 1-year graft failure rate remains a major concern among ethnic disparities in the deceased donor kidney transplantation (KT). The aim of the study was to evaluate graft failure within a year and determine risk factors associated with these events in ethnic groups.

**Methods:** The KT data between 2000 to 2020 was obtained from Organ Procurement and Transplantation Network. After data preprocessing (n=75,000 White, n=35,000 Black, and n=3,000 Asian KT were qualified for further data analysis. The random forest (RF) and light gradient-boosting machine (LGBM) models were used to classify the most important variables for further 1-year GF-associated risk factors.

**Results:** Thus, the number of initial variables was reduced from 490 to 490 to 490 to in every three groups after significance-test validation. LGBM demonstrated better discrimination over the RF model. The area under the curve (AUC) was 0.78 (White), 0.77 (Black), and (AUC=0.73; Asian) in fivefold cross-validation. Interestingly, the top features for prediction of graft failure were such as donor hepatitis C virus (HCV) antibody, donor and recipient diabetes, type of perfusion solution, arterial blood gas pH level, diabetes, hypertension, etc. Then, LGBM predicted variables were further analyzed in Cox proportional hazard ratio (HR), and the leading risk factor for graft failure was donor HCV antibody level (HR 1.9; White, HR 2.2; Black, and HR 1.75; Asian, all p values were 0.005). In contrast, donor and recipient tattoos were independent risk factors (HR 1.2; P <0.02) for Asian. Hypertension was not associated with 1-year graft failure for all three groups. Interestingly, Cox proportional HR analysis demonstrated that ML-predicted risk factors such as diabetes, age, BMI, and hypertension were not associated with 1-year graft failure in all three groups.

**Conclusions:** Taking together, ML algorithms predicted risk factors accuracy almost the same as traditional statistical methods on prediction of 1-year graft failure among ethnic disparities.

**TH-PO037**

Prospective Study of a Predictive Algorithm of Real-Time Fluid Status in Hemodialysis Patients

**Background:** An accurate per-session determination of volume status in dialysis patients would have considerable clinical utility.

**Methods:** We prospectively assessed a predictive algorithm for fluid status in an observational study of hemodialysis (HD) patients. Algorithm performance was compared to clinical volume assessment. Individualised predictions were compared with biometrical parameters (BCM) measures at 2-week intervals. Internal validation for linear regression algorithms predicting BCM-based noromohydration weight and pre-HD overhydration (OH) has been described (SA-PO351 ASN 2022). MAE, RMSE and Bland-Altman plots were used for continuous outcomes. Precision, recall and F1 score were used for fluid categories. In a larger, heterogeneous dataset would be expected to improve precision of fluid status predictions.

**Results:** 630 HD sessions were assessed. Root mean squared error (RMSE) for the pre-dialysis overhydration index≥2.1kg compared to RMSE=1.6kg in the internal validation set. No significant difference was observed between the BCM noromohydration weight versus the predicted value [mean difference 0.22 ± 2.15 kg, (95% CI) =0.96, 0.34]. A histogram showed a close alignment in distribution of predicted noromohydration weight and BCM values (Figure). Nursing staff overestimated fluid overload (Table).

**Conclusions:** The algorithm showed an ability to discriminate fluid categories compared to nursing staff, but overall accuracy was poor. Additional algorithm training in a larger, heterogeneous dataset would be expected to improve precision of fluid status predictions.

**Funding:** Commercial Support - Enterprise Ireland Disruptive Technologies Innovation Fund grant DTIF 2019_86, Government Support - Non-U.S.
TH-PO038
The Prediction of In-Hospital Mortality in Elderly Patients with Sepsis-Associated AKI Utilizing Machine Learning Models
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Background: Sepsis-associated acute kidney injury (SA-AKI) is a severe complication associated with poorer prognosis and increased mortality, particularly in elderly patients with sepsis. Currently, there is a lack of accurate mortality risk prediction models for these patients in clinic. This study aimed to develop and validate machine learning models for predicting in-hospital mortality risk in elderly patients with SA-AKI.

Methods: Machine learning models were developed and validated using the public, high-quality Medical Information Mart for Intensive Care (MIMIC)-IV critically ill database. The recursive feature elimination (RFE) algorithm was employed for key feature selection. Eleven predictive models were compared, with the best one selected for further validation. Shapley Additive Explanations (SHAP) values were used for visualization and interpretation, making the machine learning models clinically interpretable.

Results: A total of 8,426 SA-AKI patients were included in this study (median age: 77.0 years; female: 45%). They were randomly divided into a training cohort (5,934, 70%) and a validation cohort (2,492, 30%). Nine key features were selected by the RFE algorithm. The CatBoost model achieved the best performance, with an AUC of 0.844 in the training cohort and 0.804 in the validation cohort. SHAP values revealed that AKI stage, PtO2, and lactate were the top three most important features contributing to the CatBoost model.

Conclusions: We developed a model capable of predicting the risk of in-hospital mortality in elderly patients with SA-AKI.

Flowchart of this study

TH-PO039
Developing a Risk Index Predicting Kidney Transplant Dropout for African American and Hispanic Patients Using Artificial Intelligence/ Machine Learning
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Background: On average, kidney patients who receive a transplant live longer and have a better quality of life than those who remain on dialysis. Since African American (AA) and Hispanic patients are more likely to drop out before receiving a transplant than White patients, identifying patients at higher risk of dropout can improve care.

Methods: We created a dataset from Houston Methodist sources, including EPIC Clarity, Phoenix, and United Network for Organ Sharing (UNOS), and external databases including Health Resources Services Administration (HRSA), Centers for Disease Control and Prevention (CDC), and the US Census Bureau for community-level characteristics. The final transplant analytical registry included 4,245 kidney patients pursuing transplants from 6/2016 to 5/2022 and contained clinical, demographic, social, and transplant variables. The data was preprocessed to apply AI/ML methods to predict the risk index of patients who began transplant evaluation but were never listed for transplant within 12 months. F1 and AUROC were the evaluation metrics used.

Results: Of the 4,245 individuals who presented for transplant evaluation, 1,999 (47.1%) were waitlisted after 12 months, and 550 (13.0%) were transplanted. AA (7.23%) and Hispanic (12.20%) patients received fewer transplants compared to White patients (19.70%). Our AI/ML-based risk index predicted the probability of not being listed for transplant within 12 months (AUROC=0.732). Patients predicted to be low dropout risk (0-30%) had an 81.3% listing rate, middle risk (30-60%) had a 54.3% listing rate, and high risk (>60%) had a 27% listing rate within 12 months (Figure 1). Compared to low-risk patients, high-risk patients were more likely to be African American (44.2% vs. 19%), Hispanic (31.5% vs. 25.3%), unemployed (91.2% vs. 25%), spent more time on dialysis (488 vs. 131 days), without intended living donors (3% vs. 64.5%), and live in areas with more residents living below the poverty line (28% vs. 17%).

Conclusions: Applying the risk index, we will identify patients at higher risk of dropout and explore health delivery improvements within the transplant care process to slow or eliminate transplant dropout for underserved communities.

Funding: Other NIH Support - AIM AHEAD - Data Science at NIH

TH-PO040
Machine Learning-Based Approach to Classifying Risk of Progression of Membranous Nephropathy to ESKD Using Electron Microscopy
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Background: Membranous nephropathy (MN) is an immune complex-mediated process that can result in nephrotic syndrome. Machine learning applications in medicine have emerged as powerful tools that can analyze large volumes of medical data (i.e., imaging, patient records) and extract patterns and relationships with diagnostic and prognostic insights. This work aims to use clinical and classical morphological image features to determine the risk of MN progression to end-stage kidney disease (ESKD).

Methods: Eighty MN cases from multiple institutions, each with available electron micrographs (EMs) of glomerular basement membrane (GBM) and corresponding baseline clinical metrics (albumin, eGFR, creatinine) were collated. An attention U-Net model was trained to perform multiclass segmentation of the GBM, electron-dense deposits, and background. Fifteen morphological features (i.e., total number of deposits, aspect ratio, circularity) were extracted from the predicted mask. Then, an artificial neural network (ANN) was trained to classify cases according to 3 risk tiers: low, intermediate, and high progression to ESKD. The same features were used to train an ANN to predict remission (no remission or complete remission).

Results: The segmentation model achieved a Dice score coefficient of 78%. Moreover, the ANN obtained classification accuracies of 73.3%, 67%, and 73.3% on the test set using clinical metrics alone, morphological features alone, and both clinical and morphological features, respectively. Another ANN trained to predict remission achieved 40% accuracy with both clinical and morphological features.

Conclusions: Clinical and morphological features can predict risk levels with reasonable accuracy. However, the same features are poor predictors of remission. Morphological features combined with clinical features do not improve risk classification accuracy. More meaningful and discriminative morphological features are needed to enhance predictive ability.

Funding: NIDDK Support

TH-PO041
A Novel Clinical Prioritization Tool Stratifies Nephrology Patients by Acuity and Change over Time
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Background: Finding information to prioritize patient care is a difficult task with the growing amount of data in the electronic health record (EHR). Systems that highlight clinically meaningful patterns in laboratory data can support decision making, particularly
Using an Ensemble Model to Improve ESA Prescription in Hemodialysis

TH-PO042

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Methods: We have compiled a dataset from 2013-2020, including bi-monthly ESA prescriptions, Iron doses, Hb, and relevant data of HD patients in our hospital. We divided all records into six categories, status 1 to 6, based on subsequent hemoglobin(THb), using cut-off values of 10.8 and 11.2 and direction of change (not decreasing: 1-3 vs. decreasing:4-6). Indexes I, II, and III were used to evaluate how the ESA dose deviations of model recommendations theoretically impacted sHb. Index I assesses how model deviations keep sHb near 11 g/dL (positive index), while II and III are away from 11 g/dL (negative index). (Figure 1) Besides the traditional ESA-prescription algorithm (TEA, Figure 2), we have trained various models, including a meta-learning model (MLM).

Results: 25,632 records of 315 ESKD patients were included, with 71.9% of the Hb levels between 10-12mg/dL. Besides TEA, we selected a generalized linear mixed-effect tree model (GLMM) and a weighted random forests model (WRF) for sHb and ESA dose prediction. The overall results are shown in Table 1. Our WRF and MLM can almost preserve the proper prescriptions (Index I), and avoid those improbable or unacceptable recommendations (Index II & III). The MLM can theoretically improve 65.4% and 43.8% of prescriptions with sHb >11.5 and <10.5, respectively. (undetermined)

Conclusions: The ensemble model trained by new indexes can theoretically recommend more proper ESA dosages.

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

Underline represents presenting author.

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Machine Learning Approach for Hemodialysis Prescription: Model Development and Validation Study
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Background: The prediction model of hemodialysis prescription is established based on machine learning to achieve precise hemodialysis treatment.

Methods: We obtained 108,638 hemodialysis sessions in 965 independent patients who were hemodialysis patients in our hospital from October 1, 2020 to June 31, 2021 using random sampling. The sessions were randomly divided into training (70%), validation (10%), and testing (20%) sets. Apply XGBoost to analyze and extract effective feature data. XGBoost, RF, KNN, SVR, LR, MLP were used to develop the prescription model and model fusion. Training and update the model using reinforcement learning. The area under the receiver operating characteristic curve, the area under the precision-recall curve, F1 scores and MSE obtained to assess model stability and accuracy.

Results: There were 108,638 dialysis records in 965 patients, of whom 62.2 were male, the average age was 59.3 ± 13.2 years, the median BMI was 23.8 ± 3.9, and the primary disease was diabetic nephropathy (38.6%). There are 13 labels in the hemodialysis program, of which 6 labels are continuous variables and the regression model is used, and 7 labels are discontinuous variables. The average accuracy is greater than 0.8, and the mean square error is less than 0.067.

Conclusions: The artificial intelligence dialysis prescription established based on machine learning has better stability and accuracy.

Funding: Government Support - Non-U.S.

Using an Artificial Intelligence Tool Implementing Natural Language Processing to Identify Low-Prevalence Cases of ANCA-Associated Vasculitis in Electronic Health Records
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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a rare, life-threatening, systemic autoimmune disease. Due to the low prevalence and heterogenous registration, there is an urgent need to improve identification of AAV patients within the electronic health record (EHR)-system of health organizations to facilitate clinical research.

Methods: Our aim was to identify, with a high sensitivity, low-prevalence AAV patients within large EHR-systems (>2,000,000 records) using an artificial intelligence (AI)-search tool. We combined a search on structured and unstructured data with natural language processing (NLP)-based exclusion. We developed the method in an academic center with an established AV training set (n=203) and validated the method in a non-academic center with a validation set (n=84). We anonymously reviewed all identified patient records for AAV diagnosis.

Results: The final search strategy combined four queries on disease description, laboratory measurements, medication and specialisms. In the training center, this search identified 608 patients, of which 346 were AAV patients upon manual review. 197/203 patients of the training set were retrieved, indicating a sensitivity of 97%. Employing NLP-based exclusion resulted in 444 patients with 339 AAV patients, resulting in an increase of positive predictive value (PPV) from 57% to 78% and a sensitivity of 96%. In the validation center the search strategy identified 333 patients, of which 194 were AAV patients, including 82/84 (98%) patients of the validation set. After NLP-based exclusion 223 patients remained, including 196 AAV patients, improving PPV from 58 to 86% with a sensitivity of 98%. Our identification method outperformed IC-10 coding, predominantly in identifying myeloperoxidase (MPO)-positive AAV patients and patients with few specialisms involved.

Conclusions: We demonstrated excellent performance of an AI-based identification method, implementing NLP to identify AAV patients in EHRs and we validated the applicability and transportability. This method can accelerate research efforts, while avoiding the limitations of ICD-10-based registration.

Funding: Commercial Support - Fresenius Medical Care

Impact of Nationwide Utilization of a Machine Learning Model to Identify Home Therapy Candidates
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Background: Home therapy (HT) modalities offer excellent treatment options for dialysis patients but are unterutilized. As a part of a larger effort to provide support to patients, DaVita is a team of Kidney Care Advocates (KCA) who provide education on treatment modality options with a goal of empowering patients to choose a home modality when appropriate. Towards this, a machine learning (ML) predictive model was built to identify which in-center hemodialysis (ICHD) patients would be good candidates to target HT.

Methods: Patient (n=298552) data collected from 2016-2019 were used to develop an XGBoost ML model to predict the likelihood of an ICHD patient switching to peritoneal dialysis or home hemodialysis in the next 90 days and staying on that HT for at least 90 days. The data were randomly divided (training (70%) and testing (30%) data) and analyzed using the 2.5% positive prevalence in both. Data sources included ICD diagnoses, laboratory measurements, demographics (age, marital status, and vintage), comorbidities, clinical assessments, clinic history, and in-center hemodialysis information. We built and evaluated random forest and XGBoost models. We used XGBoost to identify which in-center hemodialysis (ICHD) patients would be good candidates to target HT for home therapy (HT). Towards this, a machine learning (ML) predictive model was built with a goal of identifying low-prevalence cases of ANCA-Associated Vasculitis (AAV) from electronic health records (EHRs).

Results: The model identified good achievement with an area under the curve of 0.87 for the validation dataset. Using a threshold set to the positive class prevalence (0.025), sensitivity and positive predictive value was 0.09. The top predictors used by the model were dialysis vintage, previously expressing interest in or being referred to HT, age, and dining with one’s spouse. During the time examined, KCA’s reported contacting 20734 patients. Of those, the model was the sole referral source for 5382 patients and 1219 of them expressed interest in HT. In 2020-2021, 487 ICHD patients referred to KCAs by only the ML model shifted to HT.

Conclusions: Through close collaboration with KCAs, an ML model was successfully used to identify ICHD patients who were good candidates for HT. Use of this model had measurable impact with hundreds of ICHD patients switching to HT who otherwise might not have been referred to a KCA.

Funding: Commercial Support - Fresenius Medical Care

TH-PO047
A Risk-Based Reinforcement Learning Algorithm to Predict Intradialytic Hypotension During Kidney Replacement Therapy
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Background: Kidney replacement therapy (KRT) after acute kidney injury is associated with intradialytic hypotension (IDH) in up to 30% of sessions. IDH is associated with premature termination of therapy and is an independent predictor of mortality. Thus, there is a critical need to develop a clinical decision support tool that predicts IDH and preemptively suggests optimal therapy.

Methods: We constructed a reinforcement learning (RL) algorithm that generates personalized, dynamic treatment plans for IDH during intermittent KRT. The RL model was trained and validated using clinical data from a cohort of 277 patients undergoing 1,595 hemodialysis treatments in a tertiary care center. A random forest classifier was used to generate individualized risk trajectories for IDH, which were incorporated with patients’ physiological features to define a discrete state space. The RL was trained for multiple episodes every 15 sessions. To ensure that selected actions aligned with clinical intuition, a bias term prevented the RL from over-recommending clinically rare actions.

Finally, a Q-learning algorithm used risk rewards as intermittent feedback to learn a personalized sequence of optimal actions.

Results: The RL agent tended to recommend interventions more frequently than clinicians, with an RL intervention frequency of 41.7% compared to a clinician intervention frequency of 18.4%. The most frequently recommended clinical intervention by both clinicians and the RL agent was a change in ultrafiltration rate (clinician, 17.8%, RL, 40.8%), followed by administering mannitol or vasopressors (clinician, 6.0%, RL, 0.8%). Implementing the learned policy decreased the occurrence of IDH and increased fluid goal achievement in silico, as seen in Table 1 below.

Conclusions: Dynamic risk forecasting and RL generated risk prediction of IDH and personalized treatment plans for IDH during intermittent KRT. These dynamic policies recommend more than twice as many interventions as clinicians. We showed RL agents could decrease the frequency of IDH while meeting therapeutic goals and improving clinical outcomes.

Funding: NIDDK Support

Table 1.

|     | RL Transplant Policy | Initial | Achieved Goal | %Y
|-----|---------------------|---------|---------------|
| BMI | 0.8 | 0.8 | 96%
| Glucose | 150 | 150 | 96%

|     | Clinical Transplant Policy | Initial | Achieved Goal | %Y
|-----|-----------------------------|---------|---------------|
| BMI | 0.8 | 0.8 | 96%
| Glucose | 150 | 150 | 96%

TH-PO048
Polygenic Prediction of Estimated Glomerular Filtration Rate in Individuals of African Descent and from the Americas
Holly J. Kramer,1 Amy Easley,2 Obedesca N. Hughes,3 Girish N. Nadkarni,3 Joseph Mchalecky,1 Andrew Morris,2 Nora Franceschini,4 COGENT-Kidney Consortium. 1Division of Nephrology and Hypertension, Loyola University Chicago, Maywood, IL; 2Center for Research on Genomics and Global Health, National Human Genome Research Institute, Bethesda, MD; 3The University of Manchester, Manchester, United Kingdom; 4Mount Sinai Health System, New York, NY; 5University of Virginia, Charlottesville, VA; 6The University of North Carolina at Chapel Hill, Chapel Hill, NC.

Background: Chronic kidney disease more often impacts individuals of African descent (AFR) or those from the Americas (AMS), who are under-represented in genome-wide association studies (GWAS). Polygenic scores have been proposed for disease risk prediction. However, polygenic scores developed from GWAS of individuals of European ancestry have limited transferrability into other populations, reflecting differences in allele frequencies and linkage disequilibrium across populations. Previous
studies have demonstrated their performance is poor for estimated glomerular filtration rate (eGFR) prediction in this population. Scores were significantly associated with eGFR in the validation datasets. Of the eGFR variance, compared to the AMS score that explained 2.4%. All polygenic scores in each validation studies.

Results: When applied to WHI-AA, the AFR polygenic score outperformed the AMS score and explained 12.5% of the eGFR variance, while the AFR + AMS polygenic score had the best performance, explaining 13.5% of the eGFR variance. For scores applied to BIOMA-HA, the best performance was for the AFR + AMS score, which explained 5.2% of the eGFR variance, compared to the AMS score that explained 2.4%. All polygenic scores were significantly associated with eGFR in the validation datasets.

Conclusions: In this largest aggregated GWAS of AFR and AMS individuals, we showed increased predictive power offered by a multi-population polygenic score for eGFR in both African Americans and Hispanics/Latinos. This study has shown the largest variance explained by a polygenic score in AFR, enhancing resources for disease prediction in this population.

Funding: NIDDK Support

TH-PO049
Empowering Dialysis Patients to Self-Manage Hyperphosphatemia with Mobile Health Technology: Insights from the FOSFO-OAK Study
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Background: mHealth apps are cost-effective technologies that can assist dialysis patients in achieving their therapeutic goals. Since many patients fail to control their phosphate levels, the main objective of this project is to develop a mHealth environment that empowers patients to control their hyperphosphatemia under medical supervision. Such an environment will allow nephrologists to provide patients with information beyond their traditional point of care and enable patients to receive timely feedback on their condition.

Methods: We developed a web-based management system that delivers patient’s phosphate levels results and medical recommendations through a cloud-based IT environment. Patients with phosphate levels > 6 mg/dL and PTH <88 pmol/L were included in the study. Patients were randomly assigned to receive the app or continue with the usual educational program. Changes in phosphate binders or vitamin D were allowed included in the study. Patients were randomly assigned to receive the app or continue with the usual educational program. Changes in phosphate binders or vitamin D were allowed.

Results: The study included 42 patients (21 in each group). The baseline phosphate levels were 5.9±1.43 mg/dL in the app group versus 6.0±1.0 mg/dL in the control group (p=ns). At the 3-month follow-up, the group that used the app had a phosphate of 5.4±1.73 mg/dL (81% of the patients reduced phosphate levels), while only 57% of the patients in the control group managed to reduce their phosphate level, with mean levels of 6.0±1.44 mg/dL (p=0.018). These results were maintained at 6 months, and only 38% of the patients who did not use the app. Patients who used the app found it to be useful, and nephrologists were also satisfied with the app.

Conclusion: Patients benefit from a virtual assistant via their smartphone, through an integrated system of participatory, personalized, predictive, and preventive medicine. This study demonstrates that virtual tools through a participatory and personalized medicine system help CKD patients to control hyperphosphatemia.

Funding: Commercial Support - CSL Vifor

TH-PO050
Terlipresin Therapy in Patients with HRS and Comorbidities: The North American Experience
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Background: Hepatorenal syndrome (HRS)—a rapid kidney failure—occurs in patients (pts) with decompenated cirrhosis and ascites. Terlipresin (Terl) is FDA-approved to treat pts with HRS. Certain pts with HRS and alcoholic hepatitis (AH), systemic inflammatory response syndrome (SIRS), or low mean arterial pressure (MAP) may suffer from a portal hypertension/splanchnic vasodilatation-related inflammatory response, which may be attenuated by Terl.

Methods: Data from the 3 largest prospective, randomized, placebo (Pbo)-controlled, clinical studies in pts with HRS (OT-0401; REVERSE, and CONFIRM) were pooled to assess the role of Terli vs Pbo (both plus albumin) on HRS reversal in the subpopulation of pts with AH, MAP <70 mm Hg, or SIRS. HRS reversal was defined as at least 1 serum creatinine (SC) value of ≤1.5 mg/dL while on treatment.

Results: In the pooled population, 394/608 pts had AH, SIRS, or low MAP, and 214/608 pts did not. At baseline, SCR and MELD score were comparable between treatment groups (gps). Among pts with AH, SIRS, or low MAP, HRS reversal was achieved by 81/233 (35%) pts in the Terli gp vs 21/161 (13%) pts in the Pbo gp (P<.001). Among pts with AH, SIRS, or low MAP, fewer pts in the Terli gp (vs Pbo gp) needed renal replacement therapy (RRT) by Day 30 (26% vs 35%, P<.049), Day 60 (28% vs 38%, P=.046), and Day 90 (30% vs 38%, P=.104). Overall survival (OS) up to 90 days demonstrated a positive trend in pts in the Terli gp vs the Pbo gp (P=.077; Figure).

Results: Pts with HRS who had AH, SIRS, or low MAP had a significantly higher HRS reversal rate and lower RRT rate at Days 30 and 60, and a trend for better OS when randomized to Terli vs Pbo.

Funding: Commercial Support - Malinchrodt Pharmaceuticals

Figure: OS among patients with AH, SIRS, or MAP <70 mm Hg, pooled ITT population

TH-PO061
Association of AKI-Hepatorenal Syndrome (HRS) with Mortality in Hospitalized Cirrhotic Patients Requiring Renal Replacement Therapy: Results from the HRS-HARMONY Consortium
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Background: While AKI-RRT is associated with mortality in heterogeneous inpatient populations, the epidemiology of AKI-RRT in hospitalized cirrhotic patients is not fully known. Herein, we evaluated the association of etiology of AKI with mortality in hospitalized cirrhotic patients with AKI-RRT.

Methods: This is a multicenter retrospective cohort study using data from the HRS-HARMONY consortium which included 15 hospitals in the U.S. (01/2019-12/2019). Consecutive hospitalized adult (>18 years) cirrhotic patients with AKI-RRT were included in this study. The primary outcome was 90-day mortality and the main independent variable was AKI etiology, classified as hepatorenal syndrome (HRS-AKI) vs. other AKI etiology. We performed multivariate Cox regression analysis adjusting for age, gender, race, transplant listing status, MELD-Na score, requirement of CRRT, pressor use, and study site.

Results: Of 2063 hospitalized cirrhotic patients with AKI, 374 (18.1%) had AKI-RRT. Among these, 65 (17.4%) had HRS-AKI and 309 (82.6%) had other etiologies of AKI. HRS-AKI included ATN in the majority of cases (62.6%). The HRS-AKI (vs. other AKI etiology) group required less CRRT than hemodialysis as the initial RRT modality (56.9% vs. 73.9%, P=0.006), more HRS vasconstrictor use (81.5% vs. 67.9%, P=0.03), and less mechanical ventilation use (50.8% vs. 64.3%, P=0.04). In a fully adjusted model, HRS-AKI (vs. other AKI etiology) was not associated with 90-day mortality (aHR=1.16, 95% CI: 0.75-1.79, P=0.51). Clinical parameters independently associated with 90-day
mortality included live transplant listing (aHR=0.22, 95% CI: 0.14-0.35), MELD-Na score (aHR=1.04, 95% CI: 1.02-1.05), and the need of CRRT (aHR=2.64, 95% CI: 1.68-4.13).

Conclusions: Among hospitalized adult cirrhotic patients with AKI-RRT, HRS-AKI was diagnosed in about one-fifth of patients, but did not confer an independent increased risk of mortality compared to other AKI etiologies. Higher MELD-Na score and the need of CRRT were independently associated with increased 90-day mortality in this susceptible population.

TH-PO052

Improvement in Serum Creatinine Was Associated with Favorable Clinical Outcomes in Patients with Hepatorenal Syndrome: A Post Hoc Analysis of the CONFIRM Study
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Background: Hepatorenal syndrome (HRS) is a life-threatening but potentially reversible form of acute kidney injury. More patients (pts) with HRS who were treated with terlipressin (terli), achieved verified HRS reversal than placebo (pbo) in the Phase III CONFIRM study (terli 29.1%; pbo 15.8%; P=0.012). This post hoc analysis assessed pt data from CONFIRM to determine if an improvement in serum creatine (SCr) of >30% was associated with improved clinical outcomes.

Methods: CONFIRM enrolled adult pts with cirrhosis, ascites, HRS, and a SCr ≥2.25 mg/dL, with a projected doubling in SCr within 2 weeks. Pts were treated intravenously with terli 1 mg every 6 hours or matched pbo; plus albumin, recommended. Pts from the CONFIRM intent-to-treat (ITT) population were analyzed by their improvement (>30% vs ≤30%) in SCr level from baseline (Day 0; or a prestudy value, if Day 0 value was missing) to the end of treatment (EOT) for the following: length of intensive care unit (ICU) stay; incidence of renal replacement therapy (RRT) and RRT-free survival at Days 30, 60 and 90; as well as survival at Day 90.

Results: More pts in the terli vs pbo group had a >30% improvement in SCr from baseline to EOT (43.7% vs 21.8%; P<0.001). Among pts admitted to the ICU, the mean (SD) length of stay was numerically shorter (5.8d [3.25] vs 9.4d [11.62]; P=0.673) among those who had >30% improvement in SCr. Fewer pts in the >30% improvement in SCr subgroup required RRT (Day 90: 18.3% vs 40.3%; P<0.001). Overall, a higher proportion of pts (N=306, terli + pbo combined) who achieved >30% improvement in SCr were alive (67.0% vs 42.9%, P=0.0001); and alive and RRT-free by Day 90 (55.0% vs 20.4%, P<0.001) (Figure).

Conclusions: Significantly more pts in the terli group achieved a >30% improvement in SCr versus pbo. Pts with a >30% improvement in SCr had significant improvements in clinical outcomes through Day 90.

TH-PO053

Outcomes of AKI on CKD in Hospitalized Cirrhotic Patients: Data from the HRS-HARMONY Consortium
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1Mass General Brigham Inc, Boston, MA; 2Yale School of Medicine, New Haven, CT; 3Medical College of Wisconsin, Milwaukee, WI; 4Ochsner Health, New Orleans, LA; 5Baylor College of Medicine, Houston, TX; 6University of California San Francisco School of Medicine, San Francisco, CA.

Background: The frequency of chronic kidney disease (CKD) is increasing and cirrhosis and these patients frequently suffer acute kidney injury (AKI). Direct comparisons of outcomes between AKI vs AKI on CKD are not well described in cirrhosis.

Methods: 2,057 cirrhotic patients with AKI across 11 hospital networks from the HRS-HARMONY consortium were analyzed (70% AKI without CKD and 30% AKI on CKD). Primary outcome was unadjusted and adjusted 90-day mortality, with transplant as a competing risk.

Results: Compared to patients without CKD, patients with AKI on CKD had higher admission creatinine (2.24 [IQR 1.7, 3.18] vs 1.83 [1.38, 2.58] mg/dL) and peak creatinine (2.79 [2.12, 4] vs 2.42 [1.85, 3.50] mg/dL) but better synthetic liver function (total bilirubin 1.5 [IQR 0.7, 3.1] vs 3.4 [1.5, 9.3] mg/dL; and INR 1.4 [IQR 1.2, 1.8] vs 1.7 [1.39, 2.2]; P<0.001 for all). Patients with AKI on CKD were more likely to have NASH cirrhosis (31% vs 17%) and less likely to have alcohol-associated liver disease (26% vs 45%; P<0.001 for all). Patients without CKD had higher unadjusted mortality (39% vs 30%), intensive care unit admission (52% vs 35%), and use of renal replacement therapy (29% vs 15%; P<0.001 for all). After adjusting for age, race, sex, transplant listing status and MELD-Na score, AKI on CKD was associated with a lower 90-day mortality compared to AKI without CKD (sub-HR 0.73 [95% CI 0.61, 0.88]).

Conclusions: In cirrhotic hospitalized patients, AKI on CKD is associated with lower 90-day mortality compared to AKI without CKD. This surprising finding may be due to worse synthetic liver function in the AKI without CKD group as underlying liver function is a strong driver of short-term outcomes in this population. Further study of the complicated interplay between acute and chronic kidney disease in cirrhosis is needed.

TH-PO054

Pre-Liver Transplant Acute Kidney Disease Highlights Impaired Renal Function Recovery Phase
Jacqueline Lee, Edmund Huang, Sanjeev Kumar. Cedars-Sinai Medical Center, Los Angeles, CA.

Background: Acute kidney disease (AKD), the phase between acute kidney injury (AKI) and chronic kidney disease (CKD), represents a crucial time window for initiation of therapies that may significantly augment renal function recovery. Herein, we aim to study the impact of duration of AKI in patients with decompensated cirrhosis on subsequent renal function recovery post-liver transplantation.

Methods: This is a single-center, retrospective study of adults who underwent single-organ, orthotopic liver transplant (OLT) from Jan 2015 to Dec 2021. AKD was defined as persistence of AKI for greater than a week but up to 90 days. The study cohort was classified by pre-transplant AKI duration and renal replacement therapy (RRT) status into four groups: normal kidney function, AKI requiring RRT within 7 days of onset (AKI_RRT), AKD without RRT (AKD-noRRT), and AKD with RRT (AKD-RRT). Renal function was compared with serial measurements of eGFR before and after OLT.

Results: Approximately half of the patients required RRT prior to OLT (81/170, 47.6%): 24% (41/170) required RRT within 7 days of AKI and other 23.7% (40/170) during the AKD phase. Only 6.3% (11/170) underwent OLT with AKD but without RRT. The remaining cohort had normal renal function (78/170, 45.8%). Patients who were commenced on RRT during the AKD phase had significantly lower eGFRs at 3 months and 1 year compared to AKI_RRT group [AKD-noRRT, AKD-RRT, 41.6 ml/min vs. 56.6 ml/min, p < 0.05 (3 months); and 49.7 ml/min vs. 59.2 ml/min, p < 0.05 (1 year)].

Conclusions: Our study findings suggest AKD is associated with significantly reduced renal function recovery 1-year post-liver transplantation. Our study demarcates the critical phase of AKI associated with maximal renal function recovery in cirrhotic patients for OLT and inform when best to initiate therapies that are linked with renal function recovery.

Post-liver transplant eGFR Trajectories

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Renal Function</th>
<th>AKI RRT</th>
<th>AKD noRRT</th>
<th>AKD RRT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>n=170</td>
<td>81/170</td>
<td>41/170</td>
<td>40/170</td>
<td>11/170</td>
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<td>eGFR at transplant</td>
<td>66.9 ± 46.9</td>
<td>41.6 ± 17.7</td>
<td>52.1 ± 7.8</td>
<td>54.3 ± 7.5</td>
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<tr>
<td>At 3 month*</td>
<td>77.6 ± 42.2</td>
<td>58.9 ± 27.5</td>
<td>62.3 ± 31.1</td>
<td>53.6 ± 26.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>At 1 year**</td>
<td>77.2 ± 45.2</td>
<td>59.6 ± 29.6</td>
<td>59.5 ± 22.6</td>
<td>69.7 ± 29.2</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*p=missing values - 3 for 3 months (defined as -2 weeks to +6 weeks of 3 months) ** missing values - 22 for 1 year (+4 weeks from 1 year mark)
TH-PO055

Cholemic Tubulopathy as a Cause of AKI: A Cohort Study

**Vinay Vanhose**, Dustin R. Chalmers, Lauren Cohen, Akanksh Ramanand, Juan Carlos Q. Velez. *Ochsner Health, New Orleans, LA.*

**Background:** Cholemic tubulopathy (i.e., bile cast nephropathy) is a type of acute kidney injury (AKI) described in individuals with acute cholestasis (obstructive, drug-induced, infectious, acute alcoholic). However, most of the available evidence comes from isolated case reports. We aimed to describe the clinical characteristics of patients diagnosed with cholemic tubulopathy within a single-center prospective AKI cohort.

**Methods:** We established prospective data collection in patients with AKI stage ≥ 2 (AKIN) over 5-years. Each patient completed microscopic examination of the urinary sediment (MicrExUrSed). The presence of bile casts (HC), waxy casts (WxC), renal tubular epithelial cell casts (RTECC), granular casts (GC), and muddy brown granular casts (MBGC) were recorded. We identified patients with documented cholestasis without cirrhosis. Demographic and clinical characteristics were extracted. Cases of shock liver were excluded.

**Results:** Among 483 patients with AKI without cirrhosis, 22 (4.6%) patients were found to have cholemic tubulopathy as the primary cause of AKI (32% women, 46% white, 27% black, median age 57 (20-84)). Causes of cholestasis included biliary obstruction due to primary or metastatic cancer (5), biliary stricture (1), drug-induced cholestasis (1), cholethiathiasis (6), acute viral hepatitis (3), alcoholic hepatitis (4), and acute liver failure of unknown etiology (2). One case was biopsy-proven bile cast associated acute tubular injury (acute hepatitis A). Median serum bilirubin was 22.8 (3.3-57.7) mg/dL, and serum creatinine at presentation was 3.1 (1.4-6.6) mg/dL. By MicrExUrSed, HC, RTECC, GC, MBGC, and WxC were identified 13%, 41%, 64%, 55%, and 28% of patients, respectively. Among patients which had crystals reported, leucine crystals were seen in 5/17 (29%) and bilirubin crystals were seen in 4/17 (24%). Among patients with cholemic tubulopathy, 11 (50%) patients required dialysis, 6 (27%) died, and 6 (27%) recovered kidney function.

**Conclusions:** Cholemic tubulopathy should be suspected as a cause of AKI in patients with cholestasis with severe hyperbilirubinemia without an alternative etiology of AKI. Overt evidence of tubular injury is often found by MicrExUrSed.

TH-PO056

A Case of Bile Cast Nephropathy Treated with Plasma Exchange Therapy for AKI Associated with Acute Hepatitis A

**Masahiro Arai**, Takahito Moriyama, Fumika Iemura, Rie Suzuki, Yoshinaka Miyaoaka, Yoshihiko Kanno. *Tokyo Medical University Hospital, Tokyo Ikeda Daiichi, Shinjuku-ku, Japan.*

**Introduction:** Bilirubin-induced renal injury has been reported as bile cast nephropathy (BCN) or cholemic nephropathy (CN) which is a rare form of acute kidney injury (AKI) in Japanese. Although the improvement of hyperbilirubinemia is effective for renal dysfunction, the treatment strategies of blood purification therapy has not been established. Here, we report a case of bile cast nephropathy associated with acute hepatitis A in which hyperbilirubinemia was treated by plasma exchange therapy and AKI was improved.

**Case Description:** The patient, a 45-year-old man, was admitted to the hospital with acute hepatitis A. His transaminase and serum direct bilirubin (D-Bil) was severely increased (AST: 197 IU/L, ALT: 2652 IU/L, and D-Bil: 8.31 mg/dL), but serum creatinine (Cr) was normal (0.81 mg/dL). While his transaminase tended to improve with the best supportive care his D-Bil was elevated to 37.6 mg/dL, and Cr was also elevated to 4.5 mg/dL on day 30. Based on the course of the disease, the possibility of BCN was suspected, and plasma exchange therapy was administered 5 times on alternate days from day 30. On day 42, we performed a percutaneous renal biopsy, and we observed bilirubin columns in the renal tubules, and we made diagnosis as BCN. After plasma exchange therapy, his D-Bil was dramatically decreased and the renal dysfunction was recovered as serum Cr level of 1.2 mg/dL.

**Discussion:** Despite the improvement of transaminase, the elevated D-Bil induced the renal dysfunction, and we suspected BCN as the cause of AKI and successfully treated AKI due to BCN by plasma exchange therapy. BCN is rare in Japanese, and moreover, there have been few reports of renal biopsy in surviving patients. The treatment strategies of blood purification therapy to remove bilirubin have not been established, and further study is needed.

TH-PO0077

Bile Cast Nephropathy: A Diagnostic Odyssey Beyond Hepatorenal Syndrome

**Samira M. Samant**, Camilo Cortesi. *The Permanente Medical Group Inc, Santa Clara, CA.*

**Introduction:** Bile cast nephropathy (BCN) is a rarely recognized and often overlooked complication of hyperbilirubinemia leading to acute kidney injury (AKI). We present a case of BCN in a patient with alcohol hepatitis initially managed as hepatorenal syndrome (HRS).

**Case Description:** A 66-year-old male with severe alcohol abuse and baseline creatinine of 1.5 mg/dL presented with altered mental status and acute alcohol intoxication, requiring ICU admission. Laboratory tests showed AST 751 U/L, ALT 238 U/L, ALKP 768 U/L, total bilirubin 22.9 mg/dL, direct bilirubin 12.4 mg/dL, INR 2.4, ammonia 181 umol/L, and creatinine 2.6 mg/dL with FENa 0.1%. Ultrasound revealed diffusely hypeerechoic liver, diagnosing alcoholic hepatitis with impending liver failure. Glucocorticoids were initiated, with octreotide, albumin, and midodrine for HRS. However, renal function worsened as total bilirubin peaked at 54 mg/dL. Urine microscopy identified bile-stained granular casts, prompting reassessment of the initial HRS diagnosis.

**Discussion:** HRS is often considered in AKI with liver dysfunction, but urine microscopy should not be overlooked. In AKI, urine microscopy to rule out BCN is crucial, especially when total bilirubin exceeds 20 mg/dL. Bilirubin’s nephrotoxic effects involve oxidative damage to renal tubules, bile cast obstruction, and toxicity of sulfated bile salts. Renal biopsy for definitive diagnosis is unsafe in liver disease due to coagulopathy. Treatment focuses on improving hepatic function and relieving biliary obstruction if present. Timely diagnosis and intervention can reverse renal injury; refractory cases may require plasmapheresis or dialysis. Steroids, ursodeoxycholic acid, and lactulose provide minimal benefit. This case highlights the challenges of differentiating BCN from HRS, emphasizing the importance of urine microscopy.

Bile-stained granular casts

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

*Underline represents presenting author.*
SGLT2 Inhibitor Dapagliflozin Reduces Biomarkers of Tubular Injury in Patients with Acute Heart Failure

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Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors improve renal and cardiovascular outcomes in heart failure patients, and there is growing evidence that it would decrease the risk of acute kidney injury (AKI). The aim of this study was to evaluate the effect of SGLT2 inhibitors on biomarkers of tubular injury in patients with acute heart failure (AHF).

Methods: Patients who hospitalized for AHF were randomized to dapagliflozin add-on to standard therapy or control group for 28 days. The primary outcome was to assess the effect of SGLT2 inhibition on biomarkers of tubular injury in patients with acute heart failure (AHF).

Results: A total of 32 patients underwent randomization. Compared with control group, dapagliflozin group significantly reduced urinary [TIMP-2] x [IGFBP7] by NephroCheck® from baseline. The secondary outcome was incidence of AKI, the change of serum creatinine from baseline, adverse events and 28-day mortality.

Conclusions: Initiation of SGLT2 inhibitors in patients with AHF significantly decrease the urinary AKI risk markers TIMP-2 and IGFBP7, that supported protective effect of SGLT2 inhibitor on renal tubular injury.

Funding: Government Support - Non-U.S.
2 diabetes mellitus (T2DM) without other comorbidity. Recent studies have shown that metformin has a pleiotropic effect and has been linked with lower cardiovascular mortality. The use of metformin in the inpatient setting is controversial. We are exploring if metformin use after AKI recovery is associated lower mortality and higher lactate level evaluated. The median level (IQR) WAS 1.4 (1.0-1.7) in the metformin user versus 1.4 (1.1-1.8) in non-users with P = 0.002. There was no statistical difference in the degree of lactacidosis developed between two groups.

Conclusions: Metformin therapy during hospitalization after AKI recovery is associated with lower mortality and higher lactate levels in patients with T2DM not associated with increased risk of lactacidosis. In addition, metformin use after recovery from AKI stage 2 and stage 3 is associated with lower 1-year mortality than the metformin non-users.

TH-PO066
Associations of RAASI Discontinuation with Mortality Among Hospitalized Patients with Cardiovascular Disease in Brazil

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Background: It is consensus that renin-angiotensin-aldosterone system inhibitors (RAASI) are a pillar of drugs used for cardiovascular and renal protection, however their effects during an AKI episode are still controversial and most guidelines suggest their discontinuation. The purpose of this study is to compare the mortality of hospitalized patients with cardiovascular diseases who developed AKI and discontinued the inhibitors with those who maintained their use.

Methods: We analyzed data from a cohort of hospitalized patients in Hospital de Base - Sao José do Rio Preto with cardiovascular disease (coronary artery disease and heart failure) identified by an AKI alert, in 2018 and 2020, based on the KDIGO creatinine criteria, who were using RAASI. Discontinuation of RAASI was defined as the suspension of their prescription for up to 3 days after the AKI alert. We used a Poisson model to estimate the adjusted risk of death predicted by the RAASI discontinuation. Race, age and use were used as possible confounders.

Results: Our cohort consisted of 1683 patients, with a mean age of 63 years of age with 56% male. Of the patients there were using RAASI within 24 hours of the AKI alert, 529 remained on the medications 72 hours later. The patients that discontinued RAASI had a greater risk of death (31% vs 19%) when compared to the patients who remained using them. When accounting for possible confounders, the risk of death for the RAASI discontinuation group was 54% higher (RR=1.54 (1.30, 1.83)) than for those that remained using the drugs.

Conclusions: In patients with cardiovascular disease, that developed AKI during the hospital stay, the strategy of RAASI discontinuation may be associated with higher mortality. Although there are limitations, due to the observational nature of this analysis, this data supports that this class of drugs should not be withdrawn routinely in the inpatient setting.

TH-PO064
Using Kinetic GFR for Vancomycin Dosing When Renal Clearance Is Acutely Changing: A Simulation Study

Manohar Bairy, Benjamin Z. Khoo, Sock Boon Tan, Leticia X. Peh, Siow Yu Lim, Chiang Shen Hui. Tan Tock Seng Hospital, Singapore, Singapore.

Background: Achieving target vancomycin trough (VT) levels in acutely ill patients is a challenge. Using Cockcroft Gault estimated creatinine clearance (CGeCrCl) for drug dosing lacks validation when the creatinine level is unsteady. In this cohort of hospitalised patients treated with CGeCrCl based vancomycin dosing, we used Kinetic Estimated GFR (KeGFR) and MDRD eGFR to predict VT levels and to estimate vancomycin dosing frequencies and explored the likelihood of achieving target VT levels.

Methods: Among 111 methicillin-resistant Staphylococcus aureus bacteremic patients treated with intravenous vancomycin who had creatinine levels varying by > 5% during treatment, a study subgroup (SSG) consisted of 38 patients who had VT levels checked after the first (loading) dose and before the second dose. Predicted VT using CGeCrCl, KeGFR and MDRD eGFR calculated using population pharmacokinetic equations and compared to the true (observed) VT using Bland Altman (BA) plots for agreement in the SSG. VT levels predicted using CGeCrCl and MDRD eGFR was determined using the hospital vancomycin dosing protocol and the likelihood of achieving the target VT (10-20mg/L) was estimated for each method.

Results: VT levels of 41 patients (37%) were <10mg/L. In the SSG, CGeCrCl was 23%. Kinetic model (KeGFR) and MDRD eGFR calculated using population pharmacokinetic equations and compared to the true (observed) VT using Bland Altman (BA) plots for agreement in the SSG. VT levels predicted using CGeCrCl and MDRD eGFR was determined using the hospital vancomycin dosing protocol and the likelihood of achieving the target VT (10-20mg/L) was estimated for each method.

Discussion: This patient developed AKI and hyperkalemia approximately 6 months after starting ranolazine. This is a rare adverse effect with only a few reported cases in this literature. In this case, the hyperkalemia was asymptomatic off ranolazine.

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

Poster/Thursday

AKI in a Kidney Transplant Patient Started on Ranolazine

Andrew J. Howard, Amy J. Frankston. Walter Reed National Military Medical Center, Bethesda, MD.

Introduction: Ranolazine is an antianginal agent only rarely associated with kidney failure (< 1%). We present a case of a kidney transplant recipient who experienced acute kidney injury (AKI) and hyperkalemia after starting ranolazine, and subsequently improved after it was stopped.

Case Description: A 74-year-old man with end-stage kidney disease (ESKD), presumed secondary to diabetic nephropathy, received a deceased-donor kidney transplant in 2014. Post-transplant course was complicated by BK nephropathy with persistent low-grade viremia and atypical hemolytic uremic syndrome treated with r拉动ilumab. He presented to the Emergency Department at the request of his hematologist for hyperkalemia and acute kidney injury discovered on routine labs. Baseline serum creatinine was 1.3-1.6 mg/dL. At presentation, serum creatinine was 3.23 mg/dL and potassium was 7.1 mEq/L. After a standard evaluation, there was no obvious etiology for AKI, and an urgent transplant kidney biopsy was performed. Biopsy showed severe tubular injury with interstitial inflammation and focal tubulitis, mild interstitial fibrosis and tubular atrophy (30%). There was evidence of T-cell or antibody mediated rejection, transplant glomerulopathy, or recent atypical hemolytic uremic syndrome. On review, the only new medication prescribed was ranolazine. This was held and he was treated medically for his hyperkalemia. Renal function subsequently improved, with a new baseline creatinine of 1.8-2.3 mg/dL. Hyperkalemia resolved. He was asymptomatic off ranolazine.

Discussion: This patient developed AKI and hyperkalemia approximately 6 months after starting ranolazine. This is a rare adverse effect with only a few reported cases in the literature. A previous report implicated ranolazine as a cause of AKI due to drug-induced phospholipidosis, with finding of zebra bodies on electron microscopy. Our patient’s biopsy did not have zebra bodies present, making drug-induced phospholipidosis less likely. The mechanism is unclear. This case demonstrates that a thorough medication review and cessation of any possibly offending agents is vital in assessing AKI of unclear etiology.

Disclaimer: The views expressed in this Abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the United States Government.
TH-PO067
A Case of Rhabdomyolysis and Acute Tubular Necrosis with Lower than Expected Creatinine Kinase Level in a Patient with Cocaine Abuse
Ascension Saint Francis, Evanston, IL.

Introduction: Clinicians rely on serum creatinine kinase (CK) levels to assess the severity of rhabdomyolysis (RM) and predict the development of acute kidney injury (AKI). It is widely accepted that rhabdomyolysis with CK levels less than 5000 U/L is unlikely to cause AKI. We report a case of cocaine-induced rhabdomyolysis and subsequent development of myoglobinuric acute tubular necrosis (ATN) in a young healthy male with CK levels of 928 U/L at presentation.

Case Description: A 33-year-old male with a past medical history of poly-substance abuse presented with headache following intake of crack cocaine three days prior to the presentation. Examination were remarkable for blood pressure of 171/108 mmHg and dry mucous membranes. Laboratory studies were significant for serum creatinine (Cr) of 21 mg/dl, Blood Urea Nitrogen (BUN) of 113 mg/dl and CK of 928 U/L. Urine sample obtained after bladder catheterization revealed gross blood with 3-5 red blood cells (RBCs)/hpf, proteinuria of 100 mg/dl and the urine toxicology was positive for cocaine. Renal ultrasound was non-contributory. Patient did not meet the criteria for urgent dialysis and the patient was started on intravenous (IV) fluids. The patient remained anuric. All the work ups done for etiologies of AKI were negative. Renal biopsy was consistent with diffuse ATN with myoglobin casts. Outpatient follow-up and continued supportive treatment resulted in resolution of ATN and normal kidney function.

Discussion: Cocaine induced RM can be traumatic due to seizure and/or hyperpyrexia and non-traumatic due to direct toxic effects of cocaine on skeletal muscle. CK and myoglobin levels change in parallel and CK levels correlate well with the severity of RM but its correlation and property to predict development of AKI is less reliable compared to serum myoglobin levels.

Figure showing Myoglobin Casts

TH-PO068
Cocaine-Associated Acute Tubular Injury and Acute Interstitial Nephritis
Akhila Arva P V, Jia Wei Tan. Bridgeport Hospital Internal Medicine, Bridgeport, CT.

Introduction: Cocaine can affect various compartments of the nephron, leading to conditions such as rhabdomyolysis-induced acute kidney injury (AKI) and rarely, cocaine-associated acute interstitial nephritis (AIN). In our case, the patient presented with AIN and acute tubular injury (ATI) without rhabdomyolysis.

Case Description: A previously healthy 37-year-old male presented with left flank and epigastric pain for three days. He denied taking any medication or recreational drugs. On admission, his blood pressure was 147/84 mmHg. He appeared euvolemic and had no rash, purpura, or arthralgias. Labs showed serum creatinine of 10.7 µg/dl without a prior baseline, blood urea nitrogen of 58 µg/dl, bicarbonate of 19 mmol/L, anion gap of 23, phosphorylase of 9.6 µg/dl and creatinine kinase of 66 international units. Urinalysis showed 1+ proteinuria, 1 RBC/hpf and 1 WBC/hpf. His protein/creatinine ratio was 0.57 mg/mg Cr. C3 and C4 were normal. Hepatitis B, C, and HIV were negative. ANA was negative, and the ANA was 1:40 in a perinuclear pattern. Renal ultrasound showed normal-sized kidneys and CT abdomen did not reveal any pathological findings. A renal biopsy confirmed the presence of diffuse AIN and ATI (Image 1, H & E, 40x). The patient’s kidney function gradually improved without steroid treatment and a follow-up outpatient visit showed serum creatinine of 1.67 µg/dl.

Discussion: We highlight the importance of considering cocaine-associated renal complications, even in the absence of rhabdomyolysis, and highlight the rare presentation of concomitant ATI and AIN. The clinical, biochemical and urinalysis of AIN can be subtle and non-specific, making it challenging to diagnose. However, if there is a strong clinical suspicion of AIN, renal biopsy should be pursued to allow early recognition and potential treatment. Our patient’s renal function recovered with supportive management alone, but further data are needed to fully understand the clinical course and treatment strategies for cocaine-associated AIN and ATI.

TH-PO069
Mimicking Ulcerative Collitis Flare-Ups Induced by Azathioprine Causes AKI
Mitsuru Yanai, Makoto Araki. Sapporo Tokushukai Hospital, Sapporo, Japan.

Introduction: Inflammatory bowel disease (IBD) is correlated with various renal ailments, including renal lithiasis, glomerulonephritis, renal amyloidosis, and drug-induced nephropathy. But no prior reports have documented drug-induced renal dysfunction with azathioprine (AZA) in IBD.

Case Description: A 61-year-old male was referred to our facility for ulcerative colitis flare-up. He had previously tried various medications, including 5-miniminoalicylic acid (5-ASA), AZA, and anti-TNFα antibody. Achieving remission with 30 mg prednisolone (PSL), he began novel anti-IL-12/23 antibody treatment. Over 8 weeks, the PSL dose was gradually reduced without relapse. During the second dose of the anti-IL-12/23 antibody, AZA at 25 mg/day replaced PSL. The next morning, the patient experienced chills, fatigue, and worsening diarrhea (over 10 times per day) shortly after the morning dose. Diarrhea persisted, the patient lost appetite, and became anuric. Subsequently, on the fourth day after anti-IL-12/23 antibody administration, the patient was ambulance-transported to our hospital. Compared to values from four days prior, white blood cell count increased from 7500 to 9130/µL, C-reactive protein level rose from 0.32 to 41.37 mg/dL, and creatinine level escalated from 1.01 to 8.29 mg/dL. Considering possible infectious enteritis or worsening ulcerative colitis, the patient promptly received intravenous fluids, antibiotics, and 30 mg PSL. Hemodialysis was initiated. On the fourth day of hospitalization, a renal biopsy revealed massive cellular infiltration of the interstitium, leading to the diagnosis of acute interstitial nephritis due to azathioprine hypersensitivity syndrome. The PSL dose was quickly increased to 60 mg. Renal function gradually improved, and dialysis was completed in three sessions. After one month, creatinine levels returned to baseline, and steroid treatment ceased. Subsequently, the patient received a third dose of the anti-IL-12/23 antibody without any adverse events.

Discussion: Azathioprine hypersensitivity syndrome is a systemic allergic reaction to immunosuppressive drugs, resulting in acute interstitial nephritis in the kidneys. Severe inflammatory reactions of heightened intensity mimic an exacerbation of the underlying disease or sepsis, frequently leading to delayed treatment. Timely diagnosis and prompt administration of steroids can influence the renal prognosis.

TH-PO070
Ashwagandha Overdose-Induced AKI: A Novel Case Report
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Introduction: Ashwagandha (Withania somnifera) is an Ayurvedic herb with various therapeutic properties, such as anti-inflammatory, antitumor, immunomodulatory, and adaptogenic effects. However, its safety profile is not well established. This abstract highlights the first case of kidney injury associated with ashwagandha overdose.

Case Description: A 26-year-old female presented with a 2-day history of progressive abdominal pain, nausea, and vomiting after taking high doses of ashwagandha (6000mg per meal) for a week to treat anxiety. Vital signs were normal, and the physical exam revealed right upper quadrant tenderness. Blood tests showed severe drug-induced elevated ALT/AST (>7000 U/L), total bilirubin 2.1 mg/dL, and alkaline phosphatase 82 U/L. Treatment with N-acetyl cysteine improved liver function, but renal function rapidly declined on the second day. Urinalysis showed no hematuria but identified 2+ proteinuria, and a subsequent renal biopsy revealed acute tubular injury. Temporary hemodialysis was required, and the patient eventually recovered with normal kidney function in 2 weeks.

Discussion: Ashwagandha is known for its potential therapeutic benefits in stress, anxiety, and inflammation. However, the optimal daily dosage remains to be determined. Clinical trials used 300-1000mg/day, while commercial preparations may have higher amounts. A recent in-vitro study suggested that an overdose of the herb’s primary metabolite, Withanone, may overwhelm the glutathione detoxifying system and cause DNA damage. Acute tubular injury observed may result from impaired renal tubule protection against oxidative stress. Kidney function returned to normal after discontinuing

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
An Unusual Cause of Cloudy Urine in a Patient with Sepsis

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Introduction: Cloudy urine is usually caused by pyuria. Here, we present the case of a patient whose viscous, cloudy urine was caused not by pyuria but by acyclovir crystalluria.

Case Description: A 71-year-old woman with HFpEF and history of diverticulitis was admitted for colostomy trauma. Her hospital stay was complicated by rapid atrial fibrillation, fluid overload and enterococcal urinary tract infection. In her sixth week of hospitalization she developed sepsis secondary to a hepatic abscess, requiring intensive care and treatment with Meropenem and Vancomycin. She also was treated empirically with Acyclovir 600mg IV q 8hrs for suspected HSV encephalitis. Nephrology was consulted for oliguric AKI with a creatinine increase from 0.8mg/dl to 1.57mg/dl and elevated vancomycin trough level. The urine was viscous and cloudy. On microscopy the urine was loaded with needle shaped birefringent crystals, typical of acyclovir crystalopathy. With medication dose adjustments the oliguria resolved and the urine showed no more crystals and rare granular casts. Four days later the patient's serum creatinine had decreased to 0.84mg/dl. The patient completed two weeks of acyclovir treatment, eventually recovered and was discharged to rehabilitation 6 weeks later.

Discussion: Intravenous Acyclovir can cause transient oliguric AKI with crystalluria so heavy that it resembles pyuria. Despite the dramatic presentation, renal recovery can occur swiftly with dose adjustment. There may be additional causes of AKI precipitating the event.

Anticoagulant-Related Nephropathy in Patients with Mechanical Valves: A Challenging Case and a Possible Solution

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Introduction: Anticoagulant-related nephropathy (ARN) is a novel form of acute kidney injury (AKI) associated with anticoagulant (AC) use. Management is challenging for patients on long-term AC who develop ARN.

Case Description: A 62-year-old Male with a history of chronic kidney disease [CKD, baseline serum creatinine (sCr) of 1.7 mg/dL], atrial fibrillation (Afib), mechanical aortic valve replacement on warfarin, and non-ischemic cardiomyopathy status post ICD insertion who presented with epistaxis. His medications include aspirin, carvedilol, furosemide, pantoprazole, simvastatin, and warfarin. He had a recent admission for AKI with microscopic hematuria needing workup for glomerulonephritis. The complements, ANA, ANCA, anti-GBM antibody, serum protein electrophoresis, and serum light chains were within normal range. Ultrasonography showed no evidence of kidney stones or hydronephrosis. The cause of AKI was unclear but his sCr improved to 1.96mg/dL after briefly holding warfarin for an INR of 3.9. Warfarin was continued on discharge. During this admission, labs showed a sCr level of 4.3 mg/dL and an INR of 5.8 on day 0. Warfarin was held and intravenous heparin drip was started. Patient had hematuria with a urine protein/creatinine ratio of 0.92 mg/g and a kidney biopsy was obtained for AKI on CKD. Pathology showed RBC casts and tubular injury consistent with ARN and underlying IgA nephropathy. His sCr improved to 1.7mg/dL and warfarin was restarted.
on discharge. Five months later, he developed AKI on CKD requiring intermittent hemodialysis (HD). AC was held per the patient and his family. After holding prednisone, function recovered with no further HD needs. His Scr ranged between 1.7 to 2 mg/dL for the next six months. Due to the high risk of stroke given mechanical valve and Afib without AC, Cardiology, Hematology and Nephrology coordinated the care and a trial of apixaban 2.5 mg po tid was started. His Scr has been followed closely and is stable to date.

Discussion: ARN is often caused by high intensity warfarin usage but has been reported in patients on direct-acting oral AC. For patients with ARN needing lifelong AC, risks and benefits discussion is warranted. Multidisciplinary team effort is required. Trial of alternative low dose AC with close monitoring of Scr could be a possible solution.

TH-PO073
Karyomegalic Interstitial Nephritis in a Patient Treated with Ifosfamide
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Introduction: Ifosfamide is an alkylating used in treating wide variety of cancers including germ line tumors of testes, soft tissue sarcomas, bladder cancer and cervical cancer. It can lead to reversible Fanconi syndrome, acute kidney injury (AKI). Here in, we present a case of karyomegalic interstitial nephritis (KIN) in a patient treated with ifosfamide.

Case Description: 47-year-old female with history significant for high grade extra skeletal osteosarcoma underwent tumor resection with flap reconstruction. She was started on chemotherapy with Adriamycin, Ifosfamide, Mesna and received a total of three cycles of chemotherapy. She developed AKI with creatinine of 1.5 mg/dl (baseline creatinine of 0.8 mg/dl) along with hypokalemia, hypophosphatemia and metabolic acidosis, due to which Nephrology consultation was sought. Her blood pressure was 145/79 mmHg. Heart rate was 79 beats per minute. Urine analysis was performed which showed glycosuria and microscropy was bland. Initial sodium was 141 mmol/L, potassium 2.8 mmol/L, chloride of 116 mmol/L, bicarbonate 16 mmol/L, blood urea nitrogen 12 mg/dL, Serum creatinine (Scr) of 1.59 mg/dL, phosphorus 1.5 mg/dL. She was treated conservatively with electrolyte supplementation and intravenous fluids, discharged home with outpatient follow up. Due to progressive decline in renal function (Scr 2.2 mg/dL) she underwent biopsy which showed chronic interstitial nephritis with karyomegalic features, and severe interstitial fibrosis and tubular atrophy (IFTA 70%). She was started on steroids and creatinine improved to 1.7 mg/dL. Thereafter, her creatinine remained steady at 2 mg/dL. There was no recurrence of cancer and is currently in remission.

Discussion: KIN is a rare form of familial interstitial nephritis. As per previous case reports, AKI occurs between 12 months to 5 years after exposure to the drug. In our case, AKI: Liver Disease, Nephrotoxicity, Novel Therapeutics

TH-PO075
Plasmapheresis as Adjunctive Treatment for Life-Threatening Rituximab-Induced Acute Respiratory Distress Syndrome
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Introduction: Rituximab is monoclonal antibody targeted against the B-cell surface antigen CD20. It is used as therapy for a variety of conditions including hematologic malignancies and autoimmune diseases. Use of rituximab has been associated with hypersensitivity reactions (HSR) which can be classified as infusion-related, cytokine-release, type I (EGE-non-IGE), mixed, type III, and type IV reactions. While rituximab is typically associated with largely benign infusion reactions, it occasionally leads to serious type I reactions, which can cause life-threatening anaphylaxis. Rituximab can cause lung toxicity due to immediate hypersensitivity, via cytokine release and by a delayed HSR.

We report the management of a patient with severe shock and ARDS attributed to a mixed HSR to rituximab infusion, which improved with plasmapheresis.

Case Description: A thirty-year-old woman with myasthenia gravis (MG) was admitted with an acute exacerbation of MG after missing her maintenance dose of rituximab. She was initially treated with five sessions of plasmapheresis without any complications. Subsequently, she was treated with rituximab, per the standard protocol. Several hours after her rituximab infusion, she developed refractory shock, hypoxia, and hemoconcentration (Hgb 12 to 17 g/dL). Despite high dose steroids and broad-spectrum antibiotics, she rapidly developed ARDS requiring mechanical ventilation, oliguric acute kidney injury, and severe lactic acidosis. Her echocardiogram showed normal cardiac function and infectious work-up was ultimately negative. She was initiated on mechanical ventilation with the addition of plasmapheresis. Rituximab was held as per prior case reports. She subsequently had rapid improvement in clinical parameters with resolution of shock in three days, resolution of AKI soon after and extubation after six days.

Discussion: Severe HSR, while rare, can be a potentially fatal adverse effect of rituximab. There is no well-described treatment of this reaction. We describe a case with rapid improvement after one treatment of adjunctive plasmapheresis. With the widespread use of rituximab for a variety of conditions, clinicians need to be aware regarding the diagnosis and management of the spectrum of HSRs associated with this drug.
Imatinib, other KIT mutations have been identified. F522C accounts for 1% of all SM-associated KIT mutations and has been reported to be sensitive to Imatinib.

Case Description: A 72-year-old woman was diagnosed with systemic mastocytosis (KIT F522C mutation) following bone marrow biopsy showing mast cell infiltrate and stained positive for CD117. She was commenced on antihistamines and Montelukast. Following the results of the bone marrow sample showing F522C mutation, she was commenced on Imatinib. She initially had a good response to treatment, however she subsequently lost response to Imatinib and required frequent courses of tapering steroids. Two years after diagnosis, she presented to emergency department (ED) with an acute history of facial flushing and oliguria. Her bloods on presentation to ED showed elevated creatinine and tryptase levels. She initially required renal replacement therapy for several days, renal function then recovered. A renal biopsy was arranged. The biopsy showed acute tubular necrosis (ATN) and inflammatory cell infiltration of the interstitium. Immunohistochemical staining showed focal aggregates of CD117 positive cells indicating an infiltrate of mast cells (~10%). Following discussion with the patient, she opted not for further management. She became oliguric and developed disseminated intervascular coagulation without evidence of bleeding. She was transferred to a hospice for where she passed away.

Discussion: Renal involvement in SM is rare and has not been described much in the literature. Consideration needs to be given to other causes of AKI in SM, eg. ATN or acute interstitial nephritis secondary to Imatinib. Renal mastocytosis is typically progressive and leads to chronic kidney disease/end stage kidney disease despite treatment.
TH-PO080
Cannabinergic Acid (CBGA) Ameliorates Renal Inflammation and Fibrosis in Mouse Nephropathic Models
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Background: Cannabinoids are a major class of compounds in cannabis, comprising some ~100 structurally related but diverse molecules, where cannabinol acid (CBDA) and tetrahydrocannabinol acid (THCA) being the major components in most plant varieties. In some plant varieties, cannabinergic acid (CBGA) has been reported the dominant molecular species. CBD, the decarboxylated version of CBDA, is thought have multiple biological effects, including the ability to attenuate inflammatory processes. Cannabigerols (CBGA and its decarboxylated CBG molecule) have pharmacological profiles similar to CBD. The endocannabinoid system has recently emerged to contribute to kidney disease, however, the therapeutic property of cannabinoids in kidney disease remains largely unknown. In this study, we determined whether CBD and CBGA can attenuate kidney damage in cisplatin-induced acute kidney injury model. In addition, we evaluated the anti-fibrosis effect of these cannabinoids in Unilateral Ureteral Obstruction (UUO) mice as a chronic kidney disease model.

Methods: CBD or CBGA (10 mg/kg) were injected daily in cisplatin administered mice and UUO mice. Kidneys were collected at day 3 from cisplatin administered mice and for qRT-PCR, western blotting and TUNEL assay. UUO Kidneys were collected at day 7 and used for immunostaining of Ki-67 and extracellular matrix. We also assessed the effect of CBGA and CBD to ion channel by patch-clamp technique.

Results: We find that CBGA protects the kidney from cisplatin-induced nephrotoxicity. CBGA also strongly suppressed mRNA of inflammatory cytokines and apoptosis through inhibition of caspase-3 activity in cisplatin-induced acute kidney injury, whereas CBD treatment was only partially effective. In UUO kidneys, both CBGA and CBD prevented kidney atrophy, tubule loss, proliferation and maintained overall morphology. Both cannabinoids also strongly reduced renal fibrosis in UUO kidneys. Finally, we find that in contrast to CBD, CBGA has a potent inhibitory effect on the channel-kisase TRPM7 and the TRPM7 protein expression was significantly suppressed in cisplatin-induced acute kidney injury.

Conclusions: We conclude that CBGA and CBD have a renoprotective efficacy in kidney damage, with CBGA especially having a stronger inhibitory effect to prevent inflammation in acute kidney injury by TRPM7 blockage.

Funding: Other NIH Support - National Center for Complementary and Integrative Health: R01AT011162

TH-PO081
AKI-Induced Circulating TNFR1/2 Elevations Correlate with Persistent Kidney Injury and Progression to Fibrosis
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Background: Elevated levels of circulating Tumor-Necrosis-Factor-Receptors 1 and 2 (cTNFR1/2) predict CKD progression. Whether acute kidney injury drives cTNFR1/2 elevations and whether they predict disease outcomes after AKI remains unknown.

Methods: We used AKI patient serum and urine samples, mouse models of kidney injury (ischemic, obstructive, toxic) and progression to fibrosis, nephrectomy, and related single cell RNA-sequencing datasets.

Results: We show that TNFR1/2 serum and urine levels are highly elevated in all mouse models of kidney injury tested, beginning within one-hour post-injury, and correlate with its severity. Consistent with this, serum and urine TNFR1/2 levels are increased in AKI patients and correlate with severity of kidney failure. Interestingly, the extracellular particle (EP)-bound forms of cTNFR1/2 correlate with renal function better than their soluble forms. TNF neutralization does not affect early cTNFR1/2 elevations, suggesting that cTNFR1/2 levels do not reflect injury-induced TNF activity. Kidney tissue expression of TNFR1/2 after AKI is only mildly increased and bilateral nephrectomies lead to strong cTNFR1/2 elevations, suggesting release of these receptors by extrarenal sources. cTNFR1/2 remain elevated for weeks after severe kidney injury and at these later timepoints cTNFR1/2 correlate to remaining kidney injury. During AKI-to-CKD transition, kidney expression of TNFR1/2 and cTNFR2 levels, correlate with development of fibrosis.

Conclusions: Our data demonstrate that AKI drives acute increases in cTNFR1/2 serum levels which negatively correlate with kidney function, in particular their EP-bound forms. Sustained TNFR1/2 elevations after kidney injury during AKI-to-CKD transition correlate with persistent tissue injury and progression to kidney fibrosis.

Funding: Private Foundation Support
The Role of C5aR vs. C3 in Thrombotic Microangiopathy, Ischemic Kidney Necrosis, and AKI Induced by Cholesterol Crystal Embolism


**Background:** Certain thrombotic microangiopathies (TMA) respond to inhibition of complement factor C5, which abrogates formation of the membrane attack complex and hence impairs host defense. Inhibition of C5a receptor (C5aR) avoids this safety problem and still controls autoimmune systemic vasculitis. We speculated that targeting C5aR could be sufficient also in TMA, e.g., related to cholesterol crystal embolism (CCE).

**Methods:** We induced experimental TMA in C3−/−, C5aR−/− or wildtype mice by injecting CC into the left kidney artery of mice and analyzed thrombotic angiopathy, drop in measured glomerular filtration rate (GFR), and ischemic necrosis 24 hours after CC.

**Results:** In wildtype mice, CC injection caused diffuse TMA followed by a consistent drop of GFR compared to baseline and ischemic kidney necrosis. Genetic deficiency in C5aR convertase profoundly attenuated TMA and hence GFR drop and ischemic kidney necrosis indicating a key role of the complement system in CCE-related TMA. Genetic deficiency of C5aR attenuated TMA, GFR drop and ischemic necrosis to the same extent indicating that C5aR provides the main contribution of the complement system to the pathogenesis of TMA.

**Conclusions:** We conclude that targeting the C5a/C5aR axis could be sufficient to attenuate also TMA for which a better safety profile would be expected as compared to C5 inhibition.

**Funding:** Clinical Revenue Support

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The Class B Scavenger Receptors BI and BII Exacerbate Acute Kidney and Liver Injury in Murine Abdominal Sepsis Model

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**Background:** The class B scavenger receptors BI (SR-BI) and BII (SR-BII) are expressed in multiple tissues and known to recognize various pathogen-associated molecular patterns. Recently, we found that both receptors bind and internalize bacteria and boost proinflammatory cytokine production in HeLa cells transfected with SR-Bs. Moreover, we developed human SR-BI and BII transgenic mice (done by pl-lv-11) that overexpress Irs-BI and BII transgenes in the liver (to a lesser extent in the kidney). LPS I.P. injection markedly increases expression of proinflammatory cytokines in the liver and kidney of both transgenic mice. However, their roles in a clinically relevant sepsis model are unknown.

**Methods:** We performed cecum ligation and puncture (CLP) surgery in Irs-BI and BII transgenic and wild-type (WT) mice and treated them with antibiotics and fluids. A seven-day survival study was conducted. In a separate experiment at 24 h after CLP surgery, we collected blood, portal vein ligation fluid, kidney, liver, and lungs for bacterial count, histological and biochemical examination.

**Results:** First, Irs-BI and BII transgenic mice had significantly worsened survival compared to WT mice (SR-BI vs. WT, 0.0% vs. 28.6% on Day 7, n = 5–7 per group, p = 0.002; SR-BII vs. WT, 0.0% vs. 28.6% on Day 7, n = 5–7 per group, p = 0.003). Second, the blood bacterial count was lower in both Irs-BI/BII transgenic mice than WT, while there was the similar trend in the number of bacteria in the portal vein fluid. Alanine aminotransferase levels of Irs-BI and BII transgenic mice were significantly higher than WT. The kidneys of Irs-BI/BII transgenic mice had abundant vacuole degeneration and the highest tubular injury score among the experimental groups.

**Conclusions:** In summary, our findings suggest that Irs-BI and BII overexpression contributes to higher mortality in the CLP sepsis by exacerbating liver and/or kidney injury: Future studies are planned (especially endotoxemia of bacteria via the receptors, and production of proinflammatory cytokines) to further elucidate the pathogenetic roles of SR-BI/BII in a clinically translatable abdominal sepsis model.

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

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Induction of Cell Cycle Inhibitor p16Ink4a and Cellular Senescence in Heme Protein-Mediated AKI

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**Background:** Senescent cells (SCs) exhibit cellular arrest due to upregulation of cell cycle inhibitors such as p16Ink4a. In this study, we demonstrate senescence in heme protein-mediated acute kidney injury (HP-AKI) with the upregulation of p16ink4a gene along with a senescent phenotype exhibited by murine kidneys.

**Methods:** mRNA expression was assessed by RT-PCR and RNAish in the murine glycerol model of HP-AKI and in murine kidneys after administration of hemoglobin, myoglobin, or hemin. A senescent phenotype was assessed by flow cytometry.

**Results:** Renal p16ink4a mRNA was significantly increased at 8, 24, and 48 hours in the glycerol model of HP-AKI. Localization of mRNA using RNAish revealed significantly increased p16ink4a mRNA expression in the proximal tubules. Similarly, administration of hemoglobin, myoglobin, or hemin to mice with intact kidneys significantly increased p16ink4a mRNA expression in the kidney. RNAseq analysis of the HP-AKI model showed telomere erosion as reflected by reduced expression of genes in the 1BM telomeric region in HP-AKI model. A senescent phenotype within HP-AKI kidneys was additionally demonstrated by increased β-galactosidase activity and decreased lamin B1 protein expression.

**Conclusions:** Glycerol-induced HP-AKI resulted in upregulation of the cell cycle inhibitor, p16ink4a, the latter mainly induced in proximal tubules. HP-AKI also resulted in telomere erosion as revealed by reduced expression of genes in the 1BM telomeric region. Confirmation of a senescent phenotype in HP-AKI was provided by increased β-galactosidase activity and decreased lamin B1 protein expression. The kidney subjected to HP-AKI thus exhibits a senescent phenotype which we suggest is driven by upregulation of p16ink4a mRNA expression within the injured kidney.

**Funding:** NIDDK Support

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Aging and Immune Response to the Late Recovery Phase of Ischemic AKI

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**Background:** Kidney immune cells play important roles in acute kidney injury (AKI) and the repair process. Considering that aging affects immune cell compositions and their function in multiple organs, the effect of aging on kidney and extrarenal immune responses in the recovery phase of ischemic AKI was evaluated.

**Methods:** C57Bl/6 mice with three different age groups, including 7-week, 6- and 12-month-old, underwent unilateral ischemia-reperfusion injury (UIRI) for 45 min. Mice were followed up until 4 weeks, and kidneys and spleens were collected. Serum creatinine and cystatin-C levels were measured. Kidney and splenic lymphocytes were analyzed by flow cytometry.

**Results:** Serum creatinine (7-week-old, 0.25±0.05; 6-month-old, 0.41±0.04; p=0.01; 12-month-old, 0.39±0.02mg/dL; P=0.01) and cystatin-C (545.67±30.35; 545.05±30.25, P=0.099; 914.6±96.40ng/ml; P=0.01) levels were higher in older mice at 4 weeks after UIRI, although both were comparable between groups at baseline. NK T cells (6.27±0.47 vs 2.51±0.30, P=0.01) and Tregs (13.42±1.11 vs 7.87±0.53%, P=0.01) were lower in post-ischemic kidneys of 12-month-old mice than 7-week-old mice, whereas they were comparable in contralateral kidneys (NK T cells, 10.83±1.10 vs 9.5±0.65%, P=0.82; Tregs, 2.13±0.15 vs 2.11±0.62%, P=0.99). There were no differences in the proportion of CD4 T cells and CD8 T cells among total T cells in both post-ischemic and contralateral kidneys. Activated B cells from older mice were higher in post-ischemic kidneys (10.01±1.06; 16.37±2.01, P=0.04; 19.77±1.74%, P<0.01) as well as in contralateral kidneys (2.78±0.19; 6.52±1.07, P=0.01; 7.81±0.42%, P=0.01). Splenic CD4 T cells (60.13±1.68 vs 91.32±2.35% of total T cells, P=0.01) were higher, and splenic Tregs (8.38±0.33 vs 5.34±1.22% of CD4 T cells, P=0.03) were lower in 12-month-old mice compared to 6-month-old mice. Splenic T cells from older mice had higher expression of CD69 (7.83±0.30; 15.95±2.05, P=0.097; 19.62±3.93% of total T cells, P<0.01).

**Conclusions:** Aging affects long-term intrarenal and systemic immune responses to ischemic AKI during the recovery phase. Older hosts showed an accelerated proinflammatory and diminished anti-inflammatory responses. Future studies are needed to evaluate senescent immune reaction in ischemic AKI.
Kidney Injury Released HMGB1 Is a Pathogenic Agent to the Development of Acute Lung Injury

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Background: Acute kidney injury (AKI) could induce respiratory complications, resulting in a high mortality rate, but molecular mechanisms and mediators of AKI to acute lung injury (ALI) are not yet well understood.

Methods: Male C57BL/6 mice were used to establish bilateral renal ischemia-reperfusion injury (I/R) model. Single-cell RNA sequencing analysis was used to explore which molecule play a crucial role in AKI-ALI. The role of high mobility group box 1 (HMGB1) was verified by constructing renal tubular epithelial cell-specific HMGB1 knockout mice displaying AKI and infected mice with HMGB1 neutralizing antibodies.

Results: We found renal I/R induced ALI specifically at day one after surgery. The expression of HMGB1 in renal tubular cells increased rapidly after I/R, with the cytoplasmic migration of HMGB1. Specific knockout of HMGB1 in renal tubular cells or injection of HMGB1 neutralizing antibody alleviated AKI-induced ALI. The acetylation of HMGB1 in the kidney increased after I/R, which accelerates the release of HMGB1 into the peripheral circulation. In addition, we found 2469 sites of 1050 proteins were increased in acetylated compared to that in sham mice. Knockout of HMGB1 in renal tubular epithelial cells decreased acetylated HMGB1 of 1093 sites of 696 proteins, which are key proteins involved in several energy metabolism pathways. We further found that the binding receptor for HMGB1 on the membrane of lung tissue cells is depend on the advanced glycation end products (RAGE). After antagomizing RAGE, kidney I/R-induced ALI was alleviated, but kidney damage was not affected. It was further found that the HMGB1-RAGE axis participated in the progression of ALI via impairment of oxidative phosphorylation and the subsequent mitochondrial dysfunction.

Conclusions: Our work identifies HMGB1 released by the injured kidney as a key mediator of ALI, which provides a potential therapeutic target for this specific interorgan crosstalk of AKI to ALI.

Funding: Government Support - Non-U.S.

Shiga Toxin Downregulates ERG Protein in Endothelial Cells and Impairs Angiogenesis

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Background: Shiga toxin (Stx) activates inflammatory signaling, leading to vascular dysfunction and pro-thrombotic tissue microenvironment. Stx can trigger enterohemorrhagic hemolytic uremic syndrome (HUS)—thrombocytopenia, hemolytic anemia, and AKI, most often in children, and may require dialysis. Damage may occur in GI tract, pancreas, brain and cardiovascular system, with death in 2-5%. Typical HUS is a thrombotic microangiopathy with endothelial cell (EC) injury and platelet fibrin thrombus formation in glomerular arterioles and arterioles of other affected organs. To elucidate microangiopathy mechanisms, we examined in human ECs the regulation of the platelet adhesion proteins P-selectin and von Willebrand factor, along with the downregulation of erythropoietin transformation-specific transcription factor (ERG), a key regulator of angiogenesis and megakaryocyte development.

Methods: von Willebrand Factor (VWF), P-selectin, and ERG levels were determined using immunofluorescence and western blot (WB) in human umbilical endothelial cells (HUVECs). HUVECs treated with tumor necrosis factor-alpha (TNF), Stx-1 or both, compared to normal controls. Capillary morphogenesis on Matrigel was performed in HUVECs treated, for 22 hours with TNF, Stx-1, or both, or treated 4 hours with Stx-1 alone or in combination with TNF for 22 hours.

Results: Stx-1 significantly reduced ETS transcription factor (ERG) and VWF expression on HUVECs, but upregulated P-selectin expression. ERG level decreased with Stx-1 alone or in combination with TNF in the nuclear, perinuclear and cytoplasmic regions. Stx-1 reduced capillary morphogenesis, while Stx-1-TNF combined treatment reduced capillary morphogenesis still further.

Conclusions: In the presence of Stx-1 or TNF on both treatments, ECs were activated, expressing higher levels of P-selectin and lower levels of VWF. Our findings, further, provide evidence that Stx-1 downregulates ERG, repressing angiogenesis in vitro.

Funding: NIDDK Support

Altered Signaling Pathways in ZSF1 Rats with AKI and Metabolic Disease

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Background: Acute kidney injury (AKI) is a common cause of kidney failure and mortality. No treatments are approved for AKI. We reported at ASN in 2022 (TH-P0088) that obese and diabetic ZSF1 rats subjected to ischemia-reperfusion injury (IRI) exhibit more severe renal function decline and slower renal function recovery relative to lean non-diabetic rats. To further understand the molecular mechanisms underlying the observed phenotypes, RNA-Seq and pathway analysis were performed.

Methods: RNA-Seq was conducted in obese and lean rat kidneys (n=4-6 each) collected at 24 hours (acute phase of AKI) or 7 days post IRI (repairing phase of AKI). Control group included rats without surgery and sham surgery. Pathway enrichment analysis for the differentially regulated genes was carried out using KEGG and Ingenuity Pathway Analysis (IPA). Enrichment p-values were adjusted for multiple hypothesis testing using the Benjamini-Hochberg method (p values < 0.05). Further, the correlation analysis was performed to study the potential association between the plasma creatine levels and the expression level of differentially expressed genes.
Results: Principal component analysis showed that the transcriptomic profiling data from scRNA-seq was clustered into three distinct groups: (1) Obese/IRI 24 h, (2) Lean IRI 24 h and (3) rest of the groups (Lean/IRI7d, or Obese/IRI7d or control groups). We observed that 509 and 180 genes were significantly dysregulated in obese vs lean rats at 24 hours and 7 days post IRI, respectively. Pathway analysis revealed profound downregulation of the de novo NAD synthesis and mitochondrial metabolism pathway and activation of proinflammatory interleukin-17 (IL-17) signaling pathway at 24 hours post IRI. Interestingly, IL-17 signaling pathway remained significantly activated even at 7 days post IRI. The expression of genes in the IL-17 pathway correlated with plasma creatinine levels.

Conclusions: Our study suggests de novo NAD synthesis and IL-17 as potential pathways involved in AKI progression and highlights novel therapeutic approaches for AKI.

Funding: Commercial Support - Johnson & Johnson

TH-PO091
Renoprotective Effect of Tamm-Horsfall Protein in Crystalline Nephropathy
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Background: Tamm-Horsfall protein (THP) has an immunomodulatory role in the kidney. Our hypothesis is that the immunomodulatory function of THP is impaired in acute kidney injury (AKI) induced by crystalline nephropathy, and the exogenous administration of THP can play a renoprotective role in the disease.

Methods: Eight weeks old C57BL/6J mice were randomly allocated into four groups: 1. Control (saline 0.9% i.p.), 2. THP (exogenous THP-5ug/animal, single injection), 3. NaOx (sodium oxalate-5mg/100g of body weight, single injection) 4. NaOx administration and THP treatment. The animals were placed in metabolic cages for 24 hours before euthanasia and organ harvest. The results presented as mean ±S.D. were analyzed by two-way ANOVA and a Bonferroni post hoc test using GraphPad Prism software. p<0.05 was considered statistically significant.

Results: Treatment with exogenous THP alone did not change any parameter analyzed. Urinary THP excretion was decreased in the NaOx group [arbitrary units] NaOx:100±20.2 vs. Control:195±79, p=0.0001] and the co-treatment with exogenous THP prevented that change [arbitrary units] NaOx+THP:169±31.8 vs. NaOx:100±20.2, p=0.0002. Interaction: p=0.0012. Using immunofluorescence imaging, we observed that the NaOx treatment induced THP clusters formation in the tubular lumen, which was prevented by coadministration with exogenous THP. Treatment with NaOx significantly increased mRNA expression for KIM-1, KEG, MCP-1, TNFα, IL-1β, and IL-6, consistent with kidney injury. Co-treatment with exogenous THP prevented these changes (Fold change from control for NaOx+THP vs. NaOx, respectively): KIM-1 [95.2±121.7 vs. 73.0±182.5, p=<0.0001]. Interaction p=0.0001; KEG [2.0±1.0 vs. 5.7±1.7, p=0.0001]. Interaction p=0.0006; MCP-1 [1.9±1.8 vs. 8.2±3.8, p=0.0008. Interaction p=0.0003]; TNFα [1.3±0.7 vs. 4.0±2.2, p=0.0087. Interaction p=0.0216]; and IL-6 [5.4±7.5 vs. 84.4±62.6, p=0.0002]. Interaction p=0.0010].

Conclusions: Our results indicate that exogenous THP may have a renoprotective effect on nephropathy crystalline-induced AKI.

Funding: Government Support - Non-U.S.

TH-PO092
Ischemia-Reperfusion-Mediated Kidney Injury Is Attenuated in a New Complement 5 Knockout Model
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Background: Acute kidney injury (AKI) affects over 13 million people each year around the world due to renal injury caused by ischemia. Additionally, 70% of transplanted kidneys are sourced from deceased donors, and organs are transported in static cold storage (CS) to maintain tissue viability, with the consequence of subjecting the kidney to ischemic conditions. Renal ischemia has been previously attributed to the aberrant activation of the complement system during AKI and transplant. The terminal cascade begins with the cleavage of complement 5 (C5) and drives downstream membrane attack complex (C5b-9) formation, but the role of this terminal pathway during renal ischemia is not fully understood.

Methods: In this preliminary study, we developed a novel C5 knockout (C5KO) rat model via CRISPR/Cas9 deletion of C5 exon 3. Furthermore, CSKO Lewis rats were introduced in a model of renal ischemia-reperfusion (IR) via 40-minute bilateral clamping of the renal vessels and right nephrectomy. Animals were sacrificed day 1 post procedure and characterized in terms of arterial blood gases/chemistry, mitochondrial respiration, and fluorescence activated cell sorting (FACS).

Results: We have observed a fertile animal with normal mitochondrial function and no health concerns. I/R resulted in significant elevation of serum creatinine (SCr) and blood urea nitrogen (BUN) in C5 homozygous (BUN = 7.9 vs. 8.4 ±4.6, p=0.0002). This effect was attenuated by C5-/- for SCr (n=4; p=0.005) and BUN (n=4; p=0.0223). C5+/+ also significantly decreased SCr (n=4; p=0.0165) after I/R when compared to C5+/+, but not BUN.

Conclusions: Knockout (or partial knockout) of complement component C5 results in a reduction in SCR and BUN during I/R compared to wild-type, suggesting that targeting C5 during kidney injury may confer a protective effect. This model may be useful in future studies focused on the role of C5 during AKI or CS/ Tx.

Funding: NIDDK Support

TH-PO093
Caveolin-1 Protects Against AKI via Regulating Endoplasmic Reticulum Stress
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Background: Acute renal injury (AKI) is a serious medical condition characterized by a rapid loss of renal function. Recent evidence has suggested that endoplasmic reticulum (ER) function is important for protein homeostasis (‘proteostasis’) in the kidney, and that ER stress is a component of acute kidney injury. Caveolin-1 (Cav1), a multifunctional membrane protein, is the main component of caveolae on the plasma membrane. Caveolae serve as a platform to regulate stress responses, cellular endocytosis, and signal transduction. Previous studies have shown that the expression of Cav1 was increased in AKI models induced by ischemia-reperfusion and gentamicin. However, the crucial role of Pdxf1 in AKI remains unclear.

Methods: Cav1-deficient mice were used to determine its function and potential mechanisms in AKI.

Results: In ischemic-reperfusion-induced AKI mice, a significant increase in the expression of Cav1 in kidney tissue was observed. Similar observations were also obtained in the lipopolysaccharide (LPS)-induced AKI mouse model. Likely, the expression of Cav1 was increased in patients with AKI. Cav1 deficiency worsened renal function and caused more tubular injury in AKI induced by ischemia-reperfusion and LPS. Furthermore, i.p. injection of Cav1 peptide in Cav1-/− mice improves kidney function and attenuates kidney tubular injury in ischemic-reperfusion and LPS-induced AKI mice. Additionally, knockout of Cav1 aggravated endoplasmic reticulum stress and apoptosis in primary renal tubular epithelial cells.

Conclusions: Our results revealed that Cav1 may play a protective role in AKI by regulating ER stress, thereby identifying a novel and important therapeutic target for AKI.
TH-PO094
Clathrin-Mediated HMGB1 Endocytosis Promotes Acute Kidney Ischemia-Reperfusion-Induced Lung Injury
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Background: Acute kidney injury (AKI) further increases mortality when combined with acute lung injury (ALI). Blockade of high mobility group box 1 (HMGB1) may reduce AKI induced ALI. However, the potential molecular mechanisms in kidney-lung crosstalk after AKI remain elusive. We hypothesized that circulating HMGB1, released form ischemia-reperfusion (IR) injured kidney, enters the lung cells and promotes AKI induced ALI by modulating neutrophil extracellular traps (NETs) formation.

Methods: Workflow of the study is shown in Fig. 1. Results: Analysis of cytokines and chemokines and lung histology revealed increased lung inflammation and injury following kidney I/R. Serum HMGB1 level increased gradually with the continued extracellular release of HMGB1 from kidney cells following the extension of I/R time. The interaction of clathrin, screened by mass spectrometry, with HMGB1 and its receptor TRK4 in lung endothelial cells was confirmed by co-IP and IF co-localization, and the lung specific knockdown of clathrin decreased lung inflammation and injury induced by kidney I/R in mice. Increased expression of PAD4 and CitH3 and the co-localization of CitH3 and MPO suggested that kidney I/R induced NETs formation in lung. Blockade of HMGB1 by neutralizing antibody in vivo and knockdown of HMGB1 in vitro inhibited NETs formation and ameliorated AKI induced ALI.

Conclusions: HMGB1 released from I/R kidney promotes AKI-induced ALI in mice by modulating NETs, and clathrin-mediated endocytosis is required for HMGB1-TLR4 to enter renal endothelial cells and regulate neutrophils infiltration. Induced NETs formation leads to lung injury that could be rescued by HMGB1 neutralizing antibody, suggesting that targeting NETs and the HMGB1 pathway might extend effective therapeutic strategies to minimize AKI-induced ALI.

TH-PO095
Endothelial Cells Regulate Post-Issemic Kidney Repair Through PHD/ HIF-Dependent Hyperglycolysis
Ratnakar Tiwari, Si Young An, Rajni Sharma, Gabriella Borkowski, James O’ Sullivan, Susan E. Quaggin, Pinelopi P. Kapitsinou. Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Recently, we showed that inhibiting the oxygen-sensing molecule prolyl hydroxylases (PHDs) controls human endothelial cell (EC) metabolism and angiogenic ability. However, the role of acute kidney injury (AKI), little is known about the functions of endothelial PHDs. Here, we used a genetic approach in conjunction with scRNA-seq to investigate the roles of endothelial PHDs in post-ischemic kidney repair.

Methods: To delete PHD1, PHD2, and PHD3 in ECs, VECadherin (Cdh5)-CreER transgenic mice were crossed to mice carrying conditional PHD1, PHD2, and PHD3 alleles, generating PHD- KO/ W mice. For our loss of function studies, we generated mice that lack the constitutive HIF-1β (ARNT) in ECs (ARNT-/-). Ischemia-reperfusion injury (IRI) was induced by uni-/bilateral renal artery clamping, and tamoxifen treatment was started at day 1 post IRI, followed by analysis at day 14.

Results: Compared to Cre controls, day 14 post IRI kidneys of PHD -/- mice showed significant upregulation of probiotic genes Lox1, Tgfl1, and Ace2, increased collagen deposition (n=6-8, p<0.05), higher tubular injury, and reduced capillary density. Further, PHD -/- showed a 20% reduction in glomerular filtration rate than Cre controls (n=7, p<0.01). Suppression of post-ischemic EC-HIF signaling in ARNT-/- mice ameliorated kidney injury and fibrosis assessed by similar analyses as indicated above (n=6-7, p<0.05). scRNA-seq analysis of the day 14 post-IRI kidney revealed a hyperglycolysis signature in the medullary EC of PHD -/- mice compared to Cre mice. Among the significantly upregulated genes was Sdc6, a HIF target gene that encodes for the lactate transporter MCT4, known to mediate lactate efflux. Notably, ischemic administration of the dual MCT4/MCT1 inhibitor Syrosingopine (Syro) attenuated kidney injury in PHD -/- mice (n=4, P<0.05). In vitro, Syro or MCT4 siRNA suppressed the hyperglycolysis signature (IL1Ra, IL6, and VEGF-R2) induction of EC-adhesion molecules VCAM1 and ICAM1, leading to reduced monocyte adhesion to human EC (n=3, P<0.05).

Conclusions: In summary, endothelial PHDs regulate post-ischemic kidney injury through HIF-dependent mechanisms. Furthermore, our studies identify the endothelial MCT4 as a potential target for renoprotective therapies.

Funding: NIDDK Support

TH-PO096
Hedgehog Interacting Protein (Hhip) Deficiency in Endothelial Cells Prevents Ischemia Perfusion-Induced Renal Tubular Cell Injury Through Inhibition of NF-KB Signaling
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Background: Acute kidney injury (AKI) caused by renal ischemia reperfusion injury (R I/R) is a major clinical issue that is lacking viable therapies, and its underlying mechanisms are poorly understood. One of the important role of hedgehog interacting protein in chronic kidney disease-related renal fibrosis, we investigated whether Hhip knockout in endothelial cells (EC) (Hhip-KO) could prevent R I/R-induced kidney injury in vivo and in vitro.

Methods: Male HhipWT and control HhipKO mice at 10-weeks old were subjected to 45 minutes of the unilateral R I/R or sham surgery, both with contralateral nephrectomy. The AKI time-course was examined at Day 1, Day 3, Day 7, and Day 21. In vitro, naïve renal proximal tubular cells (IRPTCs) exposed to the conditioned media from mouse endothelial cell (mECs) with or without Hhip (siRNA) + gentamicin treatment, were studied.

Results: Compared to the respective controls, R I/R mice (HhipWT and HhipKO) body weight loss (BW, g) occurred from Day 1 until Day 21, regardless of Hhip deficiency. In line with the AKI time course, HhipWT/R I/R mice displayed kidney dysfunction marked by increased urinary albumin-to-creatinine ratio; tubular/endothelial cell injury and fibrosis as assessed by kidney morphometric analysis (Periodic Acid-Schiff, Masson’s trichrome and Sirius Red) with enhanced cystatin C, kidney-injured molecular 1 and TGF-β1 expression in their kidneys. Maladaptive and inadequate renal tubular damage repair was observed by enhanced vascular cell adhesion protein 1 and NFκB (p50/p65) expression. In contrast, these changes were significantly ameliorated in the kidneys of Hhip WT -R I/R mice. In vitro, naïve IRPTCs exposed to the conditioned media treated with HhipWT mECs with or without Hhip (siRNA) + gentamicin treatment, were studied.

Conclusions: Our data suggest that Hhip knockout in endothelial cells prevented AKI-induced renal tubular injury. This action might be mediated, at least, in part, by inhibition of NF-KB signaling.

Funding: Government Support - Non-U.S.

TH-PO097
VEGF-R2 Signaling in Renal Stroma Exacerbates Post-AKI CKD Progression

Background: A dire consequence of AKI is progression to CKD. AKI patients are at more than twice the increased risk of progressive CKD that leads to excessive morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available for. Renal microvasculature, including pericytes and endothelial cells, are damaged in AKI, leading to recruitment of inflammatory cells which contributes to progression to CKD. It was recently shown that Platelet-derived growth factors (PDGFs) are predicted to signal via VEGF-R2, particularly in disease conditions. However, the functional implications of VEGF-R2 in the renal stroma, which gives rise to renal pericytes, in CKD remain poorly understood. This informed us an overarching hypothesis that renal stroma specific VEGF-R2 signaling dysregulates microvascular recovery and exacerbates post-AKI progression to CKD.

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of Fgfr2 with constitutively expressed Foxd1-Cre (VegfR2flox/flox; Foxd1-Cre) as well as tamoxifen inducible Foxd1-Cre/Jvegf2flox/flox to interrogate timing specific role of Fgfr2 in renal stroma in AKI-to-CKD. KID models induced either by a renal ischemia/reperfusion injury (IRI) or by low/dose repeated treatment of cisplatin were performed. Mice were monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis.

Results: We found that VegfR2flox/flox mice have reduced inflammation and vascular injury after renal IRI and have reduced renal interstitial fibrosis after renal IRI as well as reduced interstitial lipid deposition. Consistently, VegfR2flox/flox are protected against progression to CKD in a cisplatin KID model. Mechanistically, VegfR2flox/flox kidneys

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have reduced expression of a pro-inflammatory signaling axis of Thromboxonodin-1 (TXB1), and overexpressed expression of TNF-α. IS exposure induces mitophagy (KO 1.18±0.29 mg), contributing to the enhanced protection. Furthermore, VegfGr2+/− mice are significantly protected against renal IRI.

Conclusions: These data suggest that VEGF-R2 signaling in renal stroma exacerbates renal IRI and its CKD progression as well as cisplatin CKD.

Funding: NIDDK Support

TH-PO100

MAVS Modules Inflammation and Apoptosis in Renal Ischemia-Reperfusion Injury

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Background: Mitochondria have a central role not only in the initiation of ischemia-reperfusion injury (IRI) but also in recovered processes in mitochondria. Mitochondria are a component of innate immunity, leading to cytokine production upon activation. Here, we characterize the role of MAVS in tubular epithelial cells during the various phases of IRI-induced AKI, and their relative importance to renal fibrogenesis.

Methods: We performed unilateral renal artery clamping for 50 minutes in wild-type mice (C57BL/6) and MAVS knockout mice and assessed the pathology at the acute kidney injury phase (Day 2, Day 5) and chronic phase (Day 20).

Results: Compared with their wild-type counterparts, MAVS knockout mice showed less urine protein and tubulointerstitial scores, tubular epithelial cell apoptosis in the acute stage of AKI, and attenuated fibrosis in the late stage. Immunostaining revealed that MAVS is mainly expressed in the renal tubules in the physiological state, and strongly expressed in the injured proximal tubules after renal ischemia-reperfusion. Transient transfection of MAVS in HEK293T cells increased TRAF6 expression, nuclear localization of NFκB, and phosphorylation of MAPK (p38, ERK, JNK), suggesting that it activates inflammation and apoptosis. Moreover, MAVS inhibition resulted in less mitochondrial reactive oxygen species and pro-inflammatory cytokines production after hypoxia.

Conclusions: Collectively, we identify MAVS as a pro-inflammatory contributor to renal tubules in the early phase of AKI and it might be a therapeutic target.

Funding: NIDDK Support, Private Foundation Support

TH-PO101

Inhibition of Retinoic Acid Signaling in Proximal Tubules Protects Against AKI by Enhancing Kim-1 Dependent Efferocytosis

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Background: Retinoic acid receptor (RAR) signaling is activated in proximal tubules (PTs) and macrophages (Ms) after IRI-AKI, and systemic inhibition of RARs increases Mo-dependent injury after IRI-AKI. It is unknown whether RARs are activated in other forms of AKI and the function of RAR signaling in RAR-AKI remains unknown.

Methods: GSEA for RAR targets enriched in a snRNA seq database from patients with sepsis-associated AKI (SA-AKI) (Hinze, 2022). RARE-LacZ (RAR reporter mice); PEPCK-CRE, R26R dominant negative RAR (PT-DN RAR), bilateral IRI- or rhabdomyolysis-AKI (rhabdo-AKI). Injury and RARE-LacZ localization evaluated by BUN, QRT-PCR, LacZ staining, and IF. Renal Ms by RNA seq and FACS; PT proliferation, metabolic activity, and Kim-1 function in primary PTs. Efferocytosis by quantifying PT apoptosis, +/− a lysosome inhibitor, Bafloymcin, after IRI-AKI.

Results: These is enrichment for RAR targets in PTs from patients with SA-AKI. The same gene set was upregulated in mouse kidneys after rhabdo-AKI. In contrast to IRI-AKI where reporter activation was transient, there was prolonged activation of RARE-LacZ in PTs throughout the kidney after rhabdo-AKI. Inhibition of PT RAR signaling in PT-DN RAR mice protected against acute tubular injury (ATI) in rhabdo-, and to a lesser extent, IRI-AKI. This was unexpectedly associated with increased Kim-1 expression; PT de-differentiation, proliferation, and metabolic reprogramming (increased glycolysis and ox phos), in PT-DN RAR kidneys and cultured PTs. Kim-1-dependent uptake of oxidized LDL was increased in PT-DN RAR PTs, and there was reduced PT apoptosis after IRI and rhabdo-AKI. This was reversed by Bafloymcin treatment, indicating that decreased apoptosis is dependent on PT efferocytosis. Consistent with increased efferocytosis as a protective mechanism in AKI, there was also a reduction in pro-inflammatory renal Ms after IRI-AKI in PT DN RAR mice.

Conclusions: These findings indicate that there is extensive activation of PT RAR signaling in experimental and human AKI, and that inhibition of RAR signaling in PTs protects from AKI by promoting PT de-differentiation and enhancing Kim-1 dependent efferocytosis. This suggests that activation of RAR signaling in PTs after AKI is a compensatory response that reestablishes PT differentiation and function after AT.

Funding: NIDDK Support

TH-PO102

Indoxyl Sulfate Increases Susceptibility of Proximal Tubule Epithelial Cells to Gentamicin Cytotoxicity

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Background: Patients with chronic kidney disease (CKD) are at increased risk of acute kidney injury (AKI) following exposure to nephrotoxic medications, and there is a critical need to understand the molecular pathogenesis of acute-on-chronic kidney disease (AOC). Indoxyl sulfate (IS) leads to systemic bioaccumulation of uremic solutes, such as the tryptophan metabolite indoxyl sulfate (IS), which have direct effects on the kidneys that promote CKD progression. The objective of this study was to determine the effect of IS on proximal tubule epithelial cell (PTEC) and test the hypothesis that IS exposure increases susceptibility to gentamicin-induced cytotoxicity.

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Methods: Cultured immortalized PTECs (HK-2 cells) were treated with IS and gentamicin at varying concentrations, and cell viability was assessed using the Trypan blue and MTT assays. TMT proteomic profiling with iBAQ quantitation and gene set enrichment analysis was used to identify differentially abundant proteins and pathways that are dysregulated by IS exposure and could mediate the cytotoxic effects of IS influencing mitochondrial gene translation that could reflect broad perturbations in mitochondrial dynamics and impaired cellular respiration.

Results: Exposure to increasing concentrations (0-10 µM) of cyclosporine or voaclosporin [H7] revealed only minimal toxicity after 48 hr. in 2D culture. Similarly, exposure of primary human PTEC in either standard 2D tissue culture or when grown in a 3D kidney microphysiological system (MPS).

Conclusions: Ongoing studies include longer term CNI exposures and effects of CVX in human tissue culture. In conclusion, CVX is polymerosec in the kidney and produces isozyme-specific metabolites of cyclosporin. Our results to date support differential effects of voaclosporin versus cyclosporin on PTEC gene expression.

Funding: Other NIH Support - NCATS, Commercial Support - Aurinia Pharmaceuticals

TH-PO104
Role of KIM-1 and TBX1 in AKI to CKD Transition
Elena Tutunova-Efata,1 Shabitha Arumugamath,2 Lakshman Gunaratnam,3 Lindsay Himmelsteiff,1 Edward J. Kelly,2 University of Washington, Seattle, WA; 1Kidney Research Institute, Seattle, WA; 2Auria Pharmaceuticals Inc, Edmonton, AB, Canada.

Background: The development of calcineurin inhibitors (CNIs) dramatically changed the face of transplantation, with the majority of solid organ transplant patients prescribed CNI-based therapeutics. Cyclosporine, a CNI that complexes with cyclophilin to competitively inhibit calcineurin phosphatase activity, has significant side effects with chronic nephrotoxicity being the primary clinical concern. Cyclosporine related toxic effects include glomerulosclerosis, thrombotic microangiopathy and tubular vacuolization. Voaclosporin, a recently approved CNI for treating adults with active lupus nephritis on a background of immunosuppression, is structurally similar to cyclosporine, with improved binding to calcineurin, higher potency and better tolerability.

Methods: To compare the renal effects of IS and CVX, we exposed cultures of primary human PTEC in either standard 2D tissue culture or when grown in a 3D kidney microphysiological system (MPS).

Results: Exposure to increasing concentrations (0-10 µM) of cyclosporine or voaclosporin [H7] revealed only minimal toxicity after 48 hr. in 2D culture. Similarly, exposure of MPS to 10 µM voaclosporin or cyclosporine for 48 hr. did not significantly increase KIM-1, a urinary biomarker of acute kidney injury, in MPS effluents. To further differentiate these two CNIs, we performed bulk RNAseq analysis from the MPS studies and observed 443 differentially-expressed genes in the cyclosporine-treated MPS versus 45 genes in the voaclosporin cohort. Biological process gene ontology analysis revealed 26 significant pathways in the cyclosporine group and none in the voaclosporin group with the majority related to cell cycle processes. PTECs were labeled with a GFP-cytochrome and observed 443 differentially-expressed genes in the cyclosporine-treated MPS versus KIM-1, a urinary biomarker of acute kidney injury, in MPS effluents. To further investigate the mechanism associated with reduced Voaclosporin uptake at 10 µM of either CNI, revealed no changes whereas treatment with 10 µM of either CNI resulted in changes in mitochondria as measured by signal intensity and complexity of the network.

Conclusions: Ongoing studies include longer term CNI exposures and effects of CVX in human tissue culture. In conclusion, CVX is polymerosec in the kidney and produces isozyme-specific metabolites of cyclosporin. Our results to date support differential effects of voaclosporin versus cyclosporin on PTEC gene expression.

Funding: Other NIH Support - NCATS, Commercial Support - Aurinia Pharmaceuticals

TH-PO105
Mass Spectrometry Imaging Reveals Metabolic Switch to Glycolysis in Proximal Tubules During AKI
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Background: Abrant glucose metabolism has been reported in the pathogenesis of acute kidney injury (AKI). In vitro studies of proximal tubular cells showed damaged cells that were unable to fully recover a metabolic switch to glycolysis during the AKI to CKD transition. Additionally, in vitro data of AKI murine models also demonstrated upregulated expression of rate-limiting enzymes of glycolysis in mice with AKI. However, changes in energy metabolism under AKI in human patients remain an enigma. We performed a comprehensive analysis of metabolites in proximal tubules of kidney biopsies from AKI patients vs healthy reference tissues (HRT).

Methods: A matrix-assisted laser desorption/ionization (MALDI) mass spectrometry imaging (MSI) platform was employed to characterize the metabolic profile in kidney biopsies from AKI patients (n = 6) and HRT (n = 6) in situ (spatial resolution: 20 µm). SCILS Lab was used for raw data processing. METASPACE was applied for metabolic annotations at 20% FDR. Univariate (t-test) and multivariate (e.g., PCA and PLS-DA) analyses were performed to compare metabolic profiles in kidney biopsies between AKI and HRT.

Results: In total, 1797 m/z were annotated as different metabolite species in human kidney biopsies. Specifically, seven metabolites from the tricarboxylic acid cycle and 10 intermediates from glycolysis were measured. Multivariate analyses showed clearly separated clusters between AKI and HRT biopsies, suggesting aberrant metabolic changes in AKI kidneys. Univariate analysis revealed that 361 metabolites were significantly different in proximal tubules of AKI compared to HRT. Particularly, several glycolytic intermediates including lactate (p = 0.0251), 2-phosphoglycerate (p = 0.0152), and fructose-6-phosphate (p = 0.0013) were found to accumulate in proximal tubules of AKI renal biopsies, suggesting the potential role of metabolic switch to glycolysis in the kidney with AKI.

Conclusions: These findings demonstrate an accumulation of glycolytic intermediates in proximal tubules of kidney biopsies which may play an important role in the pathogenesis of AKI. Our human kidney biopsy data reveal a potential metabolic switch to glycolysis in damaged proximal tubular cells during the AKI to CKD transition.

Funding: NIDDK Support

TH-PO106
Mouse Model of Local Iron Homeostasis Disruption in AKI
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Background: Iron plays an essential role in many critical biological processes including oxygen transport, cell division, and mitochondrial respiration. Iron is produced in excess, it is toxic to the kidneys. Acute kidney injury (AKI) and iron-related disorders are associated with significant morbidity and mortality. Dysregulation of iron homeostasis plays an important pathogenic role in kidney disease, but limited data are available on success of iron-targeting therapies in AKI. Ferroportin (FPN) is expressed in the kidney and is known as the iron exporter and central regulator of iron metabolism, but its function in the pathogenesis of AKI still unclear. Through this work, we will determine whether the disruption of local iron homeostasis by selective depletion of FPN in renal proximal tubular cells (PTCs) modifies AKI pathology.

Methods: We are testing this hypothesis by generating conditional knockout mice to target iron trafficking proteins and determine their roles in AKI and the molecular and genetic mechanisms regulating of PTCs. We selectively expressed Cre in PTCs with a floxed allele. We monitored mice over time and observed that, when iron is present in excess, it is toxic to the kidneys. Acute kidney injury (AKI) and iron-related disorders are associated with significant morbidity and mortality. Dysregulation of iron homeostasis plays an important pathogenic role in kidney disease, but limited data are available on success of iron-targeting therapies in AKI. Ferroportin (FPN) is expressed in the kidney and is known as the iron exporter and central regulator of iron metabolism, but its function in the pathogenesis of AKI still unclear. Through this work, we will determine whether the disruption of local iron homeostasis by selective depletion of FPN in renal proximal tubular cells (PTCs) modifies AKI pathology.

Results: FPN-KO mice were generated and depletion of FPN was confirmed. Mutant mice showed no gross morphology or renal phenotype. FPN-OK and controls mice were subjected to either folic acid or renal ischemia-reperfusion models. Blood and tissue

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AKI: Mechanisms - I

TH-PO107

Proximal Tubular-Specific Cell Cycle Arrest Ameliorates AKI in Mice

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Background: Acute kidney injury (AKI) is a major medical and economic burden. Renal tubular epithelial cells are normally arrested in the G0 phase of the cell cycle (CC), but are rapidly entering the CC after AKI. Recent studies indicate that regulated CC is required for optimal regeneration following AKI. Cyclin D1 (Ccd1) is essential for CC progression from G1- to S-phase. We characterized a proximal tubular (PT)-
specific Ccd1 knock-out (KO) and a siRNA-based Ccd1 knock-down (KD) in a murine ischemia-reperfusion (IRI) model.

Methods: Tamoxifen (tand) inducible proximal tubular Ccd1 KO mice (Ccd1Ifox.
fox:Slc34a1CreERT2) underwent IRI surgery following vehicle (veh) or tam treatment. Serum creatinine/urea, histology, leukocyte count, cell cycle phases, and fibrosis were assessed at 2h, 1d, 2d, and 1w post-IRI (n=6-8/group). IRI in KD mice was established in vitro (primary tubular epithelial cells) and in vivo (Imlm/siRNA)
mouse; 24h before and at reperfusion) and evaluated by the abovementioned parameters on day 14 after IRI. To evaluate the underlying mechanisms, RNAseq analysis of isolated PTs from Ccd1 KO and WT kidneys was performed.

Results: PT-specific Ccd1 KO attenuated the functional decline of AKI (S-crea 312±74% vs. 142±11% 3d relative to 0d; p=0.036). KD mice showed a comparable outcome. At day 1 and 3 after IRI, KO kidneys had reduced histological damage (AKI score maximal 4; 1d: 2.26±0.13 vs. 1.84±0.11; p=0.026; 3d: 2.60±1.2 vs. 2.06±0.16. p=0.009). KO kidneys showed a 15-fold reduction in leukocyte infiltration (3d.
12±8.075% leukocytes/all cells vs. 0.81±0.14%; p=0.0001). At later time points after IRI (2d), KD mice showed no damage/regeneration benefit (histology and brush border staining). RNAseq analysis revealed a decreased expression of CC-associated genes in KO proximal tubules. Moreover, depletion of adenosine monophosphate was strongest in the cortex of WT kidneys.

Conclusions: Specific ablation of Ccd1 in the proximal tubule or systemic antagonism of Ccd1 protected mice from injury after IRI. This was associated with reduced AKI injury at early time points after IRI in KO and KD models. Our data suggest a cell cycle-associated, energy-dependent mechanism of protection.

TH-PO108

Autophagy Inhibition Aggravates Renal Micronuclear Inflammatory Secondary to Ischemia-Reperfusion

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Background: Ischemia-reperfusion injury (IRI) is an integral component of kidney transplantation. Programmed cell death (PCD) of endothelial cells (EC) in peritubular capillaries (PTCs) post-IRI is a major predictor of long-term loss of renal function. We have shown that caspase-3-deficient mice show reduced PTC apoptosis post-IRI and preserved long-term renal function. Autophagy is a cellular stress response that protects against PCD. However, the precise role of PTC autophagy post-IRI remains unclear. Here, we investigated the effect of PCD inhibition on cisplatin-induced renal injury.

Methods: Tamoxifen (tand) inducible proximal tubular Ccnd1 KO mice (Ccnd1flox::Slc34a1CreERT2) underwent IRI surgery following vehicle (veh) or tam treatment. Autophagy was assessed by immunofluorescence microscopy for GFP-LC3 puncta. PTC rarefaction, myofibroblast accumulation, and tissue structure were analyzed.

Results: IRI induced a specific pattern of apoptosis, necrosis, and autophagy in PTCs. PTCs showed sustained apoptosis from day 1 to day 21 post-IRI, whereas necrosis showed an early increase at days 1 and 2 with a rapid return to basal level at day 7. GFP-LC3+ autophagy puncta increased steadily until day 21 in PTCs. CHC (cycloheximide) treatment led to failure in PTC and worsened renal function with higher serum creatinine levels post-IRI 1 day. In the long term (21 days), microvascular rarefaction was significantly increased in the CHC-injected group compared to the vehicle-treated group. This was associated with increased renal fibrosis, increased α-SMA, and collagen deposition within the PTC.

Conclusions: The results indicate that IRI induces progressive autophagy activation in PTC. Inhibition of autophagy aggravates renal dysfunction and increases microvascular injury, myofibroblast differentiation, and collagen deposition post-IRI.

Funding: Government Support - Non-U.S.

TH-PO109

Effect of Peroxidase Reductase 5 and Ferroptosis in Contrast-Induced AKI (CI-AKI)

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Background: Our previous study described the expression of urinary peroxidase reductase 5 (PRDX5) decreased significantly in CI-AKI patients with proteinuria, and ferroptosis was involved in CI-AKI. The aim was to identify PRDX5 involved in the mechanism of ferroptosis in CI-AKI.

Methods: Human renal tubule epithelial cells (HK-2) were cultured and divided into control group, CI-AKI group (HK-2 cells were added 200 mg I/ml iodohexol for 12h), CI-AKI+ FeI group (HK-2 cells were added 200 mg I/ml iodohexol and ferroptosis inhibitor, 10μmol/L for 12h), PRDX5 overexpression group (PRDX5 overexpression plasmid was constructed), PRDX5 overexpression +CI-AKI group (9d after plasmid were added 200 mg I/ml iodohexol). The cell activity was determined by MTT assay. The expressions of ferroptosis related protein GPX4, SLC7A11 and ACSL4 were detected by western blot. Iron Assay Kit was used to measure intracellular iron. Mitochondrial ROS levels were detected by DCFDA/ H2DCFDA fluorescent probes.

Results: Compared with control group, the cell proliferation rate of CI-AKI group slowed down significantly, while that of CI-AKI+ FeI group was increased, compared with CI-AKI group, (P<0.05). In terms of ferroptosis mechanism, compared with control group, the protein content of ACSL4, GPX4 and SLC7A11 in HK-2 cells in CI-AKI group was significantly increased (p<0.05), the protein contents of GPX4 and SLC7A11 were significantly decreased (p<0.05), the iron content was significantly increased (p<0.05), and the mitochondrial ROS level was significantly increased (p<0.05). After adding ferroptosis inhibitor, the above indexes were relieved (p<0.05). The expression of PRDX5 (CI-AKI group) was significantly increased compared with control group (p<0.05), and that in PRDX5 overexpression group was significantly increased (p<0.05). Compared with CI-AKI group, CI-AKI+ FeI group increased cell proliferation rate (P<0.05). Compared with CI-AKI group, the expression of ferroptosis related protein GPX4, ACSL4, GPX4 and SLC7A11 were significantly decreased (p<0.05), iron content was significantly decreased (p<0.05), and mitochondrial ROS level was significantly decreased (p<0.05) after overexpression of PRDX5.

Conclusions: Ferroptosis is involved in CI-AKI. PRDX5 has a protective effect on the mechanism of ferroptosis in CI-AKI.

TH-PO110

SIRT2 Regulates Cisplatin-Induced Endothelial Reticulum Stress Through Heat Shock Factor 1 Deacetylation

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Background: Nephrotoxicity is an important cisplatin-induced adverse reaction and restricts the use of cisplatin to treat malignant tumors. Endoplasmic reticulum (ER) stress is caused by the accumulation of misfolded proteins, and can be induced by cisplatin in the kidney. SIRT2, a nicotinamide adenine dinucleotide (NAD)-dependent deacetylase, is a member of the siruin family. In this study, we evaluated the role of SIRT2 in cisplatin-induced ER stress.

Methods: To investigate the effect of SIRT2 on cisplatin-induced ER stress, we used SIRT2 knockout mice and human proximal tubular epithelial cells (HK-2 cells). cisplatin (10 μmol/L) and SIRT2 overexpression plasmid (ON-TARGET plus human SIRT2 siRNA) or the SIRT2 inhibitors, AGK2 and CPT1 were added 200 mg I/ml iodohexol and cisplatin (10 μmol/L) for 12h, CI-AKI+ FeI group (HK-2 cells were added 200 mg I/ml iodohexol and ferroptosis inhibitor, 10μmol/L i.p.) to mice to induce acute kidney injury. We evaluated the changes of ER stress and its related protein.

Results: In vivo experiment, cisplatin administration was found to significantly increase the expressions of PRK-like ER kinase (PERK), phosphorylation of eukaryotic translation initiation factor 2α (p-eIF2α), and the C/EBP homologous protein (CHOP) and caspase-12 in the kidneys of SIRT2-null type mice. However, cisplatin-induced increases in the expressions of p-PERK, p-eIF2α, CHOP, and caspase-12 were diminished in kidneys of SIRT2 knockout mice. In vitro, cisplatin significantly increased the expressions of p-PERK, p-eIF2α, CHOP, and caspase-12 in HK-2 cells. When the effect of SIRT2 on cisplatin-induced ER stress was evaluated using SIRT2 siRNA (ON-TARGET plus human SIRT2 siRNA) or the SIRT2 inhibitors, AGK2 and CPT1, knockdown or inhibition of SIRT2 significantly attenuated the cisplatin-induced protein expression of p-PERK, p-eIF2α, CHOP, and caspase-12. Immunoprecipitation studies showed SIRT2 bound physically to heat shock factor (HSF1) and that HSF1 acetylation was significantly increased by cisplatin. In addition, knockdown of SIRT2 increased cisplatin-induced HSF1 acetylation and increased the expression of heat shock protein (HSP70).

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

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Conclusions: These observations suggest that suppression of SIRT2 ameliorates cisplatin-induced ER stress by increasing HSFL1 acetylation and HSP expression.

Funding: Government Support - Non-U.S.

TH-PO111

Kinetics of the De Novo NAD/NADH Pathway from AKI to CKD

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Background: Energy metabolism deficiency is part of the acute kidney injury (AKI) pathophysiology. Recent studies highlighted the role of nicotinamide adenine dinucleotide (NAD) production in the pathogenesis of AKI. NAD is an electron carrier for mitochondria and a cofactor for cytoplasmic redox reactions. Its production is decreased during AKI following a decrease of the expression of PGC1α (Peroxisome proliferator activated receptor gamma co-activator-1α) and an alteration of its de novo synthesis pathway: with a reduction in the expression of the Quinoline PhosphoribosylTransferase (QPT). The modulation of this de novo pathway has been studied mainly in the acute phase immediately after AKI. However, its correlation with the severity of the ischemic insult and its evolution during the transition from AKI to CKD have not been described yet.

Methods: Renal ischemia-reperfusion was performed in C57BL/6J male mice after nephrectomy of the contralateral kidney. For the severity study, a 5-30 minutes ischemia was performed. Renal function was assessed 24h after ischemia. For the ‘AKI to CKD’ study, renal ischemia was performed during 1, 2, 3, 6, and 28 days after ischemia. PGC1α and QPRT mRNA expression was measured by Real-time PCR.

Results: We induced AKI in mice by unilateral ischemia-reperfusion injury of increasing time to induce several degrees of AKI severity. PGC1α and QPRT mRNA expression decreased progressively with ischemia severity until reaching a plateau at 15 minutes of ischemia for PGC1α, like plasma creatinine and urea, whereas QPRT decrease is linear until 30 min of ischemia. PGC1α mRNA decrease is also inversely correlated to kidney dysfunction (ρ=-0.001). A 10-minute ischemia led to the development of Chronic Kidney Disease (CKD), as evidenced by an incomplete recovery of the kidney function at 28 days. QPRT and PGC1α mRNA expression showed a progressive but incomplete recovery during the transition from AKI to CKD compared to sham mice.

Conclusions: In addition to confirming the decrease of PGC1α and QPRT mRNA expression during AKI, we show that it is correlated to the severity of the ischemic AKI. Furthermore, we describe the recovery during renal repair and transition to CKD.

Funding: Government Support - Non-U.S.

TH-PO112

Targeting Oxidative Stress to Prevent Cardiorenal Syndrome in Right Ventricular Failure

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Background: Renal dysfunction remains an independent risk predictor of death and hospitalization in right ventricular failure (RVF) and RV function plays a pivotal role in RVF pathophysiology. However, the pathophysiology of RV failure in RVF remains poorly understood. The heart and the kidney have complex bidirectional interlinks and there is a growing body of evidence that oxidative stress is a major bidirectional crosstalk mediator of the Heart-kidney in left ventricular dysfunction. Clinically driven experimental modeling is crucial to investigate pathophysiology based therapy.

Methods: This study on RVF-Induced CRS investigated changes in antioxidants and oxidative stress in mice with Right Ventricular Failure (RVF). At 2 weeks post-AKI injury were sacrificed 1, 2, 3, 6 and 28 days after AKI. PGC1α and QPRT mRNA expression was measured by Real-time PCR.

Results: We induced AKI in mice by unilateral ischemia-reperfusion injury of increasing time to increase several degrees of AKI severity. PGC1α and QPRT mRNA expression decreased progressively in RV with ischemia severity until reaching a plateau at 15 minutes of ischemia for PGC1α, like plasma creatinine and urea, whereas QPRT decrease is linear until 30 min of ischemia. PGC1α mRNA decrease is also inversely correlated to kidney dysfunction (ρ=-0.001). A 10-minute ischemia led to the development of Chronic Kidney Disease (CKD), as evidenced by an incomplete recovery of the kidney function at 28 days. QPRT and PGC1α mRNA expression showed a progressive but incomplete recovery during the transition from AKI to CKD compared to sham mice.

Conclusions: In addition to confirming the decrease of PGC1α and QPRT mRNA expression during AKI, we show that it is correlated to the severity of the ischemic AKI. Furthermore, we describe the recovery during renal repair and transition to CKD.

Funding: Other NIH Support - NIGMS

TH-PO113

Renal Mitochondria Exhibit Cell Type-Specific Heterogeneity and Are Functionally Dynamic

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Background: Mitochondrial dysfunction is a key component of both acute and chronic kidney disease. Across tissues, mitochondria differ in composition and substrate utilization. In the kidney, the specificity contains many different cell types, we hypothesize that there is intra-renal mitochondrial heterogeneity contributing to cell-specific mitochondrial function. To interrogate this, we utilized a novel mitochondrial tagging technique to isolate mitochondria in a cell-type specific manner. Here, we investigate the proteomes, metabolomes, and mitochondrial functional capacities of the early and late proximal tubule (PT) and distal convoluted tubule (DCT).

Methods: We generated three lines of mutant mice: early PT (Slc34a1-CreERT2;MITO-Tag); late PT (Gprl-Cre;MITO-Tag); and DCT (PAsb-Cre;MITO-Tag). In each of these mutant mice, we performed a lethality/time window of AKI followed by an ischemia/reperfusion injury (IRI) leading to AKI.

Results: These mice-TITO-Tag models, we demonstrated the ability to isolate renal mitochondia in a cell-specific manner. We observed differential mitochondrial protein and gene expression as well as a profile of cell death markers in both baseline and in fasting conditions. Pathway analysis revealed FAO as a key differentially regulated process, including CPT1 and CPT1B. CPT1A expression significantly increased with fasting in the late PT, and CPT1B expression was significantly higher in the DCT as compared to the PT controls. Compared to the fed state, CPT1-dependent mitochondrial FAO capacity significantly increased in both the late PT and DCT in the fasted state. Surprisingly, when mitochondrial FAO capacity was assayed independent of CPT1, DCT mitochondria had significantly lower FAO capacity compared to late PT mitochondria in both baseline and fasting conditions.

Conclusions: We demonstrated the successful use of a system to study cell type-specific mitochondria in the mouse kidney. Our data suggest that FAO is differentially regulated in the renal PT and DCT.

Funding: Other NIH Support - NIGMS

TH-PO114

Renal Tubular CD24 Upregulation Aggravates Folic Acid-Induced AKI Through Inhibition of T-Regulatory Cells in Mice

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Background: Acute kidney injury (AKI) is characterized by cell death and inflammation. CD24 is a protein which is induced during tissue damage and is not expressed in matured renal tissue. We explored the role of CD24 in the pathogenesis of folic acid induced AKI (FA-AKI) in mice.

Methods: A single i.p. injection of folic acid induced AKI in WT and CD24-/- mice. Renal function tests, histological analysis, immunohistochemistry, Western blot analysis, and ELISA were performed to assess the severity of renal damage and the intensity of the inflammatory response.

Results: FA-AKI induced CD24 in the distal tubular epithelial cells. Compared to WT, AKI FA-AKI CD24-/- mice exhibited an attenuated reduction in renal function and histological injury, lower serum IL-10 and interferon γ, and decreased expression of renal TNFα. In contrast, renal and systemic IL-33 upregulation were augmented. CD24-/- FA-AKI animals exhibited increased splenic margination and renal infiltration of CD8+ and γδ T cells. At day 7, FA-AKI CD24-/- mice exhibited increased expression of tubular pro-apoptotic and decreased anti-apoptotic proteins compared to WT animals. Anti CD24 antibody administration to FA-AKI mice attenuated the decrease in renal function and attenuated histological injury. Renal biopsies from mice treated with Captopril showed strong for CD24 in the distal tubule.

Conclusions: During AKI, upregulation of CD24 promotes renal inflammation through inhibition of Treg infiltration and diversion of cell death towards necrosis rather than apoptosis. Neutralization of CD24 may prove as a target for future therapies in AKI.

TH-PO115

Stress-Inducible p53 Isoform in the Kidney

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Background: The need for understanding p53 biology and controlling p53 expression in the setting of AKI is compelling. Beyond its role as a tumor suppressor, p53 acts as a crucial stress-response gene involved in a variety of pathophysiological conditions. The basic functions of p53 include cell cycle arrest, cell cycle arrest, apoptosis, and DNA repair. p53 has many other nuanced properties and the role of p53 under various circumstances remains elusive. Here, using a murine model of endotoxemia, we report a distinct p53 isoform that emerges during AKI.

Methods: C57BL/6 male mice were injected with endotoxin 4 mg/kg and kidney tissues were harvested at various time points. Full-length cDNA sequencing was done.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Using the direct cDNA Nanopore protocol on MinION Flow Cells (total n = 40). DEXseq was used to identify differentially expressed isoforms across the time course. Based on the mouse data, we generated two p53 mutant human cell lines in which 1) cryptic exon splicing signals were abolished by sequentially applying the CRISPR knock-in strategy, or 2) the entire cryptic exon was excised by using the dual-sgRNA strategy.

Results: We found that RNA isoform switching is prevalent during the recovery phase of endotoxemia in the kidney. The isoform switching was observed in a distinct set of stress-responsive genes including p53. The alternative p53 isoform involves a cryptic exon that is repressed under basal condition and appears exclusively in the late phases of endotoxemia. To investigate the role of the alternative p53 isoform, we generated human cell lines that cannot express the alternative isoform. We found that these mutant cell lines (lacking the cryptic exon or its splicing signals) exhibit increased expression of the canonical p53 transcript as well as its downstream target genes such as p21. As a result, the proliferation rate decreased in these mutant cell lines.

Conclusions: The alternative p53 isoform encodes no protein and emerges during the recovery phase of endotoxemia at the expense of canonical p53 expression. Such reciprocal isoform switching could serve as an endogenous downregulation mechanism for canonical p53, enabling cells to exit cell cycle arrest and promote tissue recovery. We envision that controlling the balance between canonical p53 and its non-coding isoform could provide a route for rescuing cells from a maladaptive state or extending a beneficial adaptive state.

Funding: Other NIH Support - NIAID, Veterans Affairs Support

TH-PO116
Prioritizing Pathways Shared Between Humans and Mice in AKI-to-CKD Transition
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Background: Gaps in our understanding of the transition from acute kidney injury (AKI) to chronic kidney disease (CKD) remain a major unmet medical need due to lack of effective therapeutics for CKD in >850 million people worldwide. Pathways with important roles in AKI-to-CKD transition have not been prioritized on a cross-species level, potentially impeding the development of new target approaches and drugs for human kidney disease.

Methods: Here, we analyzed recent single-cell datasets from humans with AKI and CKD as well as several mouse models along the AKI-to-CKD spectrum. Using 3 human and 3 mouse datasets generated by different research groups, we performed differential gene expression analysis between disease conditions. Differentially expressed genes (DEGs) were mapped to orthologous human genes, if necessary, and fed into pathway enrichment analysis, allowing for a standardized, unified comparison of datasets in AKD-related disease conditions. Finally, we validated our results on 2 separate human and mouse proximal tubule trajectory datasets.

Results: Despite an unexpectedly low overlap among top DEGs of clinically similar models/conditions along the AKI-to-CKD axis (suggesting high disease state specificity), biological processes and pathways along this continuum were well-conserved: processes already enriched during mild AKI, such as hypoxia, TNFα/NFκB signaling, immune processes, epithelial-to-mesenchymal transition, and IL18 signaling, were sustained and increasingly enriched as AKI severity increased and AKI transitioned to CKD. Conversely, cell matrix and adhesion pathways were enriched specifically in milder AKI, whereas pathways related to tissue repair and injury and function were evaluated by plasma creatinine, BUN, and KIM-1 mRNA expression. The alternative p53 isoform involves a cryptic exon that is repressed under basal condition and appears exclusively in the late phases of endotoxemia. To investigate the role of the alternative p53 isoform, we generated human cell lines that cannot express the alternative isoform. We found that these mutant cell lines (lacking the cryptic exon or its splicing signals) exhibit increased expression of the canonical p53 transcript as well as its downstream target genes such as p21. As a result, the proliferation rate decreased in these mutant cell lines.

Conclusions: The alternative p53 isoform encodes no protein and emerges during the recovery phase of endotoxemia at the expense of canonical p53 expression. Such reciprocal isoform switching could serve as an endogenous downregulation mechanism for canonical p53, enabling cells to exit cell cycle arrest and promote tissue recovery. We envision that controlling the balance between canonical p53 and its non-coding isoform could provide a route for rescuing cells from a maladaptive state or extending a beneficial adaptive state.

Funding: Other NIH Support - NIAID, Veterans Affairs Support

TH-PO118
Polyploid Tubular Cells Promote Tubulointerstitial Fibrosis After AKI via TGF-β1 Activation
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Background: We recently showed that tubular cell (TC) polyploidy is triggered by Acute Kidney Injury (AKI). Polyploid TC are required for promotion of fibrosis in the early phase after AKI, but promote fibrosis and chronic kidney disease (CKD) progression in the long term. However, the molecular mechanism governing the link between polyploid TC and fibrosis remains to be clarified.

Methods: We employed a tubular cell polyploidization mouse models based on the Fucci2AR reporter and in vivo single cell RNA-sequencing (scRNA-seq) to identify polyploid TC. In vitro scRNA-seq followed by sorting of polyploid TC was employed to characterize the expression profile of pro-fibrotic polyploid TC.

Results: Importantly after AKI, the expression of cell cycle markers identifies a population of DNA damaged polyploid TC. Polyploid TC accumulate DNA damage and survive, eventually resting in G1 phase of the cell cycle, while diploid TC die. In vivo and in vitro scRNA-seq along with sorting of polyploid TC show that these cells expressing CK18 acquire a pro-fibrotic phenotype culminating in TGF-β1 expression. In vitro stimulation proved that TGF-β1 directly promotes TC polyploidization. In vivo interactive analysis revealed that TGF-β1 signaling fosters a reciprocal activation loop among polyploid TC, macrophages and fibroblasts to sustain kidney fibrosis and promote CKD progression.

Conclusions: Collectively, this study contributes to the ongoing revision of the paradigm of kidney tubule response to AKI, supporting the existence of a tubulointerstitial crosstalk mediated by TGF-β1 signaling produced by polyploid TC with DNA damage. Finally, these results further demonstrate that TC polyploidization is a self-sustained mechanism.

Funding: NIH, VA, Fondazione Dondi, European Union

TH-PO119
PPPI13G Promotes Necroptosis in Ischemia Reperfusion-Induced AKI by RIPK1 Dephosphorylation
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Background: Recent discoveries have revealed necroptosis as a major contributor to the pathogenesis of acute kidney injury (AKI). Protein phosphatase 1 regulatory subunit 3G (PPPI13G) has been linked to the essentiality of RIPK1-dependent apoptosis and type 1 necroptosis. Nonetheless, the involvement of PPPI13G in the regulation of necroptosis during ischemia reperfusion-induced acute kidney injury (IR-AKI) has yet to be investigated.

Methods: Here, we investigated the role of PPPI13G in the regulation of necroptosis in IR using an in vitro cellular I/R model and in vivo IRI-AKI mouse model. Primary proximal tubular cells (PTCs) from C57BL/6 and Ppp1r3g−/− mice were cultured and cell death was induced through hypoxia/reoxygenation. Cell viability and necroptosis were analyzed using a LUNA-II cell counter and flow cytometry, respectively. The expression levels of necroptosis, oxidative stress, and inflammation factors were determined by real-time PCR, western blotting, immunofluorescence staining, and ELISA. In the in vivo IR model, the kidney injury and function were evaluated by plasma creatinine, BUN, and KIM-1 mRNA expression. The alternative p53 isoform involves a cryptic exon that is repressed under basal condition and appears exclusively in the late phases of endotoxemia. To investigate the role of the alternative p53 isoform, we generated human cell lines that cannot express the alternative isoform. We found that these mutant cell lines (lacking the cryptic exon or its splicing signals) exhibit increased expression of the canonical p53 transcript as well as its downstream target genes such as p21. As a result, the proliferation rate decreased in these mutant cell lines.

Conclusions: Importantly after AKI, the expression of cell cycle markers identifies a population of DNA damaged polyploid TC. Polyploid TC accumulate DNA damage and survive, eventually resting in G1 phase of the cell cycle, while diploid TC die. In vivo and in vitro scRNA-seq along with sorting of polyploid TC show that these cells expressing CK18 acquire a pro-fibrotic phenotype culminating in TGF-β1 expression. In vitro stimulation proved that TGF-β1 directly promotes TC polyploidization. In vivo interactive analysis revealed that TGF-β1 signaling fosters a reciprocal activation loop among polyploid TC, macrophages and fibroblasts to sustain kidney fibrosis and promote CKD progression.

Conclusions: Collectively, this study contributes to the ongoing revision of the paradigm of kidney tubule response to AKI, supporting the existence of a tubulointerstitial crosstalk mediated by TGF-β1 signaling produced by polyploid TC with DNA damage. Finally, these results further demonstrate that TC polyploidization is a self-sustained mechanism.

Funding: NIH, VA, Fondazione Dondi, European Union

TH-PO117
Acrinol Promotes Tubular Cell Death in Ischemia Reperfusion-Induced AKI
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Background: We previously showed that ischemia-reperfusion injury in the kidney was attenuated in arginase 2 knockout (KO) mice or arginase inhibitor-treated mice. Arginase 2 is an enzyme involved in arginine metabolism and one of its metabolites, polyamine, is pivotal for cell proliferation. Arginase 2 deficiency, which is known to inhibit cardiovascular disease, toxic acrolein is produced from polyamines by the enzyme spermine oxidase (SMOX). Methods: We used a mouse renal ischemia-reperfusion model to investigate changes in the amount and localization of acrolein during ischemia and reperfusion. We also used human proximal tubule cells (HK-2) to study whether acrolein induces renal tubular cell death. In order to identify acrolein-induced cell death, an acrolein scavenger cysteamine, or sputaneous oxidase (SMOX) siRNA was added to HK-2 cells. Acrinol was detected with acrolein antibodies in the kidney. In HK-2 cells, acrolein was visualized with acrolein RED. To expose cells to hypoxia-reoxygenation, HK-2 cells were cultured under 15% oxygen for 24 hours, then switched to 2% oxygen for 24 hours. Mitochondrial membrane potential was determined by using CMXRos. Cell viability was measured by WST-8.

Results: Acrinol was accumulated in ischemia-reperfusion kidneys, particularly in tubular cells. When HK-2 cells were hypoxia-reoxygenated, acrolein accumulated and fibrosis-related TGFβ1 mRNA and protein levels were increased. Acrinol induced cell death and fibrosis-related TGFβ1 mRNA in HK-2 cells. Administration of cysteamine suppressed the acrolein-induced upregulation of TGFβ1 mRNA. Cysteamine also inhibited a decrease in the mitochondrial membrane potential, and cell death induced by hypoxia-reoxygenation. The siRNA-mediated knockdown of SMOX also suppressed hypoxia-reoxygenation-induced cell death and cell death.

Conclusions: Acrinol promotes tubular cell death. Accumulated acrolein in the kidney during ischemia-reperfusion injury suggested that acrolein may be directly involved in tubular cell death. Treatment to control the accumulation of acrolein might be an effective therapeutic option for renal ischemia-reperfusion injury.

Funding: NIDDK Support
Lactate Dehydrogenase (LDH): Not Just a Marker of Kidney Injury
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Background: Lactate dehydrogenase (LDH) catalyzes the final step in glycolysis, the conversion of pyruvate to lactate. The release of LDH into extracellular fluids has been used for decades as a clinical and experimental marker of cell injury. However, the role of lactate dehydrogenase as an indicator of cell injury has been examined. Glycolysis is increased in AKI leading to the accumulation of lactate. Here we show that LDH and lactate are, in fact, not just markers but potent mediators of AKI.

Methods: C57BL/6 male mice were subjected to bilateral ischemia-reperfusion injury (IRI). Mice received LDH inhibitors (oxamate 300 mg/kg or NCATS SM1441 10 mg/kg), lactate (2g/kg), the Mr2 inhibitor CPACC (10 mg/kg) or vehicle. Renal function and structure were assessed 24 hr after reperfusion.

Results: Oxamate-treated mice developed substantially less structural damage and kidney dysfunction (BUN 38.7±9.4 mg/dl, Cr 0.37±0.06 mg/dl) than vehicle-treated mice (BUN 148.25±21.9, Cr 9.3±0.12, P<0.0001). NCATS SM1441 also prevented ischemic AKI (NCATS BUN 31±6, Cr 0.23±0.06 vs saline BUN 111±10, Cr 1.59±0.3, P<0.0001). Administration of NCATS up to 6 hours after reperfusion also reduced IRI. LDH inhibitors also reduced hypoxic and cisplatin-induced cell death in renal epithelial cells in vitro. Moreover, the administration of L-lactate (but not D-Lactate) sensitized mice to a subsequent mild (22 mm) ischemic insult (BUN L-lactate 95±8 vs D-lactate 22±6, P<0.0001) and also abrogated the protective effects of LDH inhibitors. In prior work, we showed that lactate stimulates mitochondrial Mg2+ uptake via Mr2 and that Mr2 inhibitors also reduce lactate efflux in isolated renal tubular epithelial cells. Here, we found that lactate did not exacerbate AKI in the absence of Mr2. Finally, inhibition of LDH or Mr2 starting 3 days after IRI, when injury is established, preserved kidney function and reduced fibrosis and atrophy measured at day 7 post injury.

Conclusions: These results indicate that the production of lactate via LDH is an important mediator of ischemic AKI and support the view that lactate-triggered mitochondrial Mg2+ uptake mediates AKI. These results also support the view that a sustained increase in glycolysis contributes mechanistically to the AKI-CKD transition. Finally, we provide preclinical evidence that LDH inhibitors may be highly effective in preventing ischemic AKI when administered before or shortly after injury and in preventing the development of CKD when administered after AKI.
Sexual Dimorphism and Epigenetic Control of the Kidney Disease Marker Klotho
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Background: Preclinical studies investigating physiological and pathophysiological processes in the kidney are mainly performed in males. This is due to a higher susceptibility to kidney injury and faster subsequent disease progression in male rodents. In consequence, sexual dimorphism of kidney injury markers like Klotho is often overlooked. Klotho is well-linked to renal health and its deletion in mice results in severe phenotype and premature death. Here, we identified putative Klotho enhancers and investigated their functions in males and females using mice with deletions in the Klotho-associated enhancers.

Methods: We generated mutant mice carrying deletion of putative Klotho enhancers using CRISPR/Cas9 gene editing. Warm ischemia-reperfusion surgery was performed bilaterally to induce acute kidney injury and unilaterally in a fibrosis model. Using ChIP-seq and RNA-seq, we analyzed chromatin features and gene expression in mouse kidney. ELISA assay was utilized to measure serum FGF23 levels.

Results: We detected Klotho gene expression being twice as high in males compared to females at baseline. Enhancer deletion decreased Klotho mRNA levels more effectively in female than in male mice (90 vs. 50%). ChIP-seq data suggest additional regulatory elements present only in male mice, as promoter marks remain more pronounced in males even after deletion. Weight, lifespan and fertility of the knockout mice was not impacted. Baseline serum FGF23 level was significantly higher only in female enhancer knockouts (192.4 vs. 59.6 pg/mL, p=0.0003). Severe bilateral ischemia resulted in similar creatinine increase in male and female WT and knockout mice, but only male knockout mice displayed higher Haver1 expression after injury than controls (1048 vs. 231.4, p=0.0016). 28 days after unilateral renal ischemia, fibrosis as measured by Acta2 and Tgfβ expression was validated by measuring the pure indophenol and replicating the same peak when analyzing different dilutions of derivatized ammonium chloride standards.

Conclusions: Our results demonstrate sexual dimorphism of Klotho gene expression and its enhancer regulation. Despite having a larger effect in female mice, including changes in baseline FGFR23 levels, only male knockout mice are more susceptible to acute injury and the deletion has no impact on the fibrosis model. Further dissection of the mechanisms of Klotho regulation is necessary to reexamine its efficacy as a kidney injury marker.

Funding: NIDDK Support

Development of an Analytical Approach to Quantify Ammonium Flux in Tissue and Biofluids
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Background: Ammonia is a waste product of amino acids and other nitrogen-containing compounds, and its accumulation in the body can be toxic. The detection of abundance and flux is challenging because of its volatile nature, its conversion to ammonium and its fixation and excretion in other metabolic cycles such as the urea cycle. Here, we aimed to develop a method for quantifying changes in ammonia metabolism in multiple organs, urine, and plasma.

Methods: We modified the Berthelot method to derivatize ammonium into a measurable molecule called indophenol. Using ultra-high-pressure liquid chromatography– triple quadrupole tandem mass spectrometry, this allows for quantifying both normal (14N) and stable isotope labeled ammonium (15N) in post-mortem tissues. The method was validated by measuring the pure indophenol and replicating the same peak when analyzing different dilutions of derivatized ammonium chloride standards.

Results: Standard curves correlated with initial concentrations of the standards. We then used a porcine kidney injury model with unilateral IRI and infused heavy labeled 15N-ammonium chloride to trace the handling of ammonium in different organs. The 14N to 15N ratio was used to observe changes in the handling of the infused heavy ammonia in different organs during kidney injury, revealing strong alterations in the inner medulla.

Conclusions: The data allowed for calculation of fluxes, revealing altered detoxification into urea. This method will be used in future studies to determine changes in waste product metabolism during kidney injury.

Mechanistic Representation of NAG Release in Renal Proximal Tubular Cellular Injury
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Background: N-acetyl-beta-D-glucosaminidase (NAG) is a novel biomarker for early detection of tubular injury in the event of acute kidney injury (AKI). While elevated levels of NAG in urine have been associated with renal tubular cell breakdown, the mechanism underpinnings of NAG release remain poorly understood. In this study, we investigated the relationship between NAG release and potential mechanisms of proximal tubular injury.

Methods: We developed a mathematical model of NAG release from proximal tubule cells (PTCs) within the framework of RENAsym, a quantitative systems toxicology model of drug-induced AKI. The model was designed to represent urinary NAG increase as a result of cellular necrosis and brush border loss. In RENAsym, ATP decline results in various forms of cellular injury including microfilament disruption and cellular necrosis. NAG release was simulated using a driving signal from either necrosis or microfilament disruption and parameterized using observed urinary NAG in rats treated with cisplatin [1] and cyclosporine A (CsA) [2]. [1] Weichert-Jacobsen, K J et al. Cancer research vol. 59,14 (1999): 3451-3. [2] Nephrotoxicity biomarker evaluation after repeat dose oral administration of cyclosporine A in male rats. Astrazeneca, 2007.

Results: The results of our mathematical model of the NAG response indicate that the kinetics of urinary NAG in rats treated with cisplatin and CsA can be predicted using cellular necrosis. The model correctly predicted the peak time of urinary NAG in rats after single dose of 5 mg/kg cisplatin with time to resolution of ~48 hours. Furthermore, the model could recapitulate the dose-dependent response of NAG release in rats treated daily with CsA for two weeks. Specifically, NAG peak time occurred on day 5 or 6 and levels remained elevated until day 14. Simulated urinary NAG was shown to saturate at CsA doses of 30 mg/kg and higher, in line with observed data.

Conclusions: We developed a mechanistic model of NAG release in connection with cellular necrosis. The model predicts NAG kinetics for CsA- and cisplatin-mediated AKI as a useful biomarker for monitoring tubular injury in preclinical settings.

Funding: Commercial Support - RENAsym development is funded by the RENAsym Consortium, which includes AstraZeneca, AbbVie, Servier, Merck KGaA, Gilead, and GSK as current members.
TH-PO128

The Association Between Fibroblast Growth Factor 23 and Blood Pressure in a Hemodialysis Cohort
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Background: Mineral bone disease (MBD) is associated with mortality in hemodialysis (HD) patients, and we recently found associations between hyperphosphatemia and vasoconstriction/endothelial cell dysfunction in a small HD cohort. We hypothesized that fibroblast growth factor 23 (FGF23), the earliest MBD biomarker, would be independently associated with blood pressure in this cohort.

Methods: In a cohort of hypertensive HD patients, we measured plasma FGF23 from remaining frozen samples using ELISA. We conducted correlation and linear regression analysis to determine the association between FGF23 and peridialytic BP metrics and other lab parameters.

Results: There were 34 participants (53% women, 59% Black, 45% with diabetes) with a mean age of 46.8 years, mean pre-HD systolic BP of 160 (19) mmHg, mean serum phosphate of 6.5 (2.3) mg/dL and median FGF23 of 3264 (1042-6817) ng/mL. Log(FGF23) did not differ based on diabetes status or sex, but it was higher in Black vs. White participants (p<0.003). FGF23 correlated with phosphate (r=0.5, p<0.001), but not with a mean age of 46.8 years, mean pre-HD systolic BP of 160 (19) mmHg, mean serum phosphate of 6.5 (2.3) mg/dL and median FGF23 of 3264 (1042-6817) ng/mL. Log(FGF23) did not differ based on diabetes status or sex, but it was higher in Black vs. White participants (p<0.003). FGF23 correlated with phosphate (r=0.5, p<0.001), but not with race. Table 1 shows that log(FGF23) was associated with almost all peridialytic BP metrics in univariate analysis that remained independent after controlling for phosphate, but were no longer significant after controlling for race.

Conclusions: FGF23 was associated with phosphate in hypertensive HD patients, and it was higher in Black vs. White participants. Associations between FGF23 and BP were independent of phosphate, but race was a confounding variable in this small cohort. Further larger studies are required to better understand mechanisms by which FGF23 and phosphate associate with blood pressure in this cohort of hypertensive HD patients.

Funding: NIDDK Support, Veterans Affairs Support

Linear Regression Analysis Using LogFGF23 as the Outcome Variable

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Univariate Regression Coefficient (p-value)</th>
<th>Multivariate regression coefficient (p-value) controlling for phosphate</th>
<th>Multivariate regression coefficient (p-value) controlling for phosphate and race</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic Pre-HD BP</td>
<td>12.9 (0.01)</td>
<td>14.0 (0.01)</td>
<td>8.0 (0.03)</td>
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<td>Systolic Post-HD MAP</td>
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<td>1.98 (0.2)</td>
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<td>11.0 (0.05)</td>
<td>11.0 (0.05)</td>
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<tr>
<td>Systolic Post-HD MAP</td>
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<td>10.3 (0.05)</td>
<td>10.3 (0.05)</td>
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<tr>
<td>Systolic Pre-HD SBP</td>
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<td>12.1 (0.00)</td>
<td>12.1 (0.00)</td>
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<tr>
<td>Systolic Post-HD SBP</td>
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<tr>
<td>Diastolic Pre-HD MAP</td>
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<td>11.7 (0.00)</td>
<td>11.7 (0.00)</td>
</tr>
<tr>
<td>Diastolic Post-HD MAP</td>
<td>11.2 (0.04)</td>
<td>11.2 (0.04)</td>
<td>11.2 (0.04)</td>
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</tbody>
</table>
| HD=Mobilisation, SBP=Systolic Blood Pressure, MAP=Mean Arterial Pressure

TH-PO129

Interactive Simulator for Model-Based Predictions of Parathyroid Hormone (PTH) Levels in Hemodialysis Patients
Gudrun Schappacher-Tilp,1 Nicolleta Kaehling,2 Egon Teinikier,3 Peter Kotanko2,31 FH Joanneum GmbH, Graz, Austria; 2Renal Research Institute, New York, NY; 3Ichbin School of Medicine at Mount Sinai, New York, NY

Background: Secondary hyperparathyroidism is a prevalent condition among hemodialysis (HD) patients and a significant contributor to chronic kidney disease-mineral bone disorder (CKD-MBD). CKD-MBD poses a considerable risk of vascular calcification and cardiovascular events. The KDIGO guidelines strongly emphasize the importance of managing parathyroid hormone (iPTH) levels in hemodialysis patients (Kidney Int Suppl 2017). Considering this, we have built an interactive simulator to predict PTH levels based on interventions targeting phosphate and calcitriol levels tailored to exemplary patients.

Methods: We utilized a comprehensive physiology-based mathematical model of parathyroid gland biology (Schappacher-Tilp, Physiol Rep, 2019) which has been employed successfully to predict individual PTH levels in HD patients (Pirklbauer, Front Med, 2021). The simulator follows a client-server architecture (Fig 1A) and features a user-friendly graphical user interface (GUI) allowing the user to select various parameters for the simulation (Fig 1B). Within the simulator, users can set treatment targets for serum phosphate and calcitriol levels, along with specifying the target time horizon.

Results: The interactive simulator provides users with the ability to select specific treatment targets and track the response of intact parathyroid hormone (iPTH) over time, as depicted in Fig IC.

Conclusions: Our simulator predicts iPTH levels for various patient groups based on user-specific treatment targets for phosphate and calcitriol, serving as an effective educational tool to illustrate the effect of phosphate and calcitriol on iPTH levels.

TH-PO130

Risk Factors Associated with Hip and Vertebral Fractures in CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study
Simon Hsu,1 Leila R. Zelnick,1 Nisha Banwal,2 Michelle Denburg,2 Charles Ginsberg,3 Andrew N. Ho fourteen,1 Tamara Isakova,4 Joachim H. Ix,4 Bryan R. Kestenbaum,5 Cassianne Robinson-Cohen,4 Myles Wolf,7 Ian H. de Boer,1 (University of Washington, Seattle, WA; 7Children's Hospital of Philadelphia, Philadelphia, PA; 4University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 8University of California San Diego, La Jolla, CA; 3Northwestern University Feinberg School of Medicine, Chicago, IL; 1Vanderbilt University Medical Center, Nashville, TN; 12Duke University School of Medicine, Durham, NC.

Background: Fracture risk is substantially higher in patients with chronic kidney disease (CKD) than those without CKD and may have different pathophysiology, yet risk factors for fracture in CKD have largely been generalized from studies in non-CKD populations.

Methods: We used Cox regression to test associations of putative demographic and clinical risk factors with the composite hip and vertebral fracture assessed using hospital discharge diagnosis codes in 3,939 participants from the Chronic Renal Insufficiency Cohort (CRIC). Estimated glomerular filtration rate (eGFR) and proteinuria assessed by 24-hour urine collection were time-updated exposures. Serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and 24,25-dihydroxyvitamin D were measured in a subset of 1,786 participants by liquid chromatography-tandem mass spectrometry.

Results: Mean cohort age was 58 years, 45% were female, 42% were Black, and 13% were Hispanic. Mean (standard deviation [SD]) eGFR was 44.4 (15.2) years (incidence rate 2.4 events per 1000 person-years [95% CI: 2.0, 2.9]). Black race was associated with lower fracture risk after adjusting for demographics, comorbidity, medication use,
and eGFR and proteinuria. Older age, lower body mass index, and lower eGFR were associated with higher fracture risk after full covariate adjustment. Neither proteinuria or parathyroid hormone, nor other biomarkers of mineral metabolism were associated with fracture risk after full covariate adjustment.

**Conclusions:** Older age, non-Black race, and lower body mass index and eGFR were associated with fracture risk. None of the biomarkers of mineral metabolism tested in this study were associated with elevated risk of fracture experienced by patients with CKD.

**Funding:** NIDDK Support

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**TH-PO131**

**Lower Parathyroid Hormone Levels Are Associated with Lower Risk of Fractures in Japanese Hemodialysis Patients: A Nationwide Cohort Study**

**Hirokata Kombaka,**1,2 Takahiko Imaizumi,1 Takayuki Hamano,1 Naohiko Fujii,1 Masanori Abe,1,3 Norio Hanafusa,1,2 *Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan; Tokyo University School of Medicine, Isehara, Japan; Nagoya University Hospital, Nagoya, Japan; Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan; Nihoa University School of Medicine, Tokyo, Japan; Tokyo Women’s Medical University, Tokyo, Japan.

**Background:** Secondary hyperparathyroidism is associated with high-turnover bone disease in hemodialysis patients. However, conflicting evidence exists as to whether parathyroid hormone (PTH) levels are associated with fracture risk and whether the relationship is linear or U-shaped.

**Methods:** Using data from the Japanese Society for Dialysis Therapy Renal Data Registry, we analyzed 180,333 adult hemodialysis patients with data on serum albumin, calcium, phosphorus, and intact or whole PTH at the end of 2016 and data on hospitalization in 2017. The primary outcome was the composite of hospitalizations due to hip, vertebral, and other fractures. The secondary outcomes included hospitalization due to site-specific fracture. Fracture risk was assessed using Cox proportional hazards models, adjusted for potential confounders. We also examined the association between percent change in PTH levels during a 1-year baseline period and subsequent risk of fracture.

**Results:** At baseline, the median intact PTH level was 141 pg/mL (interquartile range, 78–226 pg/mL). During the 1-year follow-up, there were a total of 3,762 fractures requiring hospitalization (1,361 hip, 1,850 others). In adjusted analyses, increasing PTH levels were associated with a monotonically increasing risk of fractures (odds ratio per 30% increase in intact PTH level, 1.06; 95% CI, 1.03–1.09). When analyzed in deciles, the risk of fracture was lowest in the decile of intact PTH levels (-39 pg/mL). The relationship between PTH levels and fracture risk was more pronounced for hip fractures, whereas there was no association between PTH levels and vertebral fractures. Changes in PTH levels were also associated with fracture risk: the odd ratio of fractures per 30% reduction in PTH levels was 0.97 (95% CI, 0.95–0.99).

**Conclusions:** Lower PTH levels are associated with a monotonically decreasing risk of fractures. Further studies are needed to determine whether intensive control of PTH decreases fracture risk.

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**TH-PO132**

**Improving Treatment of CKD-Mineral Bone Disorder (CKD-MBD) Through the Incorporation of Agatston Scores**

**Adam E. Gaweda,**1 Michael E. Brier,2,3 Eleanor D. Lederer,3 *University of Louisville School of Medicine, Louisville, KY; VA Robley Rex Medical Center, Louisville, KY; VA North Texas Health Care System, Dallas, TX; The University of Texas Southwestern Medical Center Medical School, Dallas, TX.

**Background:** KDIGO targets for CKD-MBD for Ca, P, and PTH are surrogates for the real damage that takes place in bone and the cardiovascular (CV) system. Vascular calcification (VC) correlates strongly with CV disease and death in individuals with CKD.

We have modeled CKD-MBD through a series of mass balance equations describing movement of mineral between bone and soft tissue. We hypothesize that incorporation of measures and biomarkers of VC into a quantitative systems pharmacology model optimized using reinforcement learning will improve therapy by identifying alternative targets.

**Methods:** Data were abstracted from the Chronic Renal Insufficiency Cohort (CRIC) consisting of 5499 individual subjects with a mean CKD EPI eGFR of 47.7 ml/min/1.73m2 and a range between 3.0 and 126. Total and site specific Agatston scores were calculated and used for analysis. A total of 3230 Agatston scores were reported with a mean of 330 ± 767 and a range of 0 to 8247. A Cox Proportional hazard analysis was performed on CV death comparing Agatston score, site specific scores, and measured markers of inflammation (C-react, Neutrophil/Lymphocyte Ratio (NLR), Fatty Acid Binding Protein (FABP), N-Acetyl-Beta-Glucosamidase (NAGB), Beta-2 Microglobulin (B2M), Beta-Trace Protein (BTP), and Humanery Molecule 1 (KIM1).

**Results:** The effects of inflammation markers on Total Agatston score and site-specific scores were not different, so only Total Agatston score will be reported. The results of the Cox model is shown in Table 1 following modeling with backwards elimination. All factors entered the model as an increased risk of CV death except Beta-Trace Protein.

**Conclusions:** Substituting Agatston score for Ca net balance and modeling inflammatory intermediates NLR, B2M, BTP and FABP will optimize the CKD-MBD model. Leveraging artificial intelligence in the form of reinforcement learning will yield new pathways for treatment by targeting more proximal surrogates of disease.

**Funding:** Veterans Affairs Support

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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
TH-PO134

The Vitamin D Metabolite Ratio Is Associated with Volumetric Bone Density in Older Men

Charles Ginsberg,1 Terri L. Blackwell,2 Jonathan Cheng,3 O. Alison Potok,1 Jane Cauley,4 Kristine E. Ensrud,5 Simon Hsu,4 Deborah M. Kado,6 Eric Orwoll,1 Peggy M. Cawthon,1 Joachim H. Ix,7 University of California San Diego, La Jolla, CA; 2California Pacific Medical Center Research Institute, San Francisco, CA; 3University of Pittsburgh, Pittsburgh, PA; 4Minneapolis Veterans Affairs Healthcare System, Minneapolis, MN; 5University of Washington, Seattle, WA; 6Stanford University School of Medicine, Stanford, CA; 7Oregon Health & Science University School of Medicine, Portland, OR.

Background: The ratio of vitamin D calcitropic (24,25-dihydroxyvitamin D) to 25(OH)D (vitamin D metabolite ratio or VMR) has been suggested as a superior marker of vitamin D status than 25(OH)D. High-resolution peripheral quantitative computed tomography (HR-pQCT) provides information on bone health beyond bone mineral density (BMD), providing volumetric BMD (vBMD) and bone strength data. We evaluate the associations of the VMR and 25(OH)D, with vBMD and bone strength, in the distal radius and tibia in 545 participants in the Osteoporotic Fractures in Men (MrOS) Study.

Methods: We used multivariable linear regression models adjusted for demographics, season, study site, physical activity, BMI, smoking status, diabetes, blood pressure and estimated glomerular filtration rate (eGFR) among 545 men aged a 65 years who participated in MrOS and provided HR-pQCT data in visit 4 (Year 14 of the study). Our primary outcome was vBMD and secondary outcome was estimated failure load (EFL) at both the distal radius and tibia.

Results: Mean age was 84±4 years, 88.3% were White, and 32% had an estimated glomerular filtration rate (eGFR) of ≤60 mL/min/1.73m². In fully adjusted models, each two-fold higher VMR was associated with 9% (3%, 16%) and 6% (0.4%, 11%) higher vBMD at the distal radius and tibia, respectively (Table). In contrast, we found no association of 25(OH)D with vBMD at either anatomic site. Similarly, each two-fold higher VMR was associated with 13% (5%, 21%) and 10% (4%, 16%) EFL at the distal radius and tibia, respectively (Table). In contrast, we found no association of 25(OH)D, with EFL at either anatomic site.

Conclusions: Among community-living older men, a higher VMR is associated with higher vBMD and EFL while 25(OH)D was not. The VMR may serve as a valuable predictor of skeletal health in older men at risk for osteoporosis and fractures.

Funding: Other NIH Support - NHB-LI, NIA, NIAMS, NCATS, Private Foundation Support

TH-PO135

Serum Bicarbonate Is Associated with Bone Density Among Adults with Type 2 Diabetes: Results from the African American Diabetes Heart Study

Kishan Bao,1 Jean H. Anionc,1,2 Meredith Ackerman,1 Barry I. Freedman,1 Jasmin Divers,1 Minesh Khatri,1 New York University Long Island School of Medicine, Mineola, NY; 2Division of Nephrology, Mineola, NY; 3Center for Population and Health Services Research, Mineola, NY; 4Wake Forest University School of Medicine, Winston-Salem, NC; 5Section on Nephrology, Winston-Salem, NC.

Background: Osteoporosis is a significant cause of morbidity and mortality in the aging population. Individuals with type 2 diabetes (T2D) typically have higher bone density but also a higher rate of fractures. Serum bicarbonate may be a risk factor for bone loss, but studies are conflicting, and little is known about this relationship in T2D, especially in African Americans.

Methods: We examined the longitudinal relationship between serum bicarbonate and change in bone density in 300 participants with T2D in the African American - Diabetes Heart Study (AA-DHS). Serum bicarbonate was measured at baseline, and bone density was assessed using CT volumetric bone mineral density (vBMD) scans of the thoracic and lumbar spines at baseline and after an average of five years of follow up. Multivariable linear regression models assessed associations between baseline serum bicarbonate and longitudinal change in vBMD.

Results: At baseline, the cohort was 50% female, with a mean age of 55.1 years and a mean duration of diabetes of 10.2 years. The mean baseline serum bicarbonate was 26.8 (SD 3.3) mEq/L, the median baseline lumbar spine vBMD was 179.3 (IQR 148.2, 208.9) mg/cm³, and the median baseline thoracic spine vBMD was 204.9 (IQR 171.1, 231.9) mg/cm³. In adjusted analyses, every 1 mEq/L increase in baseline serum bicarbonate was significantly associated with a relative improvement in lumbar vBMD (1.04 (0.73, 1.36) mg/cm³, p<0.01), as well as thoracic vBMD (1.36 (0.47, 1.94) mg/cm³, p<0.01).

Conclusions: In this cohort of African-Americans with T2D, higher baseline serum bicarbonate levels associated with improved changes in bone density over time. Further studies are needed to determine if treatment of metabolic acidosis would lessen bone loss and fractures in this population.

Funding: Other NIH Support - Funding: 2R01DK071891

TH-PO136

Effect of Citrate-Buffered, Magnesium-Enriched Dialysate on Calcification Propensity in Hemodialysis Patients: Results of a Randomized Controlled Trial (CitMag Study)

Daniel Cejka,1 Ursula Thiem,2 Eric Blinenzl,3 Jennifer D. Machack,2 Jakob Voell,1 Edward R. Smith,1 Andreas Pasch,1,4 Maria C. Haller,1 1Ordensklinikum Linz GmbH, Linz, Austria; 2The Royal Melbourne Hospital, Parkville, VIC, Australia; 3Eugen Steiger AG, Bied, Switzerland; 4Johannes Kepler Universität Linz, Linz, Austria.

Methods: Accelerated serum calcification propensity (lower T50) is directly associated with increased risk of cardiovascular events and mortality in dialysis patients. Several solitary interventions have been reported to improve T50 but whether a combination of these interventions yields further increases T50 is unknown. Therefore, the effect of substituting acetate for citrate buffer in combination with increases in magnesium concentration in dialysate on T50 was investigated.

Methods: In a randomized, controlled trial, 60 chronic hemodialysis patients were allocated either continue on standard (S) dialysate (3 mmol/l acetate, 0.5 mmol/l magnesium) or a sequence of magnesium-enriched (Mg0.75) dialysate (3 mmol/l acetate, 0.75 mmol/l magnesium) for 2 weeks followed by citrate-buffered, magnesium-reduced (Cit+Mg0.3) dialysate (1 mmol/l citrate, 0.75 mmol/l magnesium) for 3 weeks. The primary endpoint was the difference in T50 times between the S group and the Cit+Mg0.75 group at 5 weeks.

Results: There was no significant difference in T50 time between the S group compared to the Mg0.75 group (236±77 vs. 265±97 minutes, p=0.23). The combination of citrate-buffered with increased magnesium concentration in dialysate does not improve T50 and may even be antagonistic when administered concurrently.

Funding: Government Support - Non-U.S.

TH-PO137

Histologic Specificity in Calciphylaxis

W. Charles O’Neill,1 Justin T. Cheeley,1 Carla L. Ellis,1 Grechtia Jagannathan,1 Emory University School of Medicine, Atlanta, GA; 2Northwestern University Feinberg School of Medicine, Chicago, IL.

Background: Skin biopsy is often used to support the diagnosis of calciphylaxis, otherwise termed calcific uremic arteriolopathy (CUA), but the specificity is unknown. We previously showed that many of the findings ascribed to CUA were also present in amputation specimens of patients without CUA. To better understand the specificity of histology in CUA and thus the underlying pathophysiology, we prospectively compared involved and uninvolved tissue from 18 subjects with a clinical diagnosis of CUA.

Methods: 18 patients undergoing skin biopsies for CUA consented for a biopsy of uninvolved skin, usually on the contralateral extremity. In an additional 2 cases, involved and uninvolved tissue from 18 subjects with a clinical diagnosis of CUA.

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

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Bone and Mineral Metabolism: CKD-MBD Updates

TH-PO138

Patients’ Experience of Calciphylaxis: Living with a Disease of Uncertain Etiology and Management

Ombremin Sane,1,2 Carmen Salhi,1 Sagar U. Nigwekar,1 Kidney Research Center.
1Massachusetts General Hospital, Boston, MA; 2Northeastern University Bouve College of Health Sciences, Boston, MA.

Background: Calciphylaxis is a condition with sudden, unpredictable onset that predominantly affects people with end-stage renal disease (ESRD). Caused by the calcium-based occlusion of the microvasculature, calciphylaxis results in large, extremely painful non-healing skin ulcers. Calciphylaxis has no cure and a one-year mortality between 40 and 80% for patients who have ESRD. Prior research has focused on identifying the biological mechanisms of the disease with the goal of developing treatment. Little is known about how patients currently living with calciphylaxis manage their illness and care, especially regarding the treatment options and severity, often debilitating, symptoms.

Methods: Using purposive sampling, we recruited participants (n=15) who had contact with a calciphylaxis clinical practice in the Northeast United States. This qualitative study utilized semi-structured phenomenological interviews to investigate the lived experience of patients with calciphylaxis. These 1-hour interviews focused on specific domains of patient experience: process to diagnosis, treatment process, and social and emotional support.

Results: There were 5 major findings of this study: 1) unpredictability resulting from acuity of disease and uncertain clinical diagnosis and treatment options; 2) severity of pain affecting basic functioning and access to clinical care; 3) central role of social support due to the debilitating nature of pain; 4) coping and challenges of the disease; 5) becoming a self-advocate in the clinical setting in order to navigate clinical care. Two issues tie these findings together. A lack of clinical attention to pain management affected both daily functioning and patients’ ability to access other aspects of calciphylaxis care. Patients’ experiences of uncertainty were exacerbated by limited communication and lack of coherent calciphylaxis clinical knowledge.

Conclusions: Our findings are the first to describe, in depth, patients’ experiences with calciphylaxis. They inform clinical recommendations, for both calciphylaxis and other conditions with acute, unpredictable onset and potentially debilitating symptoms. In particular, inclusion of pain management specialists as core members of a care team could improve the quality of life of calciphylaxis patients and help communicate the challenges patients face to other members of the care team.

TH-PO139

Decision Tree Model Simulating the Burden of Hyperphosphatemia in US Adult Patients with ESKD on Dialysis

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Background: Hyperphosphatemia is a common complication in patients with end-stage kidney disease (ESKD) on dialysis. It can lead to vascular calcification, secondary hyperparathyroidism, increased risk for fractures, and other health outcomes. It is important to understand the extent of serum phosphate control benefit in this population.

Methods: A decision tree model was built to simulate the population-level effect of reducing serum phosphate levels in US adult patients with ESKD on in-center hemodialysis (n=480,516) over a 5-year time horizon. Patients were assigned an initial serum phosphate level derived from the US Renal Data System’s 2022 Annual Data Report, after which a reduction of 2.0 mg/dL was applied. Changes in hospitalization (all-cause, cardiovascular, and fracture), parathyroidectomies, mortality, and healthcare costs were calculated by the model based on published literature and Medicare cost data. The model does not specify how patients’ serum phosphate levels did not fluctuate as they would in the real world, and that the data were derived from older retrospective studies that may not represent the present-day ESKD population.

Results: Simulated reduction of serum phosphate levels in patients with ESKD on dialysis decreased mortality. This pronounced effect in mortality leads to an increase in all-cause hospitalization, resulting in additional Medicare costs. However, serum phosphate control is only one component of managing patients with ESKD on dialysis; there are numerous compelling comorbidities and extenuating factors. These results highlight the need to continue exploring how management of patients with ESKD can improve the quality of life of calciphylaxis patients and help communicate the challenges they inform various clinical recommendations, for both calciphylaxis and other conditions with acute, unpredictable onset and potentially debilitating symptoms. In particular, inclusion of pain management specialists as core members of a care team could improve the quality of life of calciphylaxis patients and help communicate the challenges patients face to other members of the care team.

TH-PO140

Impact of Accessibility to Non-Calcium-Based Phosphate Binders and Calcimimetics on Mineral Outcomes in Maintenance Hemodialysis

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Background: Traditional management of CKD-MBD with calcium and active vitamin D results in hypercalcemia and calcification. Newer drugs including non-calcium-based phosphate binders (NCBPBs) and calcimimetics may help achieving the treatment targets with less hypercalcemia and calcification. In our country, NCBPBs and calcimimetics are not covered in social security and universal coverage reimbursement schemes (SS/UC), whereas they are covered in civil servant and state enterprise reimbursement schemes (CS/SE). Our institution serves both groups of patients providing a unique opportunity to study the differences in mineral outcomes.

Methods: This is a retrospective cohort study that included maintenance hemodialysis (MHD) patients between 2015–2022. Patients were categorized into two groups according to their reimbursement schemes (SS/UC or CS/SE). Differences in mineral parameters were compared using linear mixed models. The composite endpoint of parathyroidectomies and severe hyperparathyroidism (HTP) (PTH ≥450 pg/mL) was analyzed using multivariate Cox-Proportional Hazard regression.

Results: A total of 714 patients were included. The average serum calcium and phosphate and proportions of patients with hypercalcemia and hyperphosphatemia were substantially higher in SS/UC group compared with CS/SE group. Parathyroid hormone levels were comparable but the proportion of patients with HPT was significantly higher in SS/UC group. The composite endpoint of parathyroidectomy and severe HPT was also significantly higher in SS/UC group. A sensitivity analysis in 563 patients who were prescribed at least 1 type of CKD-MBD medications yielded similar findings.

Conclusions: MHD patients who did not have access to NCBPBs and calcimimetics showed poorer mineral outcomes compared with those who had access to the drugs.
**TH-PO141**

**Effects of a Low Phosphorus Diet on Phosphorus and Calcium Whole-Body Balance and Intestinal Absorption: Results of a Pilot Study in Adults with Moderate CKD**

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**Background:** Dietary P restriction is often used as a management strategy to prevent and treat hyperphosphatemia and CKD-MBD progression. It is presumed that a low P diet results in lower P balance or retention, but this has not been determined, nor the effects on Ca absorption and balance.

**Methods:** This pilot two-phase crossover, controlled feeding, metabolic balance study investigated the effects of dietary P level (low P [LP], 800 mg/d; high P [HP], 1500 mg/d) on P and Ca balance and absorption in N=3 adults with moderate CKD. Nutrient content was similar, including low Ca (500 mg/d). Each phase consisted of 1 wk run-in on the diet, 1 wk isocaloric metabolic balance, and 3 wk washout between phases. Complete timed urine and feces were collected. Intrapl V and Ca P isotopes were administered and serial serum and urine samples analyzed for their concentrations to determine fractional intestinal absorption by kinetic modeling. Balance was calculated as intake minus urine and fecal excretion. Serum iPTH, iFGF, and 1,25D were measured at baseline and end of each phase.

**Results:** Intestinal fractional P absorption varied widely among participants (51-95%) but appeared unaffected by dietary P level in all participants. Thus, absolute intestinal P absorption (mg/d) was approximately doubled in the HP compared to the LP. 24 h urine P was lower in all participants with the LP diet. The response in P balance to dietary P level varied among subjects. The response in fractional intestinal Ca absorption and Ca balance also varied. 24 h urine Ca was very low in all subjects (6-20 mg/d) and did not change with the LP diet. Serum 1,25D was not associated with intestinal fractional P or Ca absorption nor in response to dietary P. iPTH and iFGF23 were lower with LP in two participants who had moderately elevated levels at baseline and with HP.

**Conclusions:** In adults with moderate CKD, Ca and P balance and intestinal absorption are variable in response to different controlled dietary P intakes. In this pilot study, fractional P absorption did not change with dietary P level and was not associated with 1,25D. Further studies are needed to identify explanatory factors for the observed variation in whole-body Ca and P physiology in adults with CKD.

**Funding:** NIDDK Support

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**TH-PO142**

**Management of Serum Phosphorus over a Six-Month Follow-Up in Home Hemodialysis Patients Prescribed Sucroferric Oxalate as Part of Routine Clinical Care**

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**Background:** With the growing use of home hemodialysis (HHD) and the increasing trend of physicians prescribing sucroferric oxalate (SO) in recent years, this real-world data analysis examines the serum phosphorus (sP) management with SO in HHID patients (pts) over 6 months.

**Methods:** Eligible HHID pts (n=713) were adults from Fresenius Kidney Care first prescribed SO monotherapy during 9/2016-12/2020 and had sP measured the month (mo) before SO start (−1M). sP was assessed up to 3 months (mos) before (baseline, BL; −3M to −1M) and 6 mos following SO initiation (follow up, FU; M1 to M6). Pts were censored from the analysis upon transplant (n=53), discharge (n=94), and discontinuation of SO (n=177 including n=80 prescribed another phosphate binder (PB) after SO stop). Comparisons of parameters were made between −1M and other mos.

**Results:** Pts (n=713) were on average 53 years, 42 mos vintage, and 34% female. The PB distribution in pts with PB recorded at BL (78%): sevelamer 51%, calcium acetate 21%, lanthanum carbonate 3%; ferric citrate 8% and >1 PB 16%. sP increased over the BL, from 6.1 mg/dL at −3M to 6.6 mg/dL at −1M but declined after SO start (5.9 to 6.1 mg/dL during FU; p<0.0001). Accordingly, the % of pts with sP ≥5.5 mg/dL increased from 22% at −1M to 43% at M6 (p<0.0001), and the % with sP 4.5 mg/dL increased from 9% at −1M to 19% at M6 (p<0.0001), with pill burden decreasing from 8.3 to 4.7 pills/day (p<0.0001). Serum calcium showed a significant decrease from −1M to M6 (9.15 to 9.03 mg/dL; p<0.001). No significant changes (p>0.3) were observed in iPTH following SO prescription. Tenapanor (TEN) was added to 118 (16%) pts with 25 to 553 pg/mL during FU.

**Conclusions:** HHD pts prescribed SO as part of routine clinical care experienced improvements in sP control and reductions in PB pill burden over a 6-month FU, compared to BL.

**Funding:** Commercial Support - Fresenius Medical Care

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**TH-PO143**

**Optimal Initiation of Tenapanor Treatment Analyzed by Baseline Phosphate Binder Dose: A Subanalysis of the OPTIMIZE Study**

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**Background:** Tenapanor (TEN) is a novel phosphate absorption inhibitor that blocks paracellular phosphate absorption by local inhibition of the intestinal sodium hydrogen exchanger isoform 3 (NHE3). TEN is being evaluated for control of serum phosphate (sP) in adult patients (pts) with chronic kidney disease (CKD) on maintenance dialysis. Real world data shows that nearly 80% of pts are unable to consistently maintain adequate control of sP over a 6 month period with the use of phosphate binders (PBs) alone. OPTIMIZE (NCT04549597) was an open-label study of TEN initiation in pts on dialysis that evaluated sP control, pill burden, and quality of life (QOL).

**Methods:** OPTIMIZE study design was previously described. In Cohort 1 (C1; n=151) pts stopped PBs and initiated TEN 30 mg bid. In Cohort 2 (C2; n=152) pts reduced PB dose by ≥50% and added TEN 30 mg bid. The PB/TEN dose could be adjusted to achieve sP ≤5.5 mg/dL. Dose up-titration for PBs was not allowed until week (wk) 2. Pts in C1 and C2 were categorized into two groups: low PB (LPB) dose (≥6 pills/day at baseline) and high PB (HPB) dose (<6 pills/day at baseline). We evaluated sP response (sP reduction ≥1.2 mg/dL, ≥2 of 3 measurements) at wks 1−4 and wks 6−10 of treatment. A QOL survey was administered at the end of wk 10.

**Results:** Overall, 87 and 93 HPB pts and 60 and 55 LPB pts were randomized to C1 and C2, respectively. For HPB pts, sP response was achieved at wk 4 by 24.1% (C1) and 47.3% (C2) of pts. Median sP-lowering pill burden (including TEN) reduction at wk 4 was 7 (C1) and 4 (C2) pills/day. For LPB pts, sP response was achieved at wk 4 by 38.3% (C1) and 47.3% (C2) of pts. Median sP-lowering pill burden reduction was 2.5 (C1) and 1 (C2) pills/day. Overall, 60−80% of those who achieved a sP response at wk 4 continued to have a ≥50% reduction in PB dose, while LPB appeared to have a similar early response regardless of TEN initiation method.

**Funding:** Commercial Support - Aredlyx, Inc.

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**TH-PO144**

Tenapanor Effect on Decrease in Phosphate Binder Pill Burden for Hyperphosphatemia in Japanese Patients Undergoing Hemodialysis: A Phase 3 Long-Term Study

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**Background:** Phosphate binders (PBs) are commonly prescribed for treating hyperphosphatemia. However, management with PBs often requires a high pill burden which is a significant issue in hemodialysis (HD) patients. Tenapanor (TEN) is a novel drug that reduces paracellular phosphorus absorption via the selective inhibition of sodium hydrogen exchanger isoform 3, and the dose consists of one small tablet taken twice daily. We aimed to evaluate the ability of TEN to decrease PB pill burden for hyperphosphatemia in Japanese HD patients in the long-term safety study. Methods: This was a multicenter, open-label, single-arm, phase 3 study. HD patients whose serum phosphorus level was ≥5.0 mg/dL at baseline received TEN 5 mg BID added to their PB regimen. The TEN dose was titrated in a stepwise manner within the range of 5, 10, 20 and 30 mg BID. The dose of TEN and PBs was adjusted based on serum phosphorus levels from Week 2, while controlling serum phosphorus levels and switching

**Funding:**
TH-PO145
Efficacy and Safety of Tenapanor in Japanese Peritoneal Dialysis Patients with Hyperphosphatemia: Results of a Phase 3 Study
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Background: Hyperphosphatemia develops in most peritoneal dialysis (PD) patients and is treated with diet and phosphorus binders (PBs), however some patients do not respond adequately to these treatments. Tenapanor is a novel drug for hyperphosphatemia that blocks intercellular influx of phosphorus from intestinal tract by binding the sodium hydrogen exchanger isoform 3 (NHE3). This study was designed to evaluate the efficacy and safety of tenapanor in Japanese PD patients with hyperphosphatemia.

Methods: This was a multicenter, open-label, single-arm, phase 3 study in Japanese PD patients with hyperphosphatemia. The study consisted of a 6-week washout period, PB washout period, and treatment period. Patients were enrolled if serum phosphorus level was 3.5–7.0 mg/dL at screening, 3.5–6.0 mg/dL at baseline, and 3.5–6.0 mg/dL after washout. Of the 113 patients enrolled, 88 entered the treatment phase. The primary endpoint was the change in serum phosphorus at week 8 from baseline. For safety analysis, the last observation was carried forward (LOCF) method was used.

Results: A total of 54 subjects received tenapanor. Serum phosphorus levels decreased from a baseline of 7.65 mg/dL to 6.14 mg/dL in week 8 and 5.44 mg/dL in week 16. The change in serum phosphorus at week 8 (primary endpoint) and at week 16 was −1.51 mg/dL (95% confidence interval [CI], −2.01, −0.91 mg/dL) and −1.65 mg/dL, respectively. The proportion of patients who achieved the target levels at week 8 and at week 16 were 46.3% (19/41) and 76.5% (26/34), respectively. The most common adverse event was diarrhea (74.1%, 40/54). All were mild or moderate in severity and only three subjects (5.6%) discontinued due to diarrhea. These results were comparable to those of the phase 3 study in Japanese hemodialysis (HD) patients.

Conclusions: Tenapanor could be a new treatment option for PD patients with hyperphosphatemia as well as HD patients.

Funding: Commercial Support - Kyowa Kirin Co., Ltd.

TH-PO147
Patient Education Improves Tenapanor Tolerability in OPTIMIZE Study
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Background: Tenapanor (TEN) is a novel phosphate absorption inhibitor that blocks paracellular phosphate absorption by local inhibition of the intestinal sodium hydrogen exchanger isoform 3 (NHE3). TEN is being evaluated for the control of serum phosphate (sP) in adult patients (pts) with chronic kidney disease (CKD) on maintenance dialysis. TEN has demonstrated efficacy and acceptable safety in the hyperphosphatemia clinical studies, BLOCK (NCT02675998) and PHREEDOM (NCT03427125). Diarrhea was the most common adverse event, observed in >5% of pts. Here, we evaluate the benefit of pt education on gastrointestinal tolerability during the OPTIMIZE (NCT04584597) study.

Methods: Methods for the trials have been previously described. The majority of patients were started on TEN at 30 mg bid. We assessed data from the analysis period in BLOCK (8-week treatment period [TP]), PHREEDOM (first 8 weeks of TP), and OPTIMIZE (second 8 weeks of TP). Baseline demographics and sP of pts educated were similar at study start. We focused on how to take TEN, what they may experience on TEN, medications to be discontinued before starting TEN, and how best to mitigate the potential onset of loose stools or diarrhea.

Results: As expected, given the mechanism of action and data from past trials, most diarrhea events (75.7%–79.6%) occurred within the first 2 weeks of treatment in all three studies and the majority of cases were mild to moderate. Overall, the diarrhea incidence was lower during the analysis period in OPTIMIZE (39.3%) than in BLOCK and PHREEDOM (47.9% and 47.7%, respectively), and was also lower during the first two weeks of study treatment in OPTIMIZE (33.6%) vs BLOCK and PHREEDOM (38.0% and 39.4%). Discontinuation rates due to diarrhea were lower during the 10-week analysis period of OPTIMIZE (6.0%) than the 8-week analysis periods of BLOCK or PHREEDOM (7.0% and 13.4%).

Conclusions: Pt education may help ameliorate TEN-related diarrhea in dialysis pts. Specifically, since many pts on dialysis take medications to alleviate constipation, advising pts to discontinue these medications prior to starting TEN may also help reduce the occurrence of diarrhea.

Funding: Commercial Support - Ardelyx, Inc.
non-sevelamer binders, sevelamer was not associated with an increased risk of GIB in elderly patients (HR 1.02, 95% CI 0.97 – 1.07) or all-cause mortality (HR 1.01 95% CI 0.98 – 1.05). Findings were similar across key subgroups, including those defined by diabetes, smoking, anticoagulation, sodium polystyrene, and cholesterolesterase status.

**Conclusions:** The initiation of sevelamer versus non-sevelamer containing phosphate binders was not associated with an increased risk of GIB hospitalization in patients on hemodialysis.

### Table 1: PTH in Incident Gastrointestinal Bleed (GIB) After Phosphate Binder Initiation in Patients on Hemodialysis using an Intention-To-Treat Analysis

<table>
<thead>
<tr>
<th>Interaction to Treat</th>
<th>Sevelamer</th>
<th>Non-Sevelamer</th>
<th>Total*</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total GIB</td>
<td>1,203 (94)</td>
<td>779 (74)</td>
<td>200 (100)</td>
<td>1.02 (0.007 - 1.07)</td>
</tr>
<tr>
<td>Upper</td>
<td>1,231 (19)</td>
<td>788 (12)</td>
<td>201 (100)</td>
<td>1.00 (0.19 - 1.01)</td>
</tr>
<tr>
<td>Lower</td>
<td>42 (14)</td>
<td>26 (13)</td>
<td>68 (100)</td>
<td>0.98 (0.08 - 1.02)</td>
</tr>
<tr>
<td>NOS</td>
<td>988 (37)</td>
<td>331 (37)</td>
<td>1320 (100)</td>
<td>0.77 (0.07 - 0.87)</td>
</tr>
<tr>
<td>GIB w/ Procedure</td>
<td>124 (10)</td>
<td>31 (8)</td>
<td>155 (100)</td>
<td>0.79 (0.07 - 0.87)</td>
</tr>
<tr>
<td>All-Cause Mortality</td>
<td>124 (9)</td>
<td>31 (8)</td>
<td>155 (100)</td>
<td>0.79 (0.07 - 0.87)</td>
</tr>
</tbody>
</table>

*Adjusted for IR covariates across demographics, medical co-morbidities, and medication history of past history.

### Figure 1

Etelcalcetide was associated with significant reductions of serum calcium specifically during the first 6 months of treatment. Phosphorus levels increased from 3.6 mg/dL to 3.9 mg/dL, and PTH levels decreased from 1050 pg/mL to 400 pg/mL. The benefits were sustained over a 1-year period, with a median follow-up of 12 months. The most common side effects were gastrointestinal (30%) and headache (20%). Overall, etelcalcetide was well-tolerated and demonstrated a favorable safety profile.

### Methods

Data from 23,359 US in-center HD patients were extracted from the prospective Dialysis Outcomes and Practice Patterns Study (DOPPS). Within-patient changes in PTH and other MBD markers in the 6 months before (pre) vs. 6 months after (post) etelcalcetide discontinuation were compared using linear regression among patients who discontinued etelcalcetide between December 2020 to April 2021 – when discontinuation was more likely driven by policy change than patient indication.

### Results

From July 2020 to July 2021, etelcalcetide use decreased from 12% to 5%. Among 713 patients who discontinued etelcalcetide between December 2020 and April 2021, the prevalence of PTH >600 pg/mL increased from 28% to 43% overall and from 32% to 50% among Black patients. The effects of the drug were sustained over a period of 3 years. Treatment with etelcalcetide was associated with significant increases in serum calcium particularly during the first 6 months of treatment. Phosphorus levels were not significantly affected by the use of etelcalcetide.

### Conclusions

Etelcalcetide was effective lowering serum PTH in a sample of predominantly black patients. The effects of the drug were sustained over a period of 3 years. Treatment with etelcalcetide was associated with significant increase in serum calcium during the first 6 months of treatment.

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**TH-PO150**

Etelcalcetide and Long-Term Control of Parathyroid Hormone Levels

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**Background:** Secondary hyperparathyroidism is a common situation in end stage kidney disease patients receiving hemodialysis. Elevated PTH levels have correlated with vascular complications, accelerated vascular calcification and abnormal bone metabolism, and in clinical practice is used as a surrogate of bone health. Etelcalcetide was approved by the FDA in 2017 for control of moderate to severe hyperparathyroidism in hemodialysis patients. Original studies evaluated the efficacy and safety for a period of up to 26 weeks. The long-term efficacy in controlling PTH levels as well as calcium and phosphorus has not been described.

**Methods:** All hemodialysis patients treated with Etelcalcetide at Emory hemodialysis centers for at least 3 months were identified and their medical records reviewed. Patients were followed while on treatment and at discontinuation. Basic demographic information and laboratory data were extracted from the medical record. Median values with IQR are presented unless stated otherwise.

**Results:** Since 2018, 209 hemodialysis patients were treated with Etelcalcetide and 185 of them received the drug for at least 3 months and represent the study cohort described here. 50% were female, 48-68 years, predominantly Black (96%) and the time on renal replacement therapy before initiation of Etelcalcetide was 4.6 (2.5-7.9) years. Figure 1 shows average PTH, calcium and phosphorus levels during treatment with Etelcalcetide. Median (IQR) PTH levels decreased from 1050 pg/mL (861-1396) at time zero to 550 pg/mL (351-890) in 6 months and the proportion of patients with PTH below 600 pg/mL was 58.4% compared to 0% at the beginning of treatment. Use of Etelcalcetide was associated with significant reductions of serum calcium specifically during the first 6 months of treatment. Phosphorus levels were not significantly affected by the use of Etelcalcetide.

**Conclusions:** Etelcalcetide was effective lowering serum PTH in a sample of predominantly black patients. The effects of the drug were sustained over a period of 3 years. Treatment with Etelcalcetide was associated with significant increase in serum calcium during the first 6 months of treatment.

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**Abbreviations:** IPTW, inverse probability of treatment-weighting; HR, hazard ratio; NOS, Not otherwise specified; ICD, International Classification of Disease; CPT, Current Procedural Terminology

**Keywords:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Post-operative hypocalcemia following parathyroidectomy (PTX) for resistant renal hyperparathyroidism (rRHPT) is a major complication that is preventable yet highly prevalent despite protocolized perioperative management. We aimed to determine the predictors of post-operative hypocalcemia in our centre from patient characteristics and routine biochemical parameters in order to aid our review of the current centre protocol.

Methods: 75 ESKD patients who underwent parathyroidectomy for rRHPT between May 2016 and October 2022 were enrolled in the study. We collected patient demographics data, serum levels of albumin, calcium, phosphate, intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), doses of phosphate binders (calcium based and non-calcium based), vitamin D and cinacalcet before and for up to seven days after parathyroidectomy. ROC curves with AUC for iPTH and ALP levels against hypocalcemia were used to determine cutoffs. Multivariable logistic regression model was used to determine the odds ratio and as the incidence rate of the outcome was high, generalized linear models using Poisson regression with robust error variance were used to estimate relative risk.

Results: 37 men and 38 women with mean age of 53.8 ± 11.4 years at the time of surgery were enrolled. The median serum iPTH and ALP levels were 169.8 pmol/L (IQR 113.7, 266.7) and 272 U/L (IQR 162.5, 492.0, 380 U/L vs. 220.5 U/L respectively) and significantly longer mean post operative hospitalization (10.5 vs 4.3 days). Preoperative iPTH level (>166 pmol/L) and ALP levels (>166 U/L) had 72% sensitivity and 73% specificity for predicting post-operative hypocalcemia with a relative risk of 2.00 [95% CI 1.27-3.33], p=0.003.

Conclusions: Pre-operative iPTH levels >166 pmol/L can predict post PTX hypocalcemia in ESRD patients. A clinical protocol utilizing this iPTH level for risk stratification to determine frequency of calcium level monitoring and calcium and vitamin D supplementation in the peri operative period may help reduce the risk of hypocalcemia.

TH-PO153
Long-Term Effects of Hypercalcemia in Kidney Transplant Recipients with Persistent Hyperparathyroidism
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Background: Hypocalcemia is prevalent in kidney transplant recipients (KTRs) with hyperparathyroidism. However, its long-term impact on graft function is uncertain.

Methods: Prospective cohort study investigating adverse graft outcomes associated with persistent hypercalcemia (free calcium >5.2 mg/dL in a s80% of measures) and inappropriately elevated PTH (>30 pg/mL) in KTRs. Asymptomatic mild hypercalcemia was observed unless complications developed.

Results: We included 385 KTRs. During a 4-year (IQR 1-8.2) median follow-up, 62% of KTRs presented persistent hypercalcemia. Compared to KTRs without hypercalcemia, there were no significant differences in graft dysfunction (10% Vs. 12%, p=0.61), symptomatic ureolithiasis (5% Vs. 3%, p=0.43), biopsy-proven calcium deposits (6% Vs. 5%, p=1.0), fractures (6% Vs. 4%, p=0.64), and a composite outcome of ureolithiasis, calcium deposits, fractures, and parathyroidectomy indication (10% Vs. 5%, p=0.55) in subjects with persistent hypercalcemia. In a subset of 76 KTRs, those with persistent hypercalcemia had higher urinary calcium (median 84 [43-170] mg/38 [24-64] mg/day, p=0.03) and iFGF23 (median 36 [24-54] Vs. 27 [19-40] pg/mL, p=0.04) levels, and lower 25D levels (11.3±1.2 Vs. 16.3±1.4 ng/mL, p=0.001). An iPTH level <300 pg/mL was associated with a reduced risk of post-transplant hypercalcemia in a multivariate analysis (OR 0.51, 95% CI 0.32-0.80).

Conclusions: Long-term persistent mild hypercalcemia, with inappropriately elevated iPTH, was frequent in KTRs after transplantation. This condition closely resembled a mild form of primary hyperparathyroidism, with hypophosphatemia and hypovitaminosis D as well as increased urinary calcium and iFGF23 levels. Despite these symptoms, the risk of adverse graft outcomes was low.
Methods: A cross-sectional retrospective observational study of all KTR at our centre between 2020 and 2022. Clinical data collected from electronic patient records including medications were grouped into; Cinacalcet, Alfacalcidol, Vitamin D3(VitD3) and/or combinations of these for treatment of MBD. The length of time KTR were on these medications and biochemical data was collected. Paired t-tests and ANOVA were used for the statistical analysis with an α level of 0.05. Significant differences were 2.5% and 0.05. Calcium adjusted (CA) levels were lower in the Alfacalcidol+VitD3 and VitD3 groups alone (0.20±0.16). Mean phosphate levels remained unchanged. Phosphate binders were used in all groups except Cinacalcet and Vitamin D3.

Results: There were 309 KTR between 2021-2022. 9 were excluded due to missing data. 275 male, 225 female with a median age 56yrs (21-87yrs). 500 KTR; 2% were on Cinacalcet, 4% Cinacalcet+Alfacalcidol, 1% Cinacalcet+Alfacalcidol+VitD3, 30% Alfacalcidol and 15% Alfacalcidol+VitD3; 21% VitD3 and 27% on none. Mean time after transplantation was; 8.1yrs, 6.4yrs, 7.1yrs, 7.7yrs, 10.6yrs, 10.7yrs and 10.9yrs, respectively. Mean Creatinine was significantly different between the 2021 and 2022 in the different treatment groups (p>0.04) with no significant changes in mean GFR. Mean levels for groups except a sole decrease in patients on Cinacalcet+Alfacalcit or Cinacalcit or Alfacalcit+VitD3 had the highest creatinine’s that decreased from 2021 to 2022. Mean PTH (pmol/L) levels decreased from 2021-2022 in all of the groups (11.7-10.7, 36.4-12.7, 71.8-61.3, 16.2-13.1, 12.8, 9.0, 9.7-8.5, respectively, p<0.05). Calcium adjusted (CA) levels were lower in the Alfacalcidol+VitD3 and VitD3 groups alone (0.20±0.16). Mean phosphate levels remained unchanged. Phosphate binders were used in all groups except Cinacalcet and Vitamin D3.

Conclusions: A range of combination therapies are used for MBD management. We propose a de-escalation of therapy post transplantation guidance will reduce polypharmacy. Limitation is a single centre experience.

TH-PO155
Bone Disease in Kidney Transplantation: How Are the Bones of Long-term Kidney Transplant Recipients? Italo R. Alves, Ana Paula Gueiros, Jose E. Gueiros, Hospital das Clinicas, Recife, Brazil.

Background: Kidney transplant (KT) recipients may present persistent chronic kidney disease mineral and bone metabolism disorder (CKD-MBD), changes in bone turnoversecondary to immunosuppression, de-novo MBD, and age-related bone loss. The aim of this study was to assess the osteometric profile and factors associated with loss of bone mass in long-term transplant patients.

Methods: This was a cross-sectional, retrospective study. Clinical parameters assessed were: age, sex, CKD etiology, dialysis time, KT time, donor type, and immunosuppression. Laboratory tests: intact parathyroid hormone (iPTH pg/dL), calcium, phosphorus, total alkaline phosphatase, 25OH vit D, creatinine and glomerular filtration rate (GFR). Bone mineral density was assessed using densitometry. According to the T-score, patients were divided into two groups: osteoporosis (T-score ≤ -2.5) and non-osteoporosis (T-score > -2.5). A comparative analysis between groups was performed; univariate and multivariate analyses were undertaken to determine the risk factors for osteoporosis.

Results: We studied 38 patients (60.5% female), with a median age of 57 years, 74% with CKD of undetermined etiology, the median time of dialysis 71 months. Seventy-one percent of KT were from deceased donors and the median time of KT was 181 months. The median GFR was 54 mL/min. The median T-score in the femoral neck and lumbar spine were -1.9 and -2.5, respectively. Twenty patients (52.6%) presented osteoporosis. Patients with and without osteoporosis were distinguished by: age (62 ± 50; p=0.002), KT time (252 ± 45; p=0.009), iPTH (131 ± 234; p=0.034) and use of tacrolimus (35% ± 72%; p=0.025). Univariate analysis revealed that age (OR: 1.13; p=0.004), KT time (OR: 1.01; p=0.047) and use of tacrolimus were associated with osteoporosis. In the multivariate analysis, only age (OR: 1.12; p=0.025) was an independent risk for osteoporosis. We observed a positive correlation between iPTH and the T-score, in the lumbar spine (R 0.25; p=0.028) and in the femoral neck (R 0.35; p=0.003).

Conclusion: In long-term kidney transplant recipients, we observed a high prevalence of osteoporosis and confirmed that the loss of bone mass is determined by aging. In the late phase of KT, lower iPTH levels seem to be more associated with loss of bone mass.

TH-PO156
Efficacy of Cinacalcet in the Treatment of Persistent Hyperparathyroidism in Late Kidney Transplantation Italo R. Alves, Ana Paula Gueiros, Jose E. Gueiros. Hospital das Clinicas, Recife, Brazil.

Background: Despite the recovery of renal function after a successful kidney transplant (KT), 20 to 50% of patients present with persistent hyperparathyroidism (PHPT) at the end of the first year, with a low chance of spontaneous remission over time. Permanently high levels of parathyroid hormone (PTH) (PTH) causes hypercalcemia, hyperphosphatemia, and increased serum levels of calcium and parathyroid hormone (PTH). In patients with PHPT, the long-term use of cinacalcet, a calcimimetic agent, has been shown to improve bone mineral density (BMD), decrease serum phosphorus levels, and reduce fracture risk.

Methods: This was a retrospective observational study. The definition of PHPT was: intact PTH (iPTH) >100 pg/dL and calcium (Ca) >10.5 mg/dL, in patients with glomerular filtration rate (GFR) <30 mL/min/1.73 m2. The median time of dialysis was 72 months. The primary outcome was evaluated by the percentage of patients who achieved target levels of iPTH and calcium (Ca) using intention-to-treat analysis. The secondary outcomes were: age, sex, etiology of chronic kidney disease (CKD), diabetes, smoking status, and BMI. Laboratory tests were performed at baseline and every 3 months.

Results: The mean age was 61 years old, and the median time of dialysis was 72 months. Seventy percent of patients had target levels of iPTH and calcium (Ca) at baseline. The mean percentage of patients who achieved target levels of iPTH and calcium (Ca) at 3, 6, 9, and 12 months were 41%, 52%, 63%, and 72%, respectively. The median time of dialysis was 72 months. The primary outcome was evaluated by the percentage of patients who achieved target levels of iPTH and calcium (Ca) using intention-to-treat analysis. The secondary outcomes were: age, sex, etiology of chronic kidney disease (CKD), diabetes, smoking status, and BMI. Laboratory tests were performed at baseline and every 3 months.

Conclusion: Cinacalcet proved to be effective and safe in the treatment of PHPT, even after almost a decade of KT. Our results suggest that the initial iPTH levels seem to influence the response to cinacalcet.
Bone and Mineral Metabolism: CKD-MBD Updates

So-young 

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Patients on Dialysis by Vascular Calcification?

Is the Discordance Between Spine and Hip Bone Mineral Density in Models: 1) unadjusted; 2) +socio-demographics; 3) +comorbidities & clinical variables; 4) +calcium & phosphorus.

TH-PO159

Is the Discordance Between Spine and Hip Bone Mineral Density in Patients on Dialysis by Vascular Calcification?

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Background: End-stage kidney disease (ESKD) patients with long-standing maintenance dialysis had at greater risk of developing vascular calcification, osteoporosis and cardiovascular disease. In general population, many studies had undergone to identify the association between vascular calcification and bone mineral density (BMD). However, the pathophysiology of vascular calcification in dialysis patients is different from general population, and the study evaluating relationship of vascular calcification with bone mineral density is scarce. In addition, it is not well-known that which bone is more affected to vascular calcification. Therefore, we aimed to evaluate the association between BMD and vascular calcification in patients with maintenance dialysis.

Methods: In this multicenter, prospective, observational study of ESKD study, 576 patients with older than 50 years old or menopausal state of women were analyzed. Vascular calcification was measured by Kaupplia score and BMD of lumbar spine and hip was measured by dual-energy X-ray absorptiometry. Using T-scores, association of vascular calcification with each site of BMD (femur, spine, and lowest score of either femur or spine) was evaluated. Additional analysis with discordance between hip and spine BMD was also performed.

Results: Among 268 (46.5%) women patients, 242 (90.3%) were menopausal state. Median age of study participants was 63.0 (57.0-70.0) years. Spine BMD showed negative correlation with vascular calcification (R=0.1, P=0.014), but hip and lowest score of both BMD were not significant (R=-0.051, P=0.02; R=-0.029, P=0.49, respectively). 282 (52%) patients were concordance between hip and spine BMD, and correlation was not significant in all the hip, spine, and lowest score of both BMD (R=0.0034, P=0.95; R=0.073, P=0.62; R=0.0337, P=0.95, respectively). In discordance group, spine BMD was also negatively correlated (R=-0.19, P=0.0023) and hip BMD was positively correlated (R=-0.12, P=0.053), with more prominent in low BMD of less than -2.5 (R=-0.22, P=0.048).

Conclusions: In dialysis patients with discordance BMD, vascular calcification is positively associated with hip BMD (especially in low BMD of less than -2.5) and negatively associated with spine BMD.

TH-PO160

Efficacy and Side Effects of Denosumab for Stage 3b-4 CKD Patients with Osteoporosis: An Open-Label, Prospective Pilot Clinical Study

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Background: We sought to evaluate the efficacy and safety of denosumab, including denosumab-induced hypoglycemia, in patients with chronic kidney disease (CKD) stage 3b-4 and osteoporosis. We also aimed to evaluate whether denosumab affects coronary artery calcium score (CAC) in these patients.

Methods: A total of 27 female patients with CKD stage 3b-4 and osteoporosis were enrolled. Twenty patients received denosumab plus calcium carbonate and vitamin D, and 7 control patients received calcium carbonate and vitamin D for 1 year. Osteoporosis was confirmed by using dual-energy X-ray absorptiometry (DXA). Coronary multi-detector CT was performed to calculate the coronary calcium score.

Results: No significant differences were found in medication history, demographics, eGFR, BMI, lumbar and hip BMD, bone turnover markers, 25(OH)D, homocysteine, CAC between the two groups at baseline. There was significant improvement of BMD in the denosumab treatment group. Lumbar spine, femur neck, total hip T score increased by 5.6±5.9%, 3.6±3.2%, 3.4±3.8% respectively, from baseline in the denosumab-treated group, while, 2.7±3.9%, -0.7±4.4%, -1.9±2.1% changes were observed in the control group. (Lumbar: P=0.273, femur neck: P=0.033, total hip: P=0.001). Among bone turnover markers, the percent change in bone ALP and CTX was -31.3±30.0% and -49.2±29.9% in the denosumab treatment group and -4.5±32.0% and -17.7±28.0% in the control group (ALP: P=0.027 and CTX: P=0.025). PTH level change were not different between two groups (denosumab; 9.0±8.1% vs. control: -0.7±7.4%, P=0.580). There were no significant changes in calcium, phosphorus, and PTH levels throughout the study. CAC, and homocysteine percent change did not differ between groups (CAC, P=0.563 and homocysteine; P=0.143).

Conclusions: Denosumab has provided significant benefits without hypocalcemia for 1 year in patients with stage 3b-4 CKD when used judiciously. However, denosumab treatment did not affect homocysteine and CAC in these patients.

Funding: Private Foundation Support

TH-PO161

International Variations in Serum PTH and Calcium Levels and Their Mortality Associations in Peritoneal Dialysis Patients: Results from PDOPPS

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Background: Mineral bone disorder (MBD) in chronic kidney disease (CKD) is associated with high symptom burden, fractures, vascular calcification, cardiovascular disease, and increased morbidity and mortality. CKD-MBD studies have been limited in peritoneal dialysis (PD) patients. Here, we describe calcium and parathyroid hormone (PTH) control, and mortality associations in PD patients.

Methods: We used data from 8 countries [Australia and New Zealand (ANZ), Canada, Japan, Thailand, South Korea, United Kingdom, United States (US)] participating in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS; 2014-2022) among patients receiving PD for >3 months. We analyzed the association of baseline PTH and albumin-adjusted calcium (calcium) with all-cause mortality using Cox regression, adjusted for potential confounders.

Results: Mean age ranged from 54.6 yrs in South Korea to 63.5 yrs in Japan. PTH and serum calcium were measured at baseline in 12,642 and 14,244 patients, respectively. Median PTH ranged from 161 (Japan) to 363 pg/ml (US); mean calcium ranged from 9.1 (South Korea, US) to 9.8 mg/dL (ANZ). The PTH/mortality relationship was U-shaped with lowest risk at PTH 300-599 pg/mL. Mortality was nearly 20% higher at serum calcium >9.6 mg/dL vs 8.4-9.6 mg/dL.

Conclusions: A large proportion of PD patients in this multi-national study have Ca and/or PTH levels in ranges associated with substantially higher mortality. These observations point to the need to substantially improve MBD management in PD to optimize patient outcomes.

Funding: Commercial Support - Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/AboutUs/Support.aspx.

TH-PO162

Serum Parathormone Trajectory During the First Year of Hemodialysis: A Roadmap to Severe Hyperparathyroidism

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Background: Previous studies have shown that uncontrolled hyperparathyroidism is more common in patients that initiate dialysis therapy with high parathormone (PTH). In Brazil, optimal control of PTH is challenging and many patients are in waiting lists for parathyroidectomy (PTX). However, data on PTH levels during dialysis initiation and its behaviour during the first year of therapy is still scarce. We hypothesized that high PTH

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

Underline represents presenting author.
levels at beginning of therapy, as well as poor control of CKD-MBD parameters would contribute to the high percentage of severe forms of hyperparathyroidism in prevalent patients on hemodialysis.

Methods: We included 1,973 individuals starting therapy between Feb 1, 2012, and Dec 31, 2016, who completed 1 year of dialysis. Data evaluated included age, sex, race, glomerular filtration rate (GFR), and last eGFR. CKD was defined using the KDIGO staging algorithm. CKD-MBD was defined according to KDIGO guidelines (Blood Purif 2012;34:1-166). The study population was divided into four groups: (1) normoalbuminuric, (2) microalbuminuric, (3) macroalbuminuric, and (4) not defined (eGFR <45 ml/min/1.73 m²). We defined IIHPT using the KDIGO guidelines (Blood Purif 2012;34:1-166).

Results: In Group I, serum iPTH decreased from 1482.5 ± 607.2 to 43.2 ± 81.6 pg/mL. At week 1, patients with IIHPT (n=150) showed similar iPTH values (150-600) and >600 pg/mL, which were 28.1%, 53.5% and 18.4%, respectively, at the study entry and 30.7%, 52.5% and 16.8% after 1 year of follow-up. Patients with a baseline PTH >600 pg/mL, 44.9% and 10.2% reached 150-600 and <150 pg/mL, respectively, but 44.9% remained with high serum PTH >600 pg/mL. Patients with PTH >600 pg/mL, at 12 months were younger, mostly non-white and financed by Public Health System, less likely to have diabetes. In addition, they had higher PTH, phosphate, alkaline phosphatase, and albumin serum levels at baseline. Multivariate analysis confirmed that age (CI 0.981 (0.973-0.990)), diabetes (CI 0.395 (0.845-0.790)), baseline alkaline phosphatase (CI 1.003 (1.001-1.004)), and baseline PTH=600 (CI 0.003 (1.055-5.325)) were independently associated with uncontrolled PTH after 1 year of therapy.

Conclusions: A considerable proportion of dialysis patients in Brazil initiate therapy with high PTH levels, indicating a poor control during conservative management. Also, the inadequate management of medically therapy during the first year of dialysis might expose high number of individuals to a risk of future need of PTX.

Funding: Government Support - Non-U.S.

TH-PO163
Serum Magnesium Levels and Cognitive Function in Hemodialysis Patients: A Cross-Sectional Study
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Background: Dementia is a global challenge for geriatric care and social welfare, including for aging dialysis patients. Previous studies have suggested a potential association between cognitive function and chronic kidney disease-mineral and bone disorder (CKD-MBD). The present study aims to evaluate this association among patients with CKD-MBD.

Methods: We conducted a cross-sectional study of patients with hemodialysis to examine the association between cognitive functions, as assessed by the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), and serum magnesium, intact parathyroid hormone (PTH), 25-hydroxyvitamin D (25(OH)D), Fibroblast Growth Factor (FGF)-23, and soluble osteocalcin (s-OC). Results: This study involved 390 patients whose median age was 74 (70-80) years and who had received hemodialysis for an average of 87 (36-168) months. The mean serum magnesium level was 2.4 ± 0.9 mg/dL, and the mean intact PTH and 25-OH levels were 157 (94-238) pg/mL and 14.1 (10-19.6) ng/mL. The median intact FGF-23 and soluble s-OC levels were 1921 (602-4840) pg/mL and 381 (300-517) pg/mL, respectively. The median MOCA and MMSE scores were 25 (22-26) and 28 (26-29). The MoCA and MMSE scores were significantly higher cognitive function is preserved in patients with higher magnesium levels than lower magnesium after adjusted multivariate analysis (β coefficient [95% confidence interval], 0.09 [0.01; 0.17]; P < 0.003 for MOCA, and 0.82 [0.13; 1.5]; P = 0.019 for MMSE). There were no significant correlations between cognitive functions and serum intact PTH, 25(OH)D, FGF-23, and soluble s-OC levels.

Conclusions: Higher serum magnesium levels were associated with preserved cognitive function in hemodialysis patients, and avoiding hypomagnesemia may be recommended for good cognitive function. On the other hand, no significant associations were observed between cognitive functions and serum intact PTH, 25(OH)D, FGF-23, and soluble s-OC levels.

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

TH-PO164
Marrow Adipocytes Do Not Suppress Mineralization by Osteocytes in Hemodialysis Patients
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Background: Increased marrow adipocytes induce low bone turnover in non-CKD and CKD subjects (Bone Rep. 21, Endocr Rev. 19). And bone marrow adiposity is increased in CKD subjects (Osteoporos Int. 15). It was revealed recently that the osteocyte plays the important roles which affect bone turnover and osteocytic pericellular/canalicular turnover in dialysis patients (Bone. 18, Kidney Int. 18, JBMR Plus. 19). In this research, the relationship between marrow adiposity and mineralization by osteocytes after parathyroidectomy for secondary hyperparathyroidism (IIHPT) was investigated in hemodialysis (HD) patients.

Methods: Thirty one HD patients with IIHPT, including Group 1 (n=15, Age; 56 ± 6.5 yr, serum intact PTH (iPTH); 1482.5 ± 860.7 pg/mL) and Group II (n=16, Age; 56.7 ± 9.1 yr, duration of HD; 13.4 ± 8.2 yr, serum iPTH; 1330.4 ± 659.2 pg/mL) were investigated. These patients were treated with total parathyroidectomy with immediate autotransplantation (PTX) and received 2mg/day of calcitriol. The patients underwent transiliac bone biopsies before and week 1 and Group I and 4 weeks after PTX. OC,S/BS (%), Ob/S/Bs (%), BFR/BS (mm/mm²/yr), hypomineralized bone area (HM.B.Ar/Br,%), and marrow adipocyte area (Ad.Ar/Ma. Ar,%), were measured in cancellous bone.

Results: In Group I, serum iPTH decreased from 1482.5 ± 607.2 to 43.2 ± 81.6 pg/mL. Oc,S/BS significantly decreased and Ob/S/BS increased after PTX. And Ad.Ar/Ma. Ar increased from 13.6 ± 8.2 to 25.8 ± 12.4 % (p = 0.002) after PTX. In Group II, serum iPTH decreased from 1330.4 ± 659.2 to 26.4 ± 24.8 pg/mL. Oc,S/BS decreased from 4.4 ± 2.7 to 2.0 ± 1.4 % (p = 0.001) after PTX. s-OC also decreased from 22.3 ± 14.0 to 17.2 ± (p = 0.004) after PTX. BFR/BS was significantly lower than that of the other HD patients with IIHPT (n = 14, iPTH; 75.5 ± 341.5 pg/mL) (0.022 ± 0.014 vs. 0.51 ± 0.027 mm²/yr, p = 0.003). HM.B.Ar/Br increased from 17.0 ± 13.5 to 2.8 ± 3.4 % (p = 0.005) although Ad.Ar/Ma. Ar increased from 16.7 ± 11.2 to 26.6 ± 8.3 % (p = 0.001) after PTX in Group II.

Conclusions: Increased marrow adiposity was closely associated with low bone turnover, however, mineralization by osteocytes was not suppressed after PTX.

Funding: Private Foundation Support

TH-PO166
Impact of an EHR Alert on SGLT2 Inhibitor Use in Patients with Type 2 Diabetes (DM2) and CKD
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Background: SGLT2-inhibitors have been shown to reduce the risk of progression to ESRD in patients with CKD. Both KDIGO and ADA strongly recommend that all patients with CKD stages 2 and above should be prescribed an SGLT2-inhibitor. However, SGLT2-inhibitors remain under prescribed, especially amongst non-nephrologists. We implemented a quality improvement project to increase SGLT2-inhibitor prescribing and to narrow the gap between nephrologists and non-nephrologists by developing an EHR alert recommending SGLT2-inhibitors at time of new patient visit.

Methods: This was a quality improvement project in which an EHR alert targeting DM2 patients with last eGFR between 30 and 60 ml/min and last ACR > 300 was rolled out on 6/22/2021. Inclusion criteria for the EHR alert were age 18-85, CKD G3
with last eGFR between 30-59 ml/min, most recent ACR > 300 mg/gm or PCR > 0.5 within past 12 months, and on ACEI or ARB or intolerance. Data was deidentified and collected cross-sectionally monthly from a diabetes registry and reviewed quarterly. We tracked SGLT2 inhibitor use within 1 year of index date. SGLT2-inhibitor use was compared to patients with eGFR > 60 ml/min with ACR > 300 mg/gm who were not included in the EHR alert.

Results: Prior to the EHR alert, SGLT2 inhibitor was prescribed at a higher rate in patients managed by nephrology vs. patient not managed by nephrology (28.5% vs. 10.7%). By 8 months after its rollout, this gap had increased further (44.5% vs. 16.5%). Prior to EHR alert, SGLT2 inhibitors were prescribed in 18.6% of patients with eGFR between 30 to 60 ml/min and ACR > 300 mg/gm vs. 10.2% in patients with eGFR ≥ 60 ml/min and ACR > 300 mg/gm. By 8 months afterwards, this had increased to 32% and 15.7%, respectively. Amongst patients not followed by nephrology, SGLT2 inhibitor was prescribed in 13% of patients with eGFR between 30 to 60 ml/min and ACR > 300 mg/gm vs. 9.4% in patients with eGFR ≥ 60 ml/min and ACR > 300 mg/gm prior and 23.6% vs. 13.3% by 8 months after the EHR alert.

Conclusions: We saw a greater increase in SGLT2 inhibitor prescribing in patients with CKD targeted by an EHR alert compared to patients not targeted by an EHR alert. However, overall SGLT2 prescribing remained low and we were unable to close the gap between patients managed and not managed with nephrology.

TH-PO167

Trajectory of Glomerular Filtration Rate Decline and Fluctuation in Albuminuria Leading to ESKD: An Observational Cohort Study of Biopsy-Confirmed Diabetic Kidney Disease
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Background: Data on trajectory of kidney function decline and fluctuation in albuminuria leading to end-stage kidney disease (ESKD) is sparse in patients with type 2 diabetes.

Methods: Using data from an observational study of biopsy-confirmed diabetic kidney disease (DKD), panel data analyses were performed to quantify patterns of trajectory of estimated glomerular filtration rate (eGFR) decline to ESKD associated with repeated measures of urine albumin-to-creatinine ratio (ACR).

Results: During a median follow-up of 3.25 years, 156 out of 312 developed ESKD. Among them, 84.0% showed a curvilinear pattern of eGFR trajectory, 62.2% moved into a different albuminuria status from that at baseline, and 84.6% of patients developed nephrotic-range albuminuria, many of whom remained nephrotic. Mixed-effects models for repeated measures showed that speed of eGFR decline for normo- [ACR <30 mg/g], micro- [ACR 30 to <300 mg/g], macro- [nephrotic range albuminuria] [ACR ≥3000 mg/g] and nephrotic-range albuminuria [ACR ≥3000 mg/g] were -5.52 (95% CI, -7.79 to -3.26; P < 0.001) and -4.76 (95% CI, -8.94 to -0.57; P = 0.026), -6.39 (95% CI, -8.31 to -4.48; P < 0.001) and -9.51 (95% CI, -11.75 to -7.28; P < 0.001) ml/min/1.73 m²/year, respectively.

Conclusions: Majority of patients with biopsy-confirmed DKD who developed ESKD showed a curvilinear eGFR trajectory with fluctuation in ACR. Although there were high inter- and intra-individual variability in changes in eGFR and ACR, ACR were inversely associated with eGFR decline, which suggests that close monitoring of ACR fluctuation over time instead of a single assessment of ACR may be necessary to detect eGFR decline to ESKD.

TH-PO168

AWARD-7 Post Hoc Analysis: Circulating Proteins Measured by Joslin Kidney Panel Identify Dulaglutide Responders
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Background: The AWARD-7 trial demonstrated that the glucagon-like peptide-1 receptor agonist (GLP1-RA) dulaglutide (DULA) can slow the decline in estimated glomerular filtration rate (eGFR) in diabetic patients with chronic kidney disease (CKD). Previously we’ve identified 21 circulating proteins (Joslin Kidney panel – JKP) that are associated with progression to end-stage kidney disease (Kobayashi et al. 2022). We aimed to investigate whether we could leverage the JKP to discern between patients for whom DULA is associated with reduced odds of rapid eGFR decline from those with no impact.

Methods: Plasma samples were obtained from AWARD-7 patients who received DULA 1.5 mg (n=124) or insulin glargine (n=125) for 52 weeks. The 21 JKP was measured using Olink custom-made platform. Proportion of fast decliners (eGFR loss ≥5.0 ml/min/yr) was evaluated according to plasma concentration of the 21 JKP proteins at baseline, 26- and 52-weeks of the trial.

Results: Concentration of 21 JKP proteins at baseline and 52 weeks did not provide information to predict effectiveness of DULA on reduction of fast decliners. Among patients with above median change in protein concentration from baseline to 26 weeks (26 DELTA), DULA was associated with lower odds of rapid eGFR decline compared with glargine. Specifically, 26 DELTA above median for EHNA4, SYND1, TNP-RA1, -R1B, GFRa1, or DULA was associated with significantly lower odds of fast eGFR decline in DULA arm. There was no difference between treatments in patients with below median change in protein concentration.

Conclusions: DULA arm was associated with lower odds of rapid eGFR decline in patients with the greatest change in 6 circulating risk proteins. Further studies are necessary to validate the use of these JKP proteins as effective biomarkers of treatment responders.

Funding: Commercial Support - Eli Lilly and Company

AWARD-7: Dulaglutide versus placebo in patients with Chronic Kidney Disease and type 2 diabetes: Post-hoc analysis of toenail thickness and associated circulating proteins

AWARD-7: Dulaglutide versus placebo in patients with Chronic Kidney Disease and type 2 diabetes: Post-hoc analysis of toenail thickness and associated circulating proteins

TH-PO169

Renal Autologous Cell Therapy (REACT) to Delay Dialysis in Advanced CKD
Joseph Stavas,1 Bijin Thajudeen,2 Steven G. Coca,3 Randal K. Detwiler,1 Arnold L. Silva,1 Johnna D. Anderson,1 Anna M. Burgner.2 ProKidney, Raleigh, NC; 2Banner University Medical Center Tucson, Tucson, AZ; 3Icahn School of Medicine at Mount Sinai, New York, NY; 4The University of North Carolina at Chapel Hill, Chapel Hill, NC; 5Boise Kidney and Hypertension, Boise, ID; 6Vanderbilt University Medical Center, Nashville, TN.

Background: Few treatments delay CKD progression. Cell-based options may offer destination therapy to preserve kidney function and avoid-delay renal replacement therapy (RRT).

Methods: Adults with Type 2 diabetes (T2DKD) and eGFRs 14-20 ml/min/1.73m² participated in a multisite, FDA-approved phase 2 open label single arm trial (NCT03270956). After a kidney biopsy and ex vivo cell expansion, 2 percutaneous injections of REACT into the renal cortex were performed ~6 months apart. Patients were followed up to 24 months to end of study (EOS) after the last injection. Outcomes

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
included estimated glomerular filtration rate (eGFR) slope change (mixed linear analysis adjusted to dialysis, and adverse events (AEs)).

**Results:** Ten patients were enrolled: 8 White race, 3 Hispanics, 5 Women. The cohort’s mean age was 58.3 ± 5.0 years and BMI 35.2 ± 8.4 kg/m². Nine patients had two injections and selected parameters are displayed in Table 1. Median time to dialysis was 19 months (IQR 13.3-27.9) and two patients were alive and dialysis free at EOS. Pre-injection eGFR slope improved 2.9 and 3.5 ml/min/1.73/m²/year post 1st and 2nd injections. AEs: Six patients progressed to sustained RRT, two deaths occurred without RRT due to COVID-19 pneumonia and diabetes complications with COVID-19. Biopsy-related AEs: 1 each hematomas (no transfusions) and AVF. Injection-related AEs: 6 small/moderate hematomas (no transfusions), 1 each: hematoma, perinephric fluid, anemia, fatigue, and pain. REACT-related AEs: none.

**Conclusions:** REACT was tolerated and preserved function to decelerate eGFR decline, suggesting a non-dialytic treatment option for T2DK progressing to RRT. Phase 3 randomized controlled trials and safety monitoring are underway.

**Funding:** Commercial Support - ProKidney

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**Table 1. Trial parameters**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Baseline (n=2141)</th>
<th>12 months (n=2141)</th>
<th>EOS (n=2141)</th>
</tr>
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<tbody>
<tr>
<td>Serum Cr (mg/dL)</td>
<td>2.3 (2.0-2.7)</td>
<td>3.0 (2.5-3.4)</td>
<td>4.0 (3.5-4.5)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>39.4 (28.3-50.6)</td>
<td>39.4 (30.6-48.1)</td>
<td>30.7 (23.4-41.3)</td>
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<tr>
<td>Thrombin-antithrombin III (ng/mL)</td>
<td>16.9 (12.9-22.9)</td>
<td>18.7 (12.9-26.9)</td>
<td>18.7 (12.9-26.9)</td>
</tr>
<tr>
<td>Fibrinopeptide A (ng/mL)</td>
<td>5.8 (5.0-6.5)</td>
<td>6.0 (5.5-6.5)</td>
<td>6.0 (5.5-6.5)</td>
</tr>
<tr>
<td>β2-microglobulin (μg/mL)</td>
<td>2.9 (2.5-3.4)</td>
<td>3.2 (2.8-3.7)</td>
<td>3.2 (2.8-3.7)</td>
</tr>
<tr>
<td>Albuminuria (mg/mL)</td>
<td>1.0 (0.5-2.0)</td>
<td>1.2 (0.8-2.0)</td>
<td>1.4 (0.8-2.4)</td>
</tr>
<tr>
<td>Calcium (mg/dL)</td>
<td>8.8 (8.6-9.0)</td>
<td>9.0 (8.8-9.3)</td>
<td>9.3 (8.9-9.6)</td>
</tr>
<tr>
<td>PFG (IU/L)</td>
<td>230 (190-290)</td>
<td>250 (230-280)</td>
<td>270 (250-300)</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>10.4 (10.0-10.9)</td>
<td>10.5 (10.0-10.9)</td>
<td>11.3 (10.9-11.8)</td>
</tr>
</tbody>
</table>

**Circulating Proteins Protein Against Fast Kidney Function Decline and ESKD in Early Diabetic Kidney Disease**

**Methods:** We followed 294 subjects (45% female) with T1D from Joslin Proteinuric Cohort (JPC) with uACR >80 mg/g with normal baseline kidney function (median GFR 100 ml/min). We conducted a replication study in an independent cohort of 162 Pima Indians with T2D and very early stage of DKD (median GFR 149 ml/min); 105 subjects had research kidney biopsies obtained in close proximity to baseline examination. We quantified 590 proteins in baseline plasma samples using the SOMAscan platform.

**Results:** In the Joslin cohort, 39% subjects reached the composite outcome of ESKD or 40% GFR loss within 10 years. Sixty-two (38%) of Pima subjects developed the composite outcome. In univariable logistic model, 54 proteins were significantly associated (Bonferroni-corrected) with protection against kidney failure/decline in the Joslin T1D cohort. Ten proteins were replicated in the Pima T2D cohort. Odds ratios remained significant after adjustment for key confounders. Proteins were clustered into 3 groups. A three-marker panel (FGF17, BMP10, PRLR) was derived and this panel, with added clinical parameters, significantly improved prediction of the composite outcome (c=0.852, p=0.026). BMP10 had significant positive correlations with podocyte density (r=0.30) and filtration slit frequency (r=0.21), and inverse correlations with global glomerular sclerosis (r=–0.28), mesangial fractional volume (r=0.21) and podocyte foot process width (r=0.20). Kidney transcriptomic profiles suggest a non-kidney source of circulating protective proteins.

**Conclusions:** In two independent cohorts with different types of diabetes and racial groups, we identified ten plasma proteins in early DKD associated with no/slow progression to ESKD, which may be therapeutic targets for delaying or preventing the onset of ESKD.

**Funding:** NIDDK Support

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**Evaluation of Extracellular Matrix Turnover Proteins as Risk Markers in Persons with Type 2 Diabetes and Microalbuminuria**

**Methods:** We followed 294 subjects (45% female) with T1D from Joslin Proteinuric Cohort (JPC) with uACR >80 mg/g with normal baseline kidney function (median GFR 100 ml/min). We conducted a replication study in an independent cohort of 162 Pima Indians with T2D and very early stage of DKD (median GFR 149 ml/min); 105 subjects had research kidney biopsies obtained in close proximity to baseline examination. We quantified 590 proteins in baseline plasma samples using the SOMAscan platform.

**Results:** In the Joslin cohort, 39% subjects reached the composite outcome of ESKD or 40% GFR loss within 10 years. Sixty-two (38%) of Pima subjects developed the composite outcome. In univariable logistic model, 54 proteins were significantly associated (Bonferroni-corrected) with protection against kidney failure/decline in the Joslin T1D cohort. Ten proteins were replicated in the Pima T2D cohort. Odds ratios remained significant after adjustment for key confounders. Proteins were clustered into 3 groups. A three-marker panel (FGF17, BMP10, PRLR) was derived and this panel, with added clinical parameters, significantly improved prediction of the composite outcome (c=0.852, p=0.026). BMP10 had significant positive correlations with podocyte density (r=0.30) and filtration slit frequency (r=0.21), and inverse correlations with global glomerular sclerosis (r=–0.28), mesangial fractional volume (r=0.21) and podocyte foot process width (r=0.20). Kidney transcriptomic profiles suggest a non-kidney source of circulating protective proteins.

**Conclusions:** In two independent cohorts with different types of diabetes and racial groups, we identified ten plasma proteins in early DKD associated with no/slow progression to ESKD, which may be therapeutic targets for delaying or preventing the onset of ESKD.

**Funding:** NIDDK Support
smoking, Hba1c, plasma creatinine, systolic blood pressure and UAE (p<0.15). None of the other markers were associated with CKD progression (p>0.20), and none of the markers were associated with mortality (p>0.11) or CVD (p>0.19).

Conclusions: In this cohort of individuals with T2D and microalbuminuria, higher level of a degradation product of collagen type I (C1M) was associated with CKD progression, but not independent of other risk factors. None of the extracellular matrix turnover proteins were associated with risk of CVD or mortality.

Funding: Private Foundation Support

TH-PO173
Plasma Biomarkers and Mortality Among REGARDS Participants with Diabetes and CKD
Teresa K. Chen,1,2 Michelle M. Estrella,1,2 Ronit Katz,2 Mark J. Sarnak,4 Morgan Grajs,3 Mary Cushman,7 Chirag R. Parikh,4 Orlando M. Gutierrez,2 Joachin H. L.2,1 Michael Shlipak,1,2 CKD Biomarkers Consortium.
1University of California San Francisco, San Francisco, CA; 2San Francisco VA Health Care System, San Francisco, CA; 3University of Washington, Seattle, WA; 4Tufts Medical Center, Boston, MA; 5New York University, New York, NY; 6Johns Hopkins University, Baltimore, MD; 7The University of Alabama at Birmingham, Birmingham, AL; 8University of California San Diego, La Jolla, CA; 9University of Vermont, Burlington, VT.

Background: Individuals with diabetes and chronic kidney disease (CKD) are at increased risk of death but their clinical course varies. We aimed to determine whether six plasma biomarkers of kidney injury, inflammation, and repair further captured mortality risk.

Methods: Among a cohort of REGARDS participants with diabetes and creatinine-based eGFR (eGFRcr) <60 ml/min/1.73 m2, and median UACR was 32 mg/g. Diabetic Kidney Disease: Clinical - I

Results: In this cohort of individuals with T2D and microalbuminuria, higher level of a degradation product of collagen type I (C1M) was associated with CKD progression, but not independent of other risk factors. None of the extracellular matrix turnover proteins were associated with risk of CVD or mortality.

Funding: Private Foundation Support

TH-PO174
Identification of Circulating Metabolites to Predict Cardiorenal Outcomes in Patients with Type 2 Diabetes (T2D)
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Background: Individuals with type 2 diabetes mellitus (T2D) are at elevated risk of adverse cardiorenal outcomes. Additional biomarkers are needed to better identify patients at highest risk of adverse outcomes and to better understand pathways associated with risk. We examined if baseline plasma metabolites predict renal and cardiovascular (CV) outcomes in the Canagliflozin Cardiovascular Assessment Study (CANVAS) participants with T2D at high cardiovascular risk.

Methods: Plasma metabolites were assayed from a subset of the CANVAS study participants by HILIC (HILIC & AMIDE)-mass spectrometry using targeted assays. Cox proportional hazard regression analysis was used to examine the association of 105 baseline metabolites with the renal outcome (40% eGFR decline, end-stage kidney disease, or renal death), and CV outcomes including heart failure, heart failure and CV death, and MACE. The predicted hazard ratio (HR) for a 1-unit increase in the log metabolite values, 95% confidence intervals, and p-values were calculated. Results were calculated overall and broken out by treatment when a significant treatment interaction was observed.

Results: We included 934 (22%) of the 4,330 CANVAS participants. The Figure below shows a summary of the metabolites across the renal and CV outcomes where a 1-unit increase in the log metabolite was associated with either increased or decreased risk in a fully adjusted model, (age, gender, race, BMI, HbA1C, cholesterol, blood pressure, history of heart failure, baseline ACR and eGFR).

Conclusions: A number of metabolites were identified and associated with higher or lower risk of cardiorenal outcomes. Further research is required to better understand and validate these findings.

Funding: Commercial Support - Janssen Research & Development, LLC.

TH-PO175
Global Proteomic Search for Circulating Proteins Associated with Albuminuria in Patients with Diabetic Kidney Disease
Sok Cin Tye,1 Helen C. Looker,2 Zaipul Md Dom,1 Eiichiro Satake,1 Joseph Ricca,1 Robert G. Nelson,2 Andrzej S. Krolevski,1 Section of Genetics and Epidemiology, Joslin Diabetes Center. 1Joslin Diabetes Center, Boston, MA; 2Chronic Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ.

Background: Fast kidney function decline and the presence of albuminuria are traditional predictors of progression to end-stage kidney disease (ESKD) in patients with diabetic kidney disease (DKD). In this study, we aim to identify circulating proteins associated with albuminuria in patients with DKD and to compare them with 46 novel proteins associated with fast kidney function decline previously reported by us [1].

Methods: Using the SOMAscan proteomics platform, we measured the baseline concentrations of 550 circulating proteins in participants with type 1 diabetes from the Joslin Kidney Cohort (JKC, N=294), and with type 2 diabetes from the Pirna Indian cohort (N=162). Spearman rank correlation was used in an untargeted analysis to assess the association between measured proteins and albuminuria in both cohorts. We used a Venn diagram to describe proteins contributing to the development of albuminuria and/or ESKD.

Funding: National Institutes of Health - National Institute of Diabetes andDigestive and Kidney Diseases (NIDDK).
Results: In the JKC and Pima Indian cohorts, 196 proteins (P<0.00001) and 55 proteins (P<0.001), respectively, were associated with albuminuria; 31 of them were common to both cohorts. Comparing these 31 proteins to the 46 proteins associated with the risk of progression to ESKD, we identified 13 proteins associated with both outcomes (Figure 1).

Conclusions: Our findings indicate that the underlying disease processes for albuminuria and progressive kidney function decline are very different. Only a few circulating proteins are common indicators for both processes. References: 1. Kobayashi, H., et al., Results of untargeted analysis using the SOMAscan proteomics platform indicates novel associations of circulating proteins with risk of progression to kidney failure in diabetes. Kidney Int. 2022. 102(2): p. 370-381.

TH-PO176
Baseline and Short-Term Change of Concentration of Plasma Proteins Measured by Joslin Kidney Panel and Progression to ESKD in the Chronic Renal Insufficiency Cohort (CRIC)
Hiroki Kobayashi,1 2 Zaipul Md Dom,1 Eiichiro Satake,1 James P. Lash,2 Andrzej S. Krolewski,1 3 Joslin Diabetes Center, Boston, MA; 4 University of Illinois Chicago, Chicago, IL; 5 NIH-National University School of Medicine, Tokyo, Japan.

Background: The Joslin Kidney Panel (JKP) of 21 circulating proteins is associated with increased risk of ESKD in patients with diabetes (Kobayashi et al. KI 2022). We evaluated the JKP as a tool for assessing prognosis in Chronic Renal Insufficiency Cohort (CRIC).

Methods: We conducted a case-cohort study involving 218 participants with diabetes and impaired renal function at baseline. Using assays developed by OLINK inc. to measure JKP 21 proteins we quantified concentration of the proteins at Baseline and at follow-up (interval 2 years apart) in study groups; cases were those who progress to ESKD within 10-years (n=89), and controls were those who did not progress to ESKD within 10-years (n=129). We employed logistic regression models to determine the association of baseline concentration, longitudinal (DELTA), and INDEX (Baseline and DELTA) for each biomarker with progression to ESKD.

Results: Higher levels of 19 of 21 proteins at baseline and 20 of 21 DELTAs and INDEXes were statistically and significantly associated with an increased risk of progression to ESKD within 10 years. Among the 20 INDEXes, 5 including TNF-R7, WTDC2, SYND1, KIM-1, and VRL4 remained statistically significant after adjusting for GFR-INDEX and baseline 24-hour urinary protein (24h-UP).

Conclusions: Higher levels of most proteins at baseline, DELTAS, and INDEXES in JKP were significantly associated with increased ESKD risk within 10 years. INDEXes for the 5 proteins were better in prediction of risk of ESKD than GFR-INDEX. Further studies are needed to validate the utility of measuring INDEXes for prediction of ESKD and monitoring the effectiveness of renin-angiotensin therapies. CRIC data was provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases, and this study was supported by a grant from Renality Inc.

Funding: NIDDK Support

TH-PO177
Serum Sphingolipids as Indicators of ESRD Risk in Diabetic Patients
Vismaya J. Kharak,1 Marcus G. Pezzolesi,1 Pezzolesi Lab. 1The University of Utah School of Medicine, Salt Lake City, UT; 2The University of Utah Department of Human Genetics, Salt Lake City, UT.

Background: Chronic kidney disease (CKD) is a complication of diabetes that affects one-third of diabetic patients; 15% of CKD patients with diabetes develop end-stage renal disease (ESRD). Underlying genetic, environmental, and biological factors contribute significantly to CKD risk. Sphingolipids are a class of lipids that have been associated with increased insulin resistance and hepatic steatosis. Through analysis of longitudinal data from participants in Chronic Renal Insufficiency Cohort (CRIC) study and newly generated lipidomic data, this project investigates the potential use of longitudinal serum sphingolipid measurements as an indicator for risk of progression to ESRD.

Methods: We analyzed ESRD outcomes in participants of CRIC with type II diabetes and ESKD (n = 1054). We performed targeted lipidomics measuring 55 sphingolipids in patient serum samples from their fifth CRIC visit. Data from this visit served as the baseline for evaluating time to progression to ESRD and change in serum sphingolipids and glycerophospholipids. Patients with ESKD, deployable through the CRIC dataset were investigated for correlation with all sphingolipids at baseline for a larger cohort of 1618 patients with diabetes and CKD. Each variable was analyzed for correlation with each sphingolipid using a standardized linear regression model; variables were then grouped using hierarchical clustering according to both p-value and adjusted R-squared value.

Results: At baseline, 506 patients had early stage CKD (CKD stages 1-3) and 546 patients had late stage CKD (CKD stages 4-5). 257 of 1054 patients developed ESRD in the range of 517 to 5048 days after the first CRIC visit, with a mean of 2619 days. Serial changes in sphingolipids were significantly (p < 0.05) associated with progression to ESRD; none explained greater than 0.01% of variability. Additionally, we identified 3 clusters of patient health variables that were significantly (p < 0.05) associated with the same sphingolipids and with each other. These clustered health variables included lipid measurements, indicators of kidney function, and quality of life evaluation.

Conclusions: Our analysis indicates that serum sphingolipids measured at baseline are correlated with progression to ESRD. As we continue our analysis, we further investigate the relationship between average sphingolipid measurements over time and rate of progression through CKD stages to ESRD.

Funding: NIDDK Support

TH-PO187
High-Density Lipoprotein Cholesterol (HDLC) Levels May Indicate a Higher Risk of ESRD and All-Cause Mortality in Patients with Type 2 Diabetes Mellitus (T2DM) and CKD
Yutong Zou, West China Hospital of Sichuan University, Chengdu, China.

Background: To investigate the relationship between high-density lipoprotein cholesterol (HDLC) - and all-cause renal disease (ESRD) and all-cause mortality in patients with diabetes mellitus (DM) and chronic kidney disease (CKD).

Methods: We enrolled 375 participants with confirmed diabetic kidney disease (DKD) via renal biopsy between January 2000 and September 2020 in our longitudinal observational study. Additionally, a total of 3,267 participants with DM and CKD from the National Health and Nutrition Examination Survey (NHANES) spanning 1999-2018 were included for the same association between HDLC concentration and all-cause mortality.

Results: Patients were divided into Group 1 (HDL-C<1.03mmol/L), Group 2 (1.55mmol/L-HDL-Ca1.03mmol/L), and Group 3 (HDL-C>1.55mmol/L). Overall, of the 375 participants, after a median follow-up of 36 months, 165 participants (44%) developed ESRD. The Kaplan-Meier curves revealed a higher risk for ESRD among patients in Group 1 (p=0.001). After adjusting for potential confounders, patients in Group 3 were still found to have a significantly higher risk of ESRD compared to patients in Group 1, with an adjusted HR (95%CI) of 1.68 (1.03, 2.71) (p=0.036). Higher levels of HDL3 and lower levels of HDL2 were associated with a higher risk for ESRD. Moreover, a total of 3,262 individuals with both DM and CKD in NHANES 1999-2018 were analyzed. After a median follow-up of 75 months, 1,369 participants (42%) had died. The weighted Kaplan-Meier curves reveal that higher HDLC levels are associated with a higher risk of all-cause mortality (p=0.02). Notably, in patients with CKD stage 1-2, multivariate Cox regression analysis suggests that patients in Group 3 had a significantly higher HR of 1.61 (95%CI: 1.19, 2.19) (p=0.002).

Conclusions: This study identified a significant positive association of high concentration of HDLC with incident ESRD and all-cause mortality in DKD patients. These findings may be different from previous beliefs about the role of HDLC as “good cholesterol”.

TH-PO179
PRO-C3 as a Risk Marker for Kidney Disease Progression and Mortality in Type 1 Diabetes
Marte Opseth Ryve,1 Alexandra L. Moller,2 Viktor Rotbain Curovic,2 Daniel Guldgader Kring Rasmussen,2 Simone Theilade,1,2 Nete Toft,2 Signe A. Winther,1 Federica Genovese,2 Morten A. Karstal,3 Tine Hansen,1 Peter Rossing,1,3 Steno Diabetes Center Copenhagen, Herlev, Denmark; 2Nordic Bioscience, Herlev, Denmark; 3Københavns Universitet, Copenhagen, Denmark.

Background: Kidney fibrosis, a hallmark of diabetic kidney disease, is characterized by interstitial extracellular matrix remodeling, causing excessive collagen deposition. We investigated if biomarkers of collagen type III (PRO-C3), VII (PRO-C7) and XXVIII (PRO-C28) formation, and a fragment of degraded crosslinked collagen type III (CTX-III), were related to kidney disease progression and mortality in people with type 1 diabetes (T1D).

Methods: The biomarkers were measured in serum by ELISA. Endpoints were 1) a composite kidney endpoint including ≥30% decline in estimated glomerular filtration rate (eGFR), onset of kidney failure (eGFR ≤15 mL/min/1.73m², dialysis, or transplantation) and all-cause mortality; and 2) all-cause mortality. Associations between biomarker levels were tested using Cox proportional hazard models after log2 transformation. Hazard ratios (HRs) are reported per doubling and adjusted for age, sex, HbA1c, eGFR, systolic blood pressure, body mass index, smoking, urinary albumin excretion rate, diabetes duration and treatment with a renin-angiotensin-aldosterone system inhibitor.

Results: We enrolled 667 individuals with T1D, 311 with normal (<30 mg/24h), 155 with proteinuria (<30 mg/24h), 155 with diabetes duration and treatment with a renin-angiotensin-aldosterone system inhibitor. We enrolled 667 individuals with T1D, 311 with normal (<30 mg/24h), 155 with proteinuria (<30 mg/24h), 155 with diabetes duration and treatment with a renin-angiotensin-aldosterone system inhibitor. We enrolled 667 individuals with T1D, 311 with normal (<30 mg/24h), 155 with proteinuria (<30 mg/24h), 155 with diabetes duration and treatment with a renin-angiotensin-aldosterone system inhibitor. We enrolled 667 individuals with T1D, 311 with normal (<30 mg/24h), 155 with proteinuria (<30 mg/24h), 155 with diabetes duration and treatment with a renin-angiotensin-aldosterone system inhibitor.
The Influence of Bone on Kidney Disease Progression in Persons with Type 1 Diabetes
Sabina C. Haage,¹ Henrik Øder Hjortkjær,² Frederik Persson,² Peter Rossing,²,³ Ditte Hansen,¹,³ Department of Nephrology, Copenhagen University Hospital – Herlev and Gentofte, Herlev, Denmark; ²Steno Diabetes Center Copenhagen, Herlev, Denmark; ³Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.

Background: The number of patients with chronic kidney disease (CKD) and diabetes is expected to increase. Identification of mechanisms influencing the progression of CKD is of great importance. In CKD, a bone–vascular cross-talk has been described, but if bone influences on kidney function has been sparsely investigated. The aim of this study was to explore the influence of bone-derived factors (sclerostin, Dickkopf-1 (DKK1), and osteoprotegerin (OPG)) on the progression of kidney disease in persons with type 1 diabetes (T1D).

Methods: This was a prospective cohort study. Blood samples from persons with T1D were collected between 2009–2011. Outcomes were: 1) End-stage kidney disease (ESKD) defined as estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m², initiation of dialysis, or kidney transplantation; 2) Progression of albuminuria (from 0-30 mg/day to 30-300 mg/day or from 30-300 mg/day to >300 mg/day); 3) An eGFR decline ≥30%; 4) A composite kidney endpoint consisting of all three endpoints. Kaplan-Meier curves and Cox proportional hazard regression models were used.

Results: Among the 318 persons, the mean age was 56 years, 50% were men, and the median eGFR was 79 mL/min/1.73m². During a median follow-up of 5.5 years, 3.5% met the ESKD endpoint, 6.3% progressed in albuminuria, 18.2% had a decline in eGFR ≥30%, and 21.1% met the composite kidney endpoint. The Kaplan-Meier curves showed no association between sclerostin or DKK1 and kidney disease progression, whereas OPG above median had a lower survival for all endpoints except for albuminuria progression (Figure 1). In unadjusted Cox regression models, sclerostin and DKK1 were significantly associated with ESKD, while OPG was significantly associated with all kidney endpoints except for eGFR decline ≥30%. After adjustment for age, gender, systolic blood pressure, diabetes duration, eGFR, and UACR, only OPG was significantly associated with the composite kidney endpoint (p=0.047).

Conclusions: In this prospective cohort study, OPG, but not sclerostin or DKK1, was associated with progression of CKD, and could have prognostic importance in patients with T1D.

Funding: Private Foundation Support

Levels of Oxidative Stress and Inflammation in Different Degrees of Diabetic Kidney Disease Caused by Diabetes Mellitus Type 2
José J. Gutiérrez Hernandez, Luis A. Salazar Soltero, Javier Soto-Vargas, Juan O. Romero Tafoya, Hugo B. Espinoza, Roxana Villanueva Macedo, Paulina De Niz Hernández, Renato Parra Michel. Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico.

Background: Chronic inflammation is related to its progression and cardiovascular and infectious complications, alterations in the immune response, which translates into a greater risk of morbidity and mortality. Oxidative stress is considered a non-traditional risk factor for all causes of mortality, considering it a prognostic factor and a target for the prevention and treatment of CKD.

Methods: Retrospective observational descriptive study in adult patients >18 years of age, with type 2 Diabetes Mellitus (DM2) and CKD grades 1-5. We included 80 patients diagnosed with diabetic CKD were included and the serum levels of Superoxide dismutase SOD and Malondialdehyde MDA were determined. We classified according to the severity of the disease using KDIGO into three groups: patients with mild, moderate and severe. Plasma SOD levels were determined in patients with CKD, the average SOD was 2.07 ± 0.64. According to

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

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Correlation Between Serum suPAR and Severity of Renal Injury and Renal Function Progression in Diabetic Kidney Disease

Yue Gu,1,2 Jing Zhou,1,2 Ren Y. Ying,1,2 Fengmin Shao,1,2 Henan Provincial People’s Hospital, Zhengzhou, China; Zhengzhou University People’s Hospital, Zhengzhou, China.

Background: To analyze the correlation between serum soluble urokinase Plasminogen Activator Receptor (suPAR) and renal dysfunction in diabetic kidney disease (DKD).

Methods: 152 DKD patients and 105 T2DM patients were recruited. The DKD group were divided into microalbuminuria group (30mg/gUACR < 300mg/g), macroalbuminuria group (UACRA300mg/g). Spearman correlation and partial correlation analysis were conducted to compare the correlation between suPAR and various clinical indicators. End events were defined as Estimated glomerular filtration rate (eGFR) decrease of ≥30%, urinary protein advancement, progress to end-stage renal disease (ESRD) or receive renal replacement therapy. According to the median serum suPAR level, all patients were divided into low-level suPAR group (suPAR < 5.76μg/ml) and high-level suPAR group (suPAR5.76μg/ml). Survival curves were plotted by Kaplan-Meier method, and differences in renal cumulative survival at different serum suPAR levels were measured by Log-rank test. Cox regression analysis was used to analyze the influence factors for renal progression in DKD. The predictive value of suPAR in renal function progression was evaluated by Receiver operating characteristic curve (ROC).

Results: The mean age was 60.30±11.89 years old. SuPAR level in T2DM group was significantly lower than that in microalbuminuria group and macroalbuminuria group (P < 0.05). Serum suPAR in DKD patients was positively correlated with UACR, BUN, Scy, SUA, RBP and CysC (all P < 0.05), and negatively correlated with Hb, Alb, TBL and eGFR (all P < 0.05). Kaplan-Meier survival analysis showed that the cumulative survival rate of kidney in the high-level suPAR group was significantly lower than that in the low-level suPAR group (P < 0.001). The results showed that higher levels of RBP and suPAR, lower levels of ALB were independent risk factors for renal function progression in DKD patients (P < 0.05). The area under ROC curve of suPAR level to predict renal function progression was 0.791, the critical value was 8.15μg/ml, the sensitivity was 66.7%, the specificity was 84.9%.

Conclusions: Serum suPAR level increased in DKD patients, which was positively correlated with the severity of renal impairment. High level of suPAR is an independent risk factor for renal progression in patients with DKD.

Funding: Government Support - Non-U.S.

TH-PO184

Autoantibodies to Erythropoietin Receptor and Clinical Outcomes in Patients with Type 2 Diabetes and CKD: A Post Hoc Analysis of the CREDENCE Trial

Akihiko Koshino,1,2 Brenton L. Neuen,3 Megumi Oshima,2 Tadashi Toyama,1 Akinori Hara,1 Clare G. Arnott,4 Bruce Neal,1 Meg Jardine,3 Sunil Badve,6 Kenneth W. Mahaffey,7 Carol A. Pollock,8 Michael K. Hansen,9 Takashi Wada,2 Hiddo J. Heerspink,5,13 University Medical Center Groningen, Groningen, Netherlands; 4Kanazawa University, Kanazawa, Japan; 3The George Institute for Global Health, Newtown, NSW, Australia; 8Royal Prince Alfred Hospital, Camperdown, NSW, Australia; 6NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; 5University of New South Wales, Sydney, NSW, Australia; 9Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, CA; 2Kolling Institute of Medical Research, St Leonards, NSW, Australia; 7Royal North Shore Hospital, St Leonards, NSW, Australia; 1Janssen Research and Development LLC, Spring House, PA.

Background: Anti-erythropoietin receptor (EPOR) antibodies have been identified in patients with various kidney diseases. This study aimed to determine the effects of canagliflozin on iron parameters in the CREDENCE trial and to determine whether the effects of canagliflozin on anaemia and clinical outcomes were modified by iron deficiency (ID).

Methods: Patients with type 2 diabetes (T2D) and CKD were randomized to canagliflozin 100mg or matching placebo. Serum anti-EPOR antibodies were modified by anti-EPOR antibodies. Canagliflozin reduced CKD progression (HR 0.70, 95% CI 0.56-0.87) regardless of ID.

Results: Of 2600 (59.1%) CREDENCE participants with available samples, 2414 (440%) participants had available serum samples. Canagliflozin, compared to placebo, increased TIBC by 2.1% (95% CI 0.4, 3.8; p=0.01) and decreased ferritin by 11.3% (95% CI 3.1, 15.4; p=0.001) with no clear effect on iron and TSIAT (Figure). At baseline, 92% (2832) participants had ID. Canagliflozin increased hemoglobin over time by 7.3 g/L (95% CI 6.2, 8.5; p=0.001) and 6.7 g/L (95% CI 5.2, 8.2; p<0.001) in patients with and without ID, respectively (p-interaction=0.38). Canagliflozin reduced CKD progression (HR 0.70, 95% CI 0.56-0.87) regardless of ID (p-interaction=0.83).

Conclusions: One-year treatment with canagliflozin increased TIBC and decreased ferritin in patients with T2D and CKD, suggesting improvement in iron use.

Funding: Commercial Support - Jansen Research and Development

TH-PO185

Iron Biomarkers and Effects of Canagliflozin in Patients with Type 2 Diabetes and CKD: A Post Hoc Analysis of the CREDENCE Trial

Akihiko Koshino,1,2 Brenton L. Neuen,1 Clare G. Arnott,4 Bruce Neal,1 Meg Jardine,3 Sunil Badve,6 Kenneth W. Mahaffey,7 Carol A. Pollock,8 Michael K. Hansen,9 Takashi Wada,2 Hiddo J. Heerspink,5,13 University Medical Center Groningen, Groningen, Netherlands; 4Kanazawa University, Kanazawa, Japan; 3The George Institute for Global Health, Newtown, NSW, Australia; 8Royal Prince Alfred Hospital, Camperdown, NSW, Australia; 6NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; 5University of New South Wales, Sydney, NSW, Australia; 9Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, CA; 2Kolling Institute of Medical Research, St Leonards, NSW, Australia; 7Royal North Shore Hospital, St Leonards, NSW, Australia; 1Janssen Research and Development LLC, Spring House, PA.

Background: Disturbed iron homeostasis occurs commonly in patients with chronic kidney disease (CKD) and is implicated in the development of anaemia and adverse clinical events. This study aimed to determine the effects of canagliflozin on iron parameters in the CREDENCE trial and to determine whether the effects of canagliflozin on anaemia and clinical outcomes were modified by iron deficiency (ID).

Methods: Patients with type 2 diabetes (T2D) and CKD were randomized to canagliflozin 100mg or matching placebo. Serum anti-EPOR antibodies were modified by anti-EPOR antibodies. Canagliflozin reduced CKD progression (HR 0.70, 95% CI 0.56-0.87) regardless of ID.

Results: Of 2600 (59.1%) CREDENCE participants with available samples, 2414 (440%) participants had available serum samples. Canagliflozin, compared to placebo, increased TIBC by 2.1% (95% CI 0.4, 3.8; p=0.01) and decreased ferritin by 11.3% (95% CI 3.1, 15.4; p=0.001) with no clear effect on iron and TSIAT (Figure). At baseline, 92% (2832) participants had ID. Canagliflozin increased hemoglobin over time by 7.3 g/L (95% CI 6.2, 8.5; p=0.001) and 6.7 g/L (95% CI 5.2, 8.2; p<0.001) in patients with and without ID, respectively (p-interaction=0.38). Canagliflozin reduced CKD progression (HR 0.70, 95% CI 0.56-0.87) regardless of ID (p-interaction=0.83).

Conclusions: One-year treatment with canagliflozin increased TIBC and decreased ferritin in patients with T2D and CKD, suggesting improvement in iron use.

Funding: Commercial Support - Jansen Research and Development

TH-PO186

Distal Tubule Urinary Biomarkers in Diabetic Kidney Disease: Results from the VA NEPHRON-D Trial

Christina L. Tamargo,1 David Hu,1 Heather Thicssen Philbrook,2 Joseph V. Bonventre,3 Linda F. Fried,6 Steven G. Coca,4 Chirag R. Parikh,1 The Johns Hopkins University School of Medicine, Baltimore, MD; 2UPMC, Pittsburgh, PA; 3Icahn School of Medicine at Mount Sinai, New York, NY; 4Brigham and Women’s Hospital, Boston, MA.

Background: Urinary biomarkers of proximal renal tubule injury (KIM-1, NGAL, EGF, UMOD) have demonstrated associations with DKD progression, but investigations of biomarkers of distal tubular health in DKD have been limited.

Methods: We evaluated associations between two distal tubular urinary biomarkers, epidermal growth factor (EGF) and uromodulin (UMOD), and DKD progression among 140 participants in the Veterans Affairs Diabetes in Nephropathy (VA NEPHRON-D) study. EGF and UMOD were measured by electrochemiluminescence assay in a single batch in urine samples collected at randomization.

Results: At baseline, the mean age was 64.9 years, the mean eGFR was 56.2 (18.9) ml/ min/1.73 m², and the median urine albumin-to-creatinine ratio was 840 (IQR 423-1761) mg/g. Of the 140 participants (13.0%) had DKD progression over a median of 2.2 years of follow-up. Higher levels of EGF and UMOD were both independently associated with a lower risk of DKD progression in continuous models after adjustment for several covariates (adjusted HR 0.58 (0.34, 0.98) and 0.80 (0.66, 0.97); Figure 1).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
In categorical models, patients with the highest tertiles of both biomarkers had the lowest risk of DKD progression. However, associations were attenuated in models that adjusted for albuminuria, particularly for EGF (adjusted HR 0.70 (0.42, 1.15) and 0.55 (0.34, 0.89) for UMOD).

**Conclusions:** Among veterans with DKD, higher levels of distal tubular health markers were inversely associated for a lower risk of DKD progression. Distal tubular health deserves further investigation in DKD cohorts and clinical trials.

**Funding:** NIDDK Support

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**Figure 1. Baseline Urinary EGF and UMOD associations with DKD progression**

<table>
<thead>
<tr>
<th>Urinary Biomarker</th>
<th>Event rate per 100 person-years</th>
<th>Hazard ratio (95% CI) for DKD progression</th>
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<tbody>
<tr>
<td><strong>EGF</strong> (ng/mM)</td>
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<tr>
<td>TT: &gt;700</td>
<td>53 (63, 74)</td>
<td>0.41 (0.27, 0.64) 0.54 (0.34, 0.89)</td>
</tr>
<tr>
<td>G1 (37, 116)</td>
<td>0.60 (0.38, 0.83)</td>
<td>0.45 (0.10, 1.04)</td>
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<tr>
<td><strong>UMOD</strong> (ng/mM)</td>
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</table>

**TH-PO187**

**Tubular Biomarker Trajectories in Type 1 Diabetes**

Christine P. Limonte,¹ David K. Prince,² Andrew N. Hoefnagle,³ Irí B. Hirsch,¹ Michael Mauer,¹ Alessandro Doria,¹ Bryan R. Kestenbaum,¹ Ian H. De Boer,³ University of Washington, Seattle, WA; ²Joslin Diabetes and Endocrinology Research Center, Boston, MA; ³Harvard Medical School, Boston, MA; ⁴University of Minnesota Twin Cities, Minneapolis, MN.

**Background:** Evaluation of kidney tubular biomarker trajectories over the course of type 1 diabetes (T1D) may provide insight into how tubulointerstitial disease progresses over time.

**Methods:** We assessed biomarkers of tubular injury and function over time in two prospective T1D cohorts: the Renin Angiotensin System Study (RASS; n=283, 5 year follow-up) of adults with early T1D and no clinical evidence of kidney disease, and the Preventing Early Renal Loss in Diabetes Study (PERL; n=530, 3 year follow-up) of adults with longstanding T1D and CKD or risk for kidney disease progression. We measured the following biomarkers: UMOD, EGF excretion in timed urine; urinary clearances of 8 secretory markers (FGF23, osteocalcin, B2-microglobulin, 17-beta estradiol, cytokines IL-1Ra, IL-6, IL-8, TNFα); and imaging biomarkers (computed tomography). All patients had an initial visit with urine specimens collected and patients were followed until the diagnosis of DKD or loss to follow up. The association between each tubular biomarker level and the risk of DKD progression was assessed through proportional hazard models adjusted for age, sex, race, BMI, systolic blood pressure, hemoglobin A1c, and treatment assignment at baseline. Results: At baseline, RASS participants had mean age 30 years, diabetes duration 11 years, eGFR 79 mL/min/1.73m², AER 6 μg/min, and HbA1c 8.6%; PERL participants had mean age 51 years, diabetes duration 35 years, eGFR 68 mL/min/1.73m², AER 285 μg/min, and HbA1c 8.2%. Overall, RASS and PERL, and UMOD were higher and arginine-citrulline ratio, EGF, and tubular secretion score were lower in PERL versus RASS (Table). Tubular biomarkers changed significantly over time at rates similar to and sometimes faster than iGFR and AER. Baseline HbA1c was associated with tubular marker changes in multivariate models (% change/year per 1% higher HbA1c [95% CI]): in RASS, KIM-1 0.8% (0.1, 1.6), sTNFR1 0.4% (0.1, 0.7), arginine-citrulline ratio 1.1% (0.4, 1.7), FGF23 1.4% (0.1, 2.7), and EGF -1.1% (-2.1, 0). Neither ACEi/ARB versus placebo in RASS nor allopurinol versus placebo in PERL affected tubular biomarker trajectories. Conclusions: Plasma KIM-1 and sTNFR1 significantly increase over the course of T1D, suggesting early onset of tubulointerstitial pathology and progression over time. Higher HbA1c is associated with faster rise in sTNFR1.

**Funding:** NIDDK Support

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**TH-PO188**

**Association of Urinary DNlite IVD-103 with CKD and Coronary Artery Disease in Diabetic Nephropathy**

Varun Kumar Bardi, Harsha Nuss, Sindhu Chaganti, Dr Pinnamneni Siddhartha Institute of Medical Sciences & Research Foundation, Vijayawada, India.

**Background:** Fetuin-A is associated with inflammation and vascular complications in diabetes. We evaluated association of urinary post-translationally modified fetuin-A (DNlite-I 103) in diabetics with chronic kidney disease (CKD) and coronary artery disease (CAD).

**Methods:** A cross-sectional study was conducted in patients with diabetic nephropathy. Patients and divided into those having only albuminuria, CKD or CAD. eGFR (Glomerular Filtration Rate) was calculated using CKD-EPI equation, and an eGFR <60mL/min/1.73m² was considered CKD. Severity of CAD was assessed using SYNTAX score. Spot urine was tested for urine albumin to creatinine ratio (UACR), and DNlite-I 103 (Fetuin) was measured using ELISA test kit. Urine Fetuin:creatinine ratio (UFCR) was calculated. Statistical analysis was carried out using SPSS v23.0. A p value of <0.05 was considered significant.

**Results:** 137 patients were included, with 61% being men. The mean age, eGFR, UACR, and FCR were 56.4±11.8 years, 64.5±36.4 mL/min/1.73m², 159±230.06 mg/g, and 175±268.9 mg/g, respectively. Of these, 20.4% of patients had CAD, 39.4% had albuminuria, and 40.1% had CKD. There was a significant difference in UACR and UFCR between the groups. UACR had significant positive correlation with age and negative correlation with eGFR (p<0.05). UFCR had significant negative correlation with eGFR. UFCR was also significantly higher in patients with CKD compared to CAD (p<0.05). Compared to albuminuria patients, UACR, and UFCR were significantly increased in patients with CAD (p<0.05) and p<0.01. In patients with CAD, SYNTAX score had significant negative correlation with UFCR (p<0.05) but not UACR (p=0.58) because of high correlation between UFCR and SYNTAX score. DNlite-I 103 was significantly associated with chronic kidney disease, coronary artery disease, and all-cause mortality risk, and is not influenced by age. It was also significantly different between CAD & CKD, and also had significant correlation with severity of CAD. UFCR could be used to stratify patients with micro- or macrovascular disease (albuminuria, CKD, CAD).

**Funding:** Commercial Support - Bio Preventive Medicine Corp, Taiwan

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**TH-PO189**

**Relationship Between Urinary DcR2/Cr Levels and Poor Prognosis of Diabetic Nephropathy**

Weidong Wang, Jia Chen, Yani He, Kehong Chen. Department of Nephrology, Daping Hospital, Army Specialized Medical Center, Chongqing, China.

**Background:** Urinary decoy receptor 2 is closely associated with interstitial injury in diabetic kidney disease, and the aim of this paper was to investigate whether urinary DcR2/Cr levels could be used as a biomarker to predict poor prognosis in diabetic kidney disease.

**Methods:** A total of 96 patients diagnosed with diabetic kidney disease by pathological biopsy and with urine specimens retained were included. Basic data, laboratory findings, and pathological information were collected for retrospective analysis, and patients were followed up, and the follow-up time and endpoint events were recorded. The follow-up (composite) endpoint was defined as a doubling of the patient's serum creatinine level or entrance into ESRD. ESRD was defined as a patient's eGFR <15 mL/min/1.73 m² or initiation of renal replacement therapy. According to the urinary DcR2/Cr levels, they were divided into three groups, group 1: DcR2/Cr <287 ng/mmol, group 2: 287 ≤ DcR2/Cr <574 ng/mmol, group 3: DcR2/Cr ≥ 574 ng/mmol. Cox regression analysis revealed that The Kaplan-Meier survival curves showed that the risk of adverse prognosis was 5.213 times higher

<table>
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**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
in the DeR2/Cr3 group than in the DeR2/Cr1 group. The higher the DeR2/Cr level, the worse the prognosis of the patients.

**Conclusions:** Urinary DeR2/Cr is closely associated with DKD interstitial injury and is a valid biomarker for predicting poor prognosis in DKD.

**Funding:** Private Foundation Support

**TH-PO190**

**Urinary Podocyte Stress Marker as a Prognostic Indicator for Diabetic Kidney Disease**

Lingfeng Zeng,1,2 The Chinese University of Hong Kong Faculty of Medicine, Hong Kong, Hong Kong; 1Prince of Wales Hospital, Hong Kong, Hong Kong.

**Background:** Diabetic kidney diseases (DKD) is the most common cause of end-stage kidney disease (ESKD) around the world. Previous studies suggest that urinary podocyte stress biomarker, e.g. podocin:nephrin mRNA ratio, is a surrogate marker of podocyte injury in non-diabetic kidney diseases.

**Methods:** We studied 118 patients with biopsy-proved DKD and 13 non-diabetic controls. Their urinary mRNA levels of nephrin, podocin, and aquaporin-2 (AQP2) were quantified. Renal events, defined as death, dialysis, or 40% reduction in glomerular filtration rate, were determined at 12 months.

**Results:** Urinary podocin:nephrin mRNA ratio of DKD was significantly higher than the control group (p=0.0019), while urinary nephrin:AQP2 or podocin:AQP2 ratios were not different between groups. In DKD, urinary podocin:nephrin mRNA ratio correlated with the severity of tubulointerstitial fibrosis (r = 0.254, p = 0.006) and was associated with the renal event-free survival in 12 months (unadjusted hazard ratio [HR], 1.523; 95% confidence interval [CI] 1.157-2.006; p = 0.003). After adjusting for clinical and pathological factors, urinary podocin:nephrin mRNA ratio have a trend to predict renal event-free survival (adjusted HR, 1.327; 95%CI 0.980-1.797; p = 0.067), but the result did not reach statistical significance.

**Conclusions:** Urinary podocin:nephrin mRNA ratio has a marginal prognostic value in biopsy-proven DKD. Further validation is required for DKD patients without kidney biopsy.

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

**TH-PO191**

**A Second Dose of Allogeneic Neo-Islets (NIs) Further Reduces Insulin Need and HbA1c and Preserves Renal Function Long Term in Autoimmune T1DM Pet Dogs (INAD 012-776)**

Anna Goode, Christof Westenfelder. SymbioCellTech, Salt Lake City, UT.

**Background:** Spontaneously T1D dogs, like T1D humans, never spontaneously revert to a non-diabetic state. Their insulin needs remain stable or increase. They experience progressive CKD, hyperlipidemia, hepatic steatosis, diabetic neuropathy and retinopathy, malignancies, hypoglycemic events, and other complications, making them an ideal translational model for T1DM. We reported (n=8 dogs) that one dose of Neo-Islets (NIs), organoids of Mesenchymal Stromal Cells (MSCs) and culture expanded Islet Cells, when administered i.p. engraft in the omentum where they physiologically secrete insulin and other islet hormones, thereby reducing the need for insulin in autoimmune, spontaneously T1DM pet dogs by up to 50% for up to 3 years. As the MSC component is immune-modulatory, NIs require no antirejection drugs. Here we demonstrate that NIs’ beneficial effects are enhanced through administration of a 2nd dose.

**Methods:** 4 of the original 8 NI-treated, autoimmune diabetic dogs were administered a second dose of 2x10^5 NIs/kg bw i.p. at various times post the first dose. Dogs were assessed for antibodies to NIs, changes in serum glucose, HbA1c, insulin need, liver and renal function, blood counts, adverse reactions or adverse events and their relation to administration of the study drug.

**Results:** A dog who had been unresponsive to the first dose of NIs received a 2nd dose 4 years post the 1st dose. 1 year later, she has a 25% reduced need for insulin, and a 17% reduction in serum glucose. Of the 3 dogs re-dosed within a year of the first administration, insulin need has decreased 25-50%, and serum glucose levels decreased 40-50%. HbA1c levels are ~4 percentage points reduced, and within normal range. No significant changes in renal function, serum chemistries or blood counts have been observed in the 2-12 months since redose. No dog has developed antibodies to NIs subsequent to either dose. No AEs or SAEs have been attributed to NI therapy.

**Conclusions:** Allogeneic-NI therapy, which delivers insulin physiologically, is safe and is durable, requires no anti-rejection drugs, can safely re-administered, and preserves renal function long term. As with human islet transplants, redosing potentiates therapeutic efficacy, and several doses may be required to achieve insulin independence.

**Funding:** Commercial Support - SymbioCellTech

**TH-PO192**

**Identification and Validation of Neutrophil Extracellular Traps-Associated Genes in Diabetic Kidney Disease: Integration Data from Bulk RNA and Single-Nucleus RNA Sequencing Analyses**

Ruixan Xie, Sin Yu Cindy Tang, Ka Ho Jason Sher, Danting Zhang, Yat Hin Desmond Yap, Dr. Yap, Yat Hin Desmond Team. Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China.

**Background:** Accumulating data shows that immune response has crucial pathogenic contributions in diabetic kidney disease (DKD), but the contribution of Neutrophil Extracellular Traps (NETs) is limited.

**Methods:** The differentially expressed genes of NETs in human DKD were selected using the bulk RNA-seq of kidney biopsy from DKD patients (GSE30528 and GSE30529). The characteristic NETs-associated genes were further identified by machine learning algorithms. The DKD bulk RNA sequencing (GSE30122) and single-nucleus RNA-seq (GSE195460) were used to validate the genes expression.

**Results:** Three candidate genes (ITGAM, ITGB2 and TLR7) were all significantly upregulated in human DKD using machine learning approach. Single-cell analysis indicated that the three transcriptional expressions were mostly increased in leucocytes. GSEA further suggested that hub genes play key roles in IL-2/STAT5 signaling pathway (p=0.029). Good diagnostic performance for DKD were also shown. Our polt data validated ITGAM and ITGB2 expressions in the peripheral active neutrophils isolated from DKD patients.

**Conclusions:** Dysregulation of ITGAM and ITGB2 may play pathogenic roles for DKD, and drugs that target these genes in neutrophil may have therapeutic potential for DKD.

**Funding:** Private Foundation Support

**NETs related targets validation in human plasma and DKD neutrophils using RT-qPCR.**
TH-PO193
The Search for Liquid Biopsies: Serum Biomarkers and Kidney Structure in Early Diabetic Kidney Disease
Helen C. Loeker,1 Zaijul Md Dom,2 Robert G. Nelson,1 Andrzej S. Krolewski.1 National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ; 2Joslin Diabetes and Endocrinology Research Center, Boston, MA.

Background: The Joslin Kidney Panel (JKP) of 21 circulating proteins biomarkers linked to inflammation, axon guidance, fibrosis, and tubular damage was associated with kidney failure in Caucasians with type 1 diabetes from the Joslin Kidney Study and in American Indians with type 2 diabetes. We examined the association of these proteins with early kidney structural lesions in a subset of the American Indians who also underwent a research kidney biopsy.

Methods: GFR was measured by the urinary clearance of iohetalamate and serum samples collected at these visits were measured on an OLINK platform using a proximity extension assay. Research kidney biopsies were obtained a median of 1.3 years from the clinical study. Kidney structure was assessed using standard morphometric techniques. Regression models with Lasso selection and k-fold cross-validation were used to assess best biomarkers for each measure.

Results: Mean age of the 107 participants (78 women) was 45.5 (SD 9.6) years, blood pressure 123 (13) / 77 (9) mmHg, HbA1c 9.2 (2.3)%, GFR 150 (47) ml/min, and median diabetes duration was 12.8 (IQR 11.0-19.4) years. All participants had GFR >60 ml/min; 40 (37%) had moderate albuminuria and 21 (20%) had severe albuminuria. Biomarker concentrations correlated positively with global glomerular sclerosis, glomerular basement membrane width, mesangial fractional volume, cortical interstitial fractional volume, podocyte foot process width and negatively with glomerular filtration surface density, total filtration surface density, podocyte density, and percentage of endothelial fenestrations (Figure). KIM1 was the leading biomarker for most morphometric parameters based on regression models (Figure).

Conclusions: The JKP of biomarkers that includes protein markers linked to multiple diabetic kidney disease (DKD) pathways demonstrated associations with a broad range of early structural lesions associated with DKD progression.

Funding: NIDDK Support.

TH-PO194
Significance of Non-B Cell-Derived Immunoglobulin G in the Renal Tubulointerstitium of Chinese Patients with Type 2 Diabetic Kidney Disease
Xinyao Wang, Zhenling Deng, Yue Wang. Peking University Third Hospital, Beijing, China.

Background: Epithelial-mesenchymal transition (EMT) is critical in the progression of DKD. Studies have reported that positive IgG staining in renal tubules in patients with DKD, but the significance is unknown. Studies have demonstrated that renal intrinsic cells, including renal tubular epithelial cells, can produce IgG (non-B IgG). Therefore, we clarified the non-B IgG in the tubulointerstitium of patients with DKD and its clinicopathological features, and may contribute to renal tubule EMT.

Methods: A total of sixty patients with type 2 diabetes mellitus and biopsy-proven DKD was studied retrospectively. The monoclonal antibody RP235 can screen out human non-B IgG rather than B-IgG. The clinicopathological features of non-B IgG deposition in the renal tubulointerstitium were compared with and without. The risk factors for poor renal function and interstitial lesions were evaluated using logistic regression analysis. In addition, the relationship between tubulointerstitial non-B IgG deposition and EMT was assessed in 30 patients with DKD.

Results: The non-B IgG positive patients showed decreased eGFR (p=0.038) and more severe anemia(p=0.002). Multivariate logistic regression analysis showed that tubulointerstitial non-B IgG deposition was an independent risk factor for poor renal function(p=0.037) and interstitial lesions(p=0.030). The positive area of non-B IgG in DKD renal tubulointerstitium and α-SMA showed a positive correlation (p=0.034).

Conclusions: Renal tubulointerstitial non-B IgG deposition in patients with DKD shows a negative relationship with renal function and severe interstitial lesions. The renal tubule EMT was more severe in positive tubulointerstitial non-B IgG staining, suggesting that non-B IgG may be involved in DKD kidney injury by promoting EMT.

Funding: Government Support - Non-U.S.

TH-PO195
Cardiovascular Benefits and Safety of Sacubitril-Valsalartan in ESKD: A Systematic Review and Meta-Analysis
Mariam Charkviani, Pajaree Krisanapan, Charat Thongprayoon, Jasmina Craici, Wist Cheungpasitporn. Mayo Clinic Minnesota, Rochester, MN.

Background: End-stage kidney disease (ESKD) patients often experience heart failure, which significantly contributes to their high mortality rates. Despite the crucial role of sacubitril-valsalartan in heart failure management, limited data exists on its cardiovascular benefits and safety in ESKD patients. This systematic review aims to assess the efficacy and safety of sacubitril-valsalartan compared to standard care in ESKD patients on dialysis, addressing this critical knowledge gap.

Methods: A comprehensive search of was conducted in Embase, MEDLINE, and Cochrane databases through February 2022 to identify studies assessing cardiovascular and/or safety outcomes of sacubitril-valsalartan in ESKD patients on dialysis. Effect estimates were derived and consolidated using a random-effect model and the generic inverse variance approach.

Results: Analysis of 12 studies involving 799 eligible ESKD patients demonstrated notable improvements in left ventricular ejection fraction (LVEF) with sacubitril-valsalartan compared to the control group, resulting in a pooled mean difference (MD) of 6.58 (95% CI 1.86, 11.29). Subgroup analysis revealed significant differences between heart failure patients with reduced ejection fraction (HFrEF) or moderately reduced ejection fraction (HFmrEF) versus preserved ejection fraction (HFpEF) (p<0.0001). LVEF significantly improved in patients with LVEF <50% (HFrEF and HFmrEF) with an MD of 12.42 (95% CI 9.39, 15.45). However, patients with LVEF >50% (HFpEF) did not show a statistically significant effect, reporting an MD of 2.6 (95% CI 1.15, 3.35). Notably, sacubitril-valsalartan significantly enhanced LVEF in HFpEF patients, with a pooled MD of 1.3 (95% CI 1.24, 15.82). Safety analysis revealed no significant differences in the incidence of hyperkalemia (pooled odds ratio [OR] 0.72; 95% CI 0.38, 1.36) or hypertension (pooled risk ratio [RR] 1.03; 95% CI 0.36, 2.90) between sacubitril-valsalartan and standard care groups. No cases of angioedema were reported.

Conclusions: Our systematic review suggests that sacubitril-valsalartan, compared to standard care, provides benefits to ESKD patients with HFpEF and HFmrEF by improving LVEF, without increasing the risk of hyperkalemia, hypotension, or angioedema.

TH-PO196
Nocturnal Systolic Blood Pressure Dipping and Progression of CKD
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Background: The relationship between declining nocturnal blood pressure (BP) and adverse cardiovascular outcomes is well-recognized. However, the relationship between diurnal BP profile and the risk of chronic kidney disease (CKD) progression is unclear.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: We analyzed 1,061 participants from Cardiovascular and Metabolic Disease Research Center-High Risk (CMERC-H). The main exposure was diurnal systolic BP (SBP) profile and diurnal SBP difference (nighttime SBP/daytime SBP×100/daytime SBP). The primary outcome was CKD progression, defined as a composite of a 50% decline in the estimated glomerular filtration rate from baseline or the initiation of kidney replacement therapy.

Results: During 4,749 person-years of follow-up (median, 4.8 years), the composite outcome occurred in 380 (35.8%) participants. Compared to dippers, the hazard ratios (HRs) for the risk of adverse kidney outcomes were 1.02 (95% confidence interval [CI], 0.69–1.52), 1.30 (95% CI, 1.02–1.66), and 1.40 (95% CI, 1.03–1.90) for extreme dipper, non-dipper, and reverse dipper, respectively. In a continuous modeling, a 10% increase in diurnal SBP difference was associated with a 1.21-fold (95% CI, 1.07–1.37) higher risk of CKD progression.

Conclusions: Decreased nocturnal SBP decline was associated with adverse kidney outcomes in patients with CKD. Particularly, patients with non-dipping and reverse dipping patterns were at higher risk for CKD progression than those with a dipping pattern.

TH-PO197

The 2021 KDIGO Blood Pressure Target and the Progression of CKD: Findings from KNOW-CKD

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Background: The 2021 KDIGO clinical practice guideline for management of blood pressure (BP) in chronic kidney disease (CKD) recommends a target systolic BP of remains unknown.

Methods: We examined the association of the 2021 KDIGO BP target with CKD progression compared with the 2012 KDIGO BP target among 1724 participants from the Korean Cohort Study for Patients With CKD. The main exposure was BP status categorized according to the 2012 or 2021 KDIGO guideline: 1) controlled within 2021 target; 2) controlled within 2012 target only; and 3) above both targets. The primary outcome was a composite kidney outcome of a 50% decline in estimated glomerular filtration rate from baseline or the initiation of kidney replacement therapy during the follow-up.

Results: During 8,078 person-years of follow-up (median, 4.9 years), the composite kidney outcome occurred in 650 (37.7%) participants. The incidence rates of this outcome were 55, 66.5, and 116.4 per 1,000 person-years in BP controlled within the 2012 and 2012 KDIGO targets, and BP above both targets, respectively. In the multivariable cause-specific hazard model, hazard ratios for the composite outcome were 0.76 (95% confidence interval, 0.60–0.95) for BP controlled within the 2021 target and 1.36 (95% confidence interval, 1.13–1.64) for BP above both targets, compared with BP controlled within 2012 target only.

Conclusions: The newly lowered BP target by the 2021 KDIGO guideline was associated with improved kidney outcome compared with BP target by the 2012 KDIGO guideline.

TH-PO198

Early Decline in GFR Predicts Long-Term Renal Events in Hypertensive CKD Patients Using Renin-Angiotensin System (RAS) Blockers

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Background: Renin-angiotensin-aldosterone inhibitors (RAAs) are essential in treating chronic kidney disease (CKD), but their initiation can lead to a decline in glomerular filtration rate (GFR). Limited research exists on the impact of RASI-induced GFR changes on long-term GFR variations and albuminuria.

Methods: This observational cohort study extends an open-label, case-controlled randomized clinical trial (NCT01552954) with hypertensive CKD patients (estimated GFR ≥60 ml/min/1.73 m², random urine albumin-to-creatinine ratio (UACR) ≥30 mg/g creatinine). After an 8-week screening phase (0-week) after discontinuing RAAs, participants were prescribed an angiotensin receptor blocker (ARB: Olmesartan 40mg/day) and underwent a second visit at 8 weeks with randomization into intensive or conventional low-salt diet education. Third visit was conducted at 16 weeks. We recruited 40mg/day and underwent a second visit at 8 weeks with randomization into intensive or conventional low-salt diet education. Third visit was conducted at 16 weeks. We recruited 450 patients, median age, TRV, and eGFR at baseline were 73 years, 2 lower eGFR at baseline. Over a median follow-up of 94 weeks, 52 patients died and 203 had an eGFR decline of ≥30% (Figure). There was no interaction by randomized group (P=0.45). Analysis using all-cause death as a competing event did not substantially change the results.

Conclusions: A higher TRV was associated with a higher risk of kidney function decline among patients with HfPEF in TOPCAT.

TH-PO200

Association of Pulmonary Arterial Pulsatility Index (PAPI) with Kidney Outcomes Among Patients Admitted for Acute Decompensated Heart Failure

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Background: Pulmonary arterial pulsatility index (PAPI), defined as (pulmonary artery (PA) systolic pressure - PA diastolic pressure)/right atrial pressure, has emerged as a novel marker to capture right ventricular failure. Lower PAPI is associated with increased risk of death but has not been studied in association with renal outcomes.

Methods: Records for patients requiring a PA catheter for acute decompensated heart failure (ADHF) admissions to a single quaternary center between 2015-2021 were reviewed. PAPI was calculated based on the initial measurements; values were transformed given their skewed distribution. Linear regression models were used to examine the cross-sectional association of PAPI with baseline estimated glomerular filtration rate (eGFR) and in-hospital eGFR slope. Patient records were linked to the US Renal Data System to capture dialysis outcomes. We used multivariable Cox proportional hazards regression models to examine the association of PAPI with death or the composite endpoint of death or heart transplant (HT). Covariates included demographics, measures of cardiac disease severity and medications.

Results: Among 753 patients with mean age 62 (SD 14) years, median PAPI was 2.0 (IQR 1.4, 3.2), mean eGFR of 58 (SD 27) ml/min/1.73 m² and mean eGFR slope was 1.2 (SD 6.2) ml/min/1.73 m²/week. For every doubling of PAPI, there was a 3.3 ml/min/1.73 m² (95% CI 1.5, 5.2) higher baseline eGFR, and 0.7 (95% CI 0.3, 1.2) ml/min/1.73 m²/week higher in-hospital eGFR slope. Over median follow-up of 23 (IQR 8, 47) months, 62% (8%) reached diabetes and 365 (48%) reached the composite endpoint. Higher PAPI was associated with a significantly lower risk of requiring dialysis both in unadjusted and adjusted models (Table). Higher PAPI also trended toward decreased risk for the composite outcome (Table).
Conclusions: Higher eGFR is associated with higher baseline eGFR, higher in-hospital eGFR slope and lower risk of progression to dialysis in patients admitted for ADHF.

Funding: NIDDK Support

Table: Tidzard ratios for risk of composite outcome of death or heart transplant and need for dialysis by doubling of eGFR

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median (IQR)</th>
<th>90th Percentile (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death/Heart Transplant</td>
<td>18.4 (12.4, 27.2)</td>
<td>47.8 (34.5, 60.0)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, ejection fraction, diabetes, estimated glomerular filtration rate and use of renin angiotensin and/or diuretics.

TH-PO202

Is the Increased Risk of Heart Failure with Preserved Ejection Fraction (HFpEF) and Heart Failure with Reduced Ejection Fraction (HFrEF) in CKD in Type 2 Diabetes (T2D) explained by Hypertension (HTN)?

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Background: CKD is a clear risk factor for HFrEF and HFpEF but the degree to which HTN it plays a role in the pathogenesis of these disorders in CKD is unknown.

Methods: We used the VA Informatics and Computing Infrastructure to create a national cohort of veterans with T2D but without HF (using ICD9/10 codes) who had at least 2 outpatient CKD-EPI eGFR measured from 1/1/2000 to 12/31/2021 (n=2,402,350).

Incident HF through 12/31/2021 were identified using ICD 9/10 codes. Using ejection fraction (EF) data extracted with natural language processing from echocardiograms done within 180 days of HF diagnosis, HFrEF (EF ≤ 50%) and HFpEF (< 50%) were defined.

Results: Out of 410,783 (16.7%) patients who developed HF over 1.78 million patient-years of follow up, 289,508 (70.5%) had an echocardiogram within 180 days of HF diagnosis (median days for the cohort echo with diagnosis 1 with IQR 0 to 13). Mean EF was 45±15%. Overall, 168,079 (6.8%) patients developed HFrEF and 121,421 (4.9%) HFpEF. As shown in the Figure, adjusted for demographics, comorbidity and other factors, more advanced CKD was associated with higher risk of HFrEF and HFpEF. Adjusting for baseline hypertension, blood pressure (BP) and BP-modulating medications.

Conclusions: HTN appears to play a role in both HFrEF and HFpEF, particularly in CKD stages 3a and b to 4. Intensive BP control might reduce the risk of HFrEF and HFpEF in stages of CKD than in stage V/ESRD.

Funding: Veterans Affairs Support

TH-PO203

Assessing Heart Rate Variability in Patients with CKD: Association with Vascular Dysfunction

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Background: Autonomic dysfunction (AD) has been recognized as an important contributor to poor outcomes in patients with chronic kidney disease (CKD) characterized by adrenergic overdrive and/or loss of parasympathetic activity. Heart rate variability (HRV) is a measure of the extent of changes between successive R-R intervals in a heartbeat and reflects the balance between sympathetic and parasympathetic tone. HRV has been associated with all-cause mortality and vascular dysfunction in patients with cardiovascular diseases, but very few studies have assessed its association with vascular disease and dysfunction in CKD. Thus, this study examined HRV in patients with CKD and how it associates with vascular dysfunction.

Methods: This study cross-sectionally pooled baseline data from three clinical studies conducted in patients with stage 3-4 CKD. Five-minute electrocardiogram recordings at rest with paced breathing were analyzed using an automated HRV analysis tool in the LabChart software. HRV parameters were compared to age-matched healthy controls. Regression models were used to evaluate associations of low HRV with other vascular parameters: endothelial dysfunction (brachial artery flow-mediated dilation (FMD [%])), central arterial stiffness (carotid-femoral pulse-wave velocity [CPF PWV]), local arterial compliance (carotid artery compliance), cerebrovascular stiffness (resting middle cerebral artery pulsatility index), and cerebrovascular reactivity (middle cerebral artery blood flow-velocity response to hypercapnia) in the CKD group.

Results: Forty-four participants with CKD (33/11 M/F; mean age (years) ± s.d 68±7, eGFR 44±11 ml/min/1.73m²) were compared to nine age-matched controls (4.5±M;

Categorical variables were compared with Fisher’s exact tests and continuous variables were compared with t-tests.

Results: 3834 charts were extracted, 257 were reviewed, and 107 were included.

65% were male and 63% had diabetic renal disease. The median dialysis vintage was 26 months (IQR:6.18months). 64.5% patients had mean pulmonary arterial pressure of >25mmHg. 43% had pulmonary capillary wedge pressure ≥15mmHg, and 22% had increased pulmonary vascular resistance of ≥3.00. The type of HD access was not associated with PH (47%/CVC vs 41%/AV, p=0.65). Among 26% patients with vascular duplex, there was no difference between AV access flow rates in those with and without PH (median 390.0 vs 408.0, p=0.58). 86% survived after 1-year of RH and mortality was not associated with prevalence of PH. There was no difference in transplant candidacy between those with and without PH (81% vs 75%, p=0.47).

Conclusions: PH was common in HD patients (42%), and the type of vascular access was not associated with PH between. Diagnosis of PH had no direct effect on transplant candidacy.

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

Underline represents presenting author.

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HF survival probability in the CKD cohort with and without abnormal HRV

Cox PH model

TH-PO205
Liver Elasticity in Heart Failure Patient: The Role of Kidney in Cardio-Hepatic Interaction
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Background: Liver elastography is a novel ultrasound technique assessing elasticity of liver tissue. Previously, it had been reported that the more elevated liver stiffness, the poorer the prognosis in heart failure indicating cardio-hepatic interaction. However, clinical indication of liver elastography remains unrevealed. Moreover, reports about relationship between liver stiffness and heart failure subtypes haven’t well been published. Therefore, we have investigated the cardio-hepatic interaction using liver elastography in heart failure subtypes.

Methods: We prospectively enrolled 58 consecutive patients with heart failure admission from April 2022 to March 2023. Liver elastography, transhepatic echocardiography and blood sampling were done at the time of discharge from heart failure treatment.

Results: Patients were divided into two groups according to the left ventricular ejection fraction (LVEF) of echocardiography: heart failure with reduced ejection fraction (HFrEF) group (EF ≤40%, n = 11) and non-HFrEF group (EF >40%, n = 31). The mean age of all patients was 83 ± 11 years. The mean age and the prevalence of hypertension and diabetes mellitus was higher in non-HFrEF group than in HFrEF group. The prevalence of taking SGLT2 inhibitors was lower in non-HFrEF group than in HFrEF group. LV end-diastolic diameter, LV end-systolic diameter was larger in HFrEF group than in non-HFrEF group. Tricuspid regurgitation pressure gradient (TRPG) was higher in non-HFrEF group than in HFrEF group. Inferior vena cava diameter was not different between two groups. The mean values of almost liver function tests of all patients were within the normal range. eGFR was lower in non-HFrEF group than in HFrEF group. Liver elasticity was higher in non-HFrEF group than in HFrEF group (7.1 ± 2.7 vs. 5.1 ± 1.5 kPa; P=0.008) indicating liver stiffness. Pearson’s correlation coefficient showed that liver elasticity was positively correlated with the prevalence of diabetes mellitus, LVEF, TRPG, serum creatinine, AST, GGT and was negatively correlated with LV end-diastolic diameter, LV end-systolic diameter.

Conclusions: Liver stiffness was elevated and renal function was decreased in EF-preserved heart failure patients. Liver elasticity was correlated with the parameter of congestion (TRPG) and useful for the assessment of congestion. Renal function was also correlated with liver elasticity.

TH-PO206
Role of Dual-Energy Computed Tomography (DECT) in Detection of Carotid Artery Monosodium Urate Deposition (MSU) in Patients with CKD


Background: To find out if a Dual energy CT can detect MSU deposition in carotid arteries in patients with CKD and whether the presence of monosodium urate crystals has any effect on atherosclerotic disease in terms of plaque volume.

Methods: This is a retrospective study. All patients with CKD who underwent Dual energy neck imaging (like carotid angiogram, neck soft tissues or cervical spine) from January 2015 to December 2022 were included. Charts were reviewed to find CKD patients and potential confounding variables like isolated gout or smoking which can add to atherosclerotic disease. Same number of healthy controls were included which were then age (within 5 years), sex and confounders-matched to CKD patients using MedCalc. DECT datasets were post-processed using Syngo.ViaVB30 with MSU application and Calcium scoring application for volumetric analysis of atherosclerotic plaque.

Results: Out of total 2157 patients who underwent dual energy neck imaging during study period, 85 were established CKD cases with confirmed clinical and laboratory evidence. Of 85 CKD cases, 2 were excluded due to presence of artefacts from dentures, n=83. Out of 83, MSU was detected in carotid arteries of 10 patients (12%). None of the matched control patient demonstrated MSU deposition. Volumetric analysis of atherosclerotic plaque demonstrated larger plaque volumes in CKD patients with MSU (n=10) than matched CKD patients without MSU (n=10) and matched control/non-CKD patients (n=10) (p value of 0.03).

Conclusions: 1. Dual energy CT is an effective tool to detect MSU deposition in carotid arteries of patients with CKD. 2. MSU deposition increases atherosclerosis which can lead to increased TIA/strokes and hence has significant role in patient’s morbidity.
Outcomes with Inpatient Use of Midodrine in Patients on Maintenance Hemodialysis with Heart Failure

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Background: Midodrine, a peripheral vasoconstrictor, is commonly used in kidney failure patients for predialytic and intradialytic hypotension. However, in patients with systolic and/or right heart failure (HF), midodrine is potentially harmful. No known studies examine the safety of midodrine in hospitalized patients with kidney failure and HF.

Methods: We queried TriNetX database for inpatients with kidney failure and systolic and/or right HF who had at least an event of hypotension (SBP < 110 mm Hg or MAP < 70 mm Hg). Patients requiring critical care, intravascular catheters or vasopressors were excluded. Cohorts were separated based on midodrine use. Temporality was established between hypotension, midodrine use, and hemodialysis, as shown in figure. Cohorts were matched for relevant comorbidities.

Results: In patients receiving midodrine, 6-month mortality risk ratio (RR) was significantly higher than no midodrine use (RR 1.53, 95% CI 1.037 to 2.246). Kaplan Meier survival analysis log-rank test at 6 months revealed a Hazard Ratio of 1.54 (95% CI 1.022 to 2.317).

Conclusions: In patients with systolic and/or right HF and kidney failure, hypotension is a limiting factor for decongestion and guided directed therapy implementation, making midodrine a tool used in real world practice for stabilization. Our exploratory results on noncritically ill inpatients show an association between use of midodrine and higher 6-month mortality. This may reflect deleterious effects from vasoconstriction and/or unmeasured confounders in sicker patients with HF and kidney failure that increase mortality risk. This study has multiple limitations. Given its observational nature, it cannot establish a cause-effect relationship. Other limitations include the lack of data regarding dosage and duration of midodrine, and severity and etiology of heart failure. Our study demonstrates increased mortality associated with midodrine use for hypotension, warranting further research and consideration of alternative strategies.

Methods

TH-PO207

Outcomes with Inpatient Use of Midodrine in Patients on Maintenance Hemodialysis with Heart Failure

TH-PO208

The Characteristics of Myocardial Fibrosis and Analysis on Related Influencing Factors in Hemodialysis Patients

Bing Zhuang, Yuan Luo, Guiling Wei, Hong Ye, Junwei Yang. The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.

Background: This study aimed to analyze the characteristics of myocardial fibrosis and related influencing factors in hemodialysis patients, and to explore whether cardiovascular magnetic resonance (CMR) based on T1 mapping technique has prognostic value in predicting cardiovascular events.

Methods: This was a prospective observational study. The clinical data and dialysis parameters were collected, and laboratory tests were conducted. All patients underwent CMR, T1 mapping technique was used to identify myocardial interstitial fibrosis and LGE positive was used to identify alternative myocardial.

Results: A total of 42 hemodialysis patients were enrolled, the mean native T1 value of the entire heart was 1277.34±54.95ms. The native T1 value was positively correlated with heart rate and the ratio of transmural Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/e') (r=0.366, P=0.017; r=0.386, P=0.014), and negatively correlated with six-minute walk distance (r=-0.474, P=0.002). E/e' was found to be a risk factor for the mean native T1 value of the entire heart in hemodialysis patients (OR=1.508, 95% CI: 1.008-2.258, P=0.046). LGE scans were completed in 39 patients, of whom 12 (30.8%) were LGE positive and 27 (69.2%) were LGE negative. Compared with the LGE negative group, the LGE positive group had a shorter six-minute walk distance (P=0.029), larger left ventricular end-systolic volume (LVEVS) and left ventricular mass (LVM) (P=0.025 and P=0.025, respectively). Left ventricular mass was found to be a factor influencing LGE positivity (OR=1.045, 95% CI: 1.033-1.058, P=0.035). Logistic regression analysis showed that the higher the native T1 value, the greater the probability of cardiovascular events occurring within six months (OR=1.1, 95% CI: 1.003-1.206, P=0.043).

Conclusions: E/e' is a factor influencing interstitial fibrosis in hemodialysis patients and the left ventricular mass is a factor influencing alternative fibrosis. The native T1 value has predictive value for cardiovascular events within six months.

Funding: Government Support - Non-U.S.
Hypertension and CVD: Clinical - I

There was significant effect modification by proteinuria. Higher CFPWV was associated with new-onset diabetes among participants with UPCR <1g/g (UHR 1.27; 95% CI 1.03–1.56) but not at all.

**Conclusions:** Among adults with CKD, LASM was associated with new-onset diabetes, particularly in those without significant proteinuria. LASM may have a key mechanistic role in abnormal glucose metabolism and could be a helpful marker of diabetes risk among patients with non-proteinuric CKD.

**Funding:** NIDDK Support

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**TH-PO212**

**Association Between Systolic Blood Pressure Time in Target Range and Progression of CKD: Findings from KNOW-CKD Study**

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**Background:** Time-in-target range (TTR) is determined by the proportion of time during which the systolic blood pressure (SBP) remains within a defined range. It has emerged as a good metric for assessing SBP control over time. However, whether TTR of SBP can predict progression of chronic kidney disease (CKD) is uncertain.

**Methods:** We investigated the association between SBP-TTR during the first year of enrollment and CKD progression among 1,758 participants from KNOW-CKD (Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease). Participants were categorized into 4 groups according to SBP-TTR (0%, 1–50%, 51–99%, and 100%). The primary outcome was a composite kidney outcome of a ≥50% decline in eGFR from baseline measurement or the initiation of kidney replacement therapy.

**Results:** During a follow-up period of 9,212 person-years (median, 5.4 years), the composite outcome occurred in 710 (40.4%) participants. In multivariable cause-specific hazard model, a 1-SD increase in SBP-TTR was associated with an 11% lower risk of the composite outcome (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.82–0.97). Additionally, compared to the patients with SBP-TTR 0%, the HRs (95% CIs) for the SBP-TTR 1–50%, 51–99%, and 100% were 0.68 (1.08–1.03), 0.77 (0.61–0.97), and 0.73 (0.56–0.95), respectively. Moreover, the corresponding slopes of eGFR decline were -2.71 (-3.13 to -2.30), -2.52 (-2.80 to -2.23), -2.25 (-2.50 to -2.01), and -2.06 (-2.34 to -1.78) ml/min/1.73m², respectively.

**Conclusions:** Higher SBP-TTR was associated with a decreased risk of CKD progression in patients with CKD.

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

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**TH-PO213**

**Uncovering the Added Benefits of Lowering Resting Heart Rate by Physical Activity in Reducing the Incidence and Mortality Risks of CKD and Proteinuria**

Chi Pang Wen, Min Kuang Tsai. National Health Research Institutes, Zhunan, Taiwan.

**Background:** Physical activity (PA) is known to be able to reduce Chronic Kidney Disease (CKD) mortality, but the effect was perceived as too little, too late to motivate exercisers. However, smart types of exercise could be employed to double the effect by simultaneously lowering resting heart rate (RHR). The added role of RHR in enlarging the benefits of physical activity to prevent or to reduce CKD has not been reported.

**Methods:** A medical screening cohort of 680,277 adults in Taiwan was successively recruited during 1996–2017, and 64,577 deaths were identified by National Death File and 5,671 cases of ESRD after a medium follow up of 18 years. CKD was analyzed by 5 component stages, eGFR values and proteinuria tested by dipstick. RHR came from electrocardiogram taken after rest in a supine position, with 80–99/min considered as elevated but within normal limits. Physical activity was expressed as MET-week, which was a product of exercise intensity and duration. Exercise status was classified as inactive, low, medium high or very high active. The association of RHR with CKD at entry points or with various CKD associated all-cause mortality risks during follow up was both calculated by Cox model.

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

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Results: A triangular interactive relationship existed among PA, RHR, and CKD, with the ability to reduce both RHR and CKD and with RHR associated with less CKD when slowed down by PA. Increasing RHR per 10 beats from 60/min up was associated with 30% increase in CKD, 39% increase in proteinuria and 30% increase in GFR<45. Physical activity, as officially recommended, was associated with 18% reduction of CKD, with the extent of reduction being larger when combined with PA and RHR, and vigorous intensity exercise for 3 months was associated with a lowering of RHR by 11 beats/min. Not all PA could slow RHR, mostly by those with vigorous intensity. Most CKD people were inactive (>80%) and could benefit from engaging in all types of PA recommended. Majority (60%) lowered RHR and small minority (9%) increased RHR, with remaining unchanged.

Conclusions: The incidence and mortality of CKD and proteinuria could be maximally reduced by vigorous physical activity when RHR was simultaneously lowered. Promoting the kind of exercise that reduced RHR may double the reduction of CKD or proteinuria.

TH-PO214

The Association Between Subclinical Reductions in Kidney Function and Major Adverse Cardiovascular Events in Young Adults: A Population-Based Retrospective Cohort Study

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Background: Cardiovascular risk factors and disease in young adults (18-39 years) are on the rise. Whether early reductions in kidney function (i.e., estimated glomerular filtration rate, eGFR) affect atherogenic risk in young adults is unclear. Here we examined if early reductions in kidney function (eGFR≥60 mL/min/1.73 m²) below age-expected values are associated with elevated risk of cardiovascular disease (CVD) among those with chronic kidney disease (CKD). Methods: We conducted a retrospective cohort study of 8.7 million individuals (3.6 million aged 18-39 years) using linked provincial healthcare datasets from Ontario, Canada from January 2008-March 2021. Cox models examined the association of categorized eGFR (50-120 mL/min/1.73m²) with CVD (first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) and CVD-plus-heart failure (CVD+Hf), stratified by age (18-39, 40-49, 50-65 years).

Results: In our cohort (mean age 41.3, mean eGFR 104.2, median follow-up 9.2 years), we identified 50,377 participants with eGFR≥60 mL/min/1.73 m², below expected age-expected values. Cardiovascular risk factors and disease in young adults (18-39 years) are on the rise. Whether early reductions in kidney function (i.e., estimated glomerular filtration rate, eGFR) affect atherogenic risk in young adults is unclear. Here we examined if early reductions in kidney function (eGFR≥60 mL/min/1.73 m²) below age-expected values are associated with elevated risk of cardiovascular disease (CVD) among those with chronic kidney disease (CKD). Methods: We conducted a retrospective cohort study of 8.7 million individuals (3.6 million aged 18-39 years) using linked provincial healthcare datasets from Ontario, Canada from January 2008-March 2021. Cox models examined the association of categorized eGFR (50-120 mL/min/1.73m²) with CVD (first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) and CVD-plus-heart failure (CVD+Hf), stratified by age (18-39, 40-49, 50-65 years).

Results: In our cohort (mean age 41.3, mean eGFR 104.2, median follow-up 9.2 years), a stepwise increase in the relative risk of MAC and MACE+ was observed as early as eGFR<90 in young adults (e.g., for MACE, at eGFR 70-80, ages 18-30: 2.37 compared to patients whom had medication administered in the morning only (p=0.001, 95% CI [1.255-2.710]). The systolic blood pressure was higher in all participants, but nitrate, calcium channel blockers, diuretics, and β-blockers were not significantly different.

Conclusions: In young adults, eGFR levels above the current threshold for chronic kidney disease associated with an elevated risk for MACE and MACE+, warranting appropriate risk stratification, proactive monitoring, and timely intervention.

TH-PO215

Seize the Night: A Retrospective Cohort Analysis on the Timing of Antihypertensive Agents on Nocturnal Blood Pressure

Sean Michael, Hammad I. Huda, Monica Felix. HCA Florida Oak Hill Hospital, Brooksville, FL.

Background: Hypertension is a long-standing modifiable risk factor in cardiovascular disease. Blood pressure follows a circadian rhythm in response to hormonal and environmental factors. However, when this balance is disrupted it may lead to an elevated daytime hypertension. This study aims to see if the timing of antihypertensive agents with hypertension and chronic kidney disease may reduce night-time blood pressure.

Methods: In this retrospective cohort analysis, 8814 patients (3975 female/4839 male, 65+9 years of age) with hypertension or chronic kidney disease who were admitted to HCA healthcare in 2021 and 2022 were categorized based on receiving blood pressure medication in the morning (n=2142), evening (n=176), or morning and evening (n=6209). In response, patients blood pressure at night time were measured to see if there was a nocturnal blood pressure lowering pattern of 10-20% at night-time.

Results: The results showed patients who had evening only blood pressure medication were 1.84 times as likely to have a night-time drop in blood pressure compared to patients whom had medication administered in the morning only (p<0.001, 95% CI [1.255-2.710]) by systolic and diastolic variables were held constant.

Conclusions: Patients who administer an evening dose blood pressure medication are more likely to have an appropriate drop in night-time blood pressure. Clinicians can therefore consider switching antihypertensive agents to evening among patient with nocturnal hypertension. Furthermore, this study raises awareness regarding nocturnal hypertension, an often overlooked aspect in the treatment of hypertension.

Funding: Private Foundation Support

TH-PO216

A Systematic Review and Meta-Analysis of Myocardial Fibrosis in CKD and ESKD Assessed by Cardiac MRI T1 Mapping

Deepak Chandramohan,1 Rhoshini Rajasekaran,1 Raghunandan Konda,1 Ashwini S. Pujari,2 Sreekant Avula,2 1The University of Alabama at Birmingham, Birmingham, AL; 2University of Minnesota Twin Cities, Minneapolis, MN.

Background: Non-atherosclerotic fibrotic changes to the cardiac myocardium occur early in Chronic Kidney Disease (CKD) and End Stage Kidney Disease (ESKD) patients. Uremic myocardial fibrosis can lead to arrhythmias and heart failure. T1 mapping technique in Cardiac MRI (CMR) estimates myocardial fibrosis and offers a non-invasive way to characterize the severity of cardiac remodeling.

Methods: A systematic search was done in PubMed, Google Scholar, Embase, and Web of Science from inception to February 2023. Studies were divided according to scanner field strength (1.5 or 3 Tesla). The random effects model was used to calculate pooled mean, 95% confidence interval, standard error (SE), and standardized mean difference (SMD). The heterogeneity between study-specific estimates was assessed by the I² statistic.

Results: The initial search retrieved 765 studies. From these, 25 studies met the inclusion criteria that had 697 CKD (mean age of 55.5 years; 65.5% males; mean eGFR of 41 mL/min/1.73m²) and 658 ESKD patients (mean age of 55.6 years; 63.3% males; mean dialysis duration of 5 years). The mean native T1 in CKD was 996.2ms (970-1026.3) for CKD and 1267.4ms (1217.8-1317.1) in ESKD patients. The SMD of native T1 measurements in CKD vs. controls is 1.09 (0.73-1.46), and SMD for ESKD vs. controls is 1.12 (0.85-1.38).

Conclusions: CKD and ESKD patients with preserved LVEF have increased T1 values indicating an increased fibrosis burden. T1 mapping can be used in the early detection of cardiomyopathy and as a risk-stratification tool. Large, randomized trials are needed to confirm these findings and find long-term effects of dialysis on cardiac fibrosis.

Forest plots of LVEF, Native T1 measurements in CKD and ESKD

TH-PO217

Health Care Resource Use and Costs in the Year Following a Major Bleeding Event in Patients with and Without ESKD

Alejandro Victorio,1 Lori D. Bash,1 Nicholas S. Roetker,2 Dena Rosen R. Ramey,1 James B. Wetmore,2 Marc P. Bonaca,1 3Merck & Co Inc, Rahway, NJ; 1Hennepin Healthcare Research Institute Chronic Disease Research Group, Minneapolis, MN; 2University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.

Background: Patients with end-stage kidney disease (ESKD) are at an elevated risk of major bleeding events which may result in substantial healthcare resource use (HCRU). There is limited information on HCRU following a major bleeding event in those with ESKD.

Methods: Retrospective cohorts of patients ≥66 years were created using the US Renal Data System (USRDS) for ESKD patients receiving in-center hemodialysis (HD) and 20% sample general Medicare database for non-ESKD patients. The index date was the date of hospital admission for an incident major bleeding event between 2015 and 2019. Only those enrolled in Medicare Part D were included in follow-up analysis. All-cause HCRU and costs were calculated (including the index event) for up to 1 year. HCRU is expressed as a percent or rate per 100 person-years. Per person per year adjusted costs are expressed in 2019 dollars.

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

Underline represents presenting author.
Results: A total of 68,608 non-ESKD patients and 11,881 ESKD patients with incident major bleeding were included in the follow-up analysis. Patients with ESKD had significantly more admissions, inpatient days, and emergency visits than those without. Use of outpatient (OP) cardiac rehabilitation was significantly lower among ESKD patients. Post-index OP encounters had the largest magnitude difference, with 460.8 more OP encounters per 100 person-years among those with ESKD. Total costs for inpatient encounters, observation unit visits, ED visits, and OP encounters were statistically significantly higher for ESKD patients compared with non-ESKD patients.

Conclusions: In the year following an incident major bleed, Medicare beneficiaries with ESKD have significantly higher all-cause HCRU and total healthcare costs than patients without ESKD who experienced the same event; these differences persist after adjustment.

Funding: Commercial Support - Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

<table>
<thead>
<tr>
<th>Table 1. HCRU in the year following incident major bleeding event in patients with and without ESKD, adjusted for age, sex, race</th>
<th>Non-ESKD</th>
<th>ESKD</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients in follow-up analysis</td>
<td>68,608</td>
<td>11,881</td>
<td></td>
</tr>
<tr>
<td>30-day readmission (%)</td>
<td>12.2</td>
<td>28.6</td>
<td>16.4 (10.5, 22.2)</td>
</tr>
<tr>
<td>90-day readmission (%)</td>
<td>50.9</td>
<td>50.2</td>
<td>28.6 (18.4, 38.9)</td>
</tr>
<tr>
<td>Number of inpatient hospital admissions</td>
<td>121.9 (10.5)</td>
<td>295.1 (1.9)</td>
<td>364.3 (307.1, 421.5)</td>
</tr>
<tr>
<td>Number of inpatient hospital ED admissions</td>
<td>0.3 (0.20)</td>
<td>2.1 (0.14)</td>
<td>1.8 (0.65, 3.1)</td>
</tr>
<tr>
<td>Number of acute inpatient hospital</td>
<td>13.3 (0.95)</td>
<td>13.5 (0.9)</td>
<td>2.2 (0.10, 3.2)</td>
</tr>
<tr>
<td>Number of observation unit encounters</td>
<td>0.2 (0.05)</td>
<td>0.3 (0.02)</td>
<td>0.3 (0.02, 0.15)</td>
</tr>
<tr>
<td>Number of emergency department encounters</td>
<td>7.4 (0.18)</td>
<td>14.0 (0.05)</td>
<td>6.6 (0.36, 0.76)</td>
</tr>
<tr>
<td>Number of OP encounters</td>
<td>191.1 (6.00)</td>
<td>532.7 (14.05)</td>
<td>341.6 (341.6, 966.4)</td>
</tr>
<tr>
<td>Number of other institutional care visits</td>
<td>307.1 (0.35)</td>
<td>406.7 (1.07)</td>
<td>99.6 (99.6, 190.7)</td>
</tr>
<tr>
<td>Number of postcardiac rehabilitation encounters</td>
<td>35.5 (1.00)</td>
<td>15.3 (0.51)</td>
<td>20.2 (0.96, 37.7)</td>
</tr>
<tr>
<td>Number of episodes</td>
<td>691.2 (32.3)</td>
<td>681.1 (33.86)</td>
<td>5.6 (0.04, 52.7)</td>
</tr>
<tr>
<td>Number of emergency/unscheduled physician encounters</td>
<td>66.4 (12.4)</td>
<td>137.1 (10.48)</td>
<td>70.7 (47.5, 104.1)</td>
</tr>
<tr>
<td>Number of remediation/unscheduled physician encounters</td>
<td>133.4 (13.9)</td>
<td>183.5 (19.04)</td>
<td>50.1 (29.6, 60.1)</td>
</tr>
<tr>
<td>Number of physician encounters</td>
<td>123.1 (12.25)</td>
<td>156.1 (14.37)</td>
<td>33.0 (10.3, 55.7)</td>
</tr>
<tr>
<td>Number of nonphysician encounters</td>
<td>155.1 (12.25)</td>
<td>156.1 (14.37)</td>
<td>1.0 (0.01, 2.0)</td>
</tr>
<tr>
<td>Number of hospitalizations</td>
<td>65.6 (7.02)</td>
<td>73.6 (7.36)</td>
<td>8.0 (1.8, 13.8)</td>
</tr>
<tr>
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</tbody>
</table>
| Kaplan-Meier curve analyses for each outcome. a. All-cause mortality, b. ischemic stroke, c. severe bleeding, and d. MACE.

Subgroup analysis for all-cause mortality, ischemic stroke, severe bleeding, and MACE according to type of oral anticoagulant.

TH-PO219
National Rates of Primary Aldosteronism Screening in Patients with CKD
Jordan B. Cohen, Maria Bonanni, Jesse Passman, Heather Wachtel, Debbie L. Cohen. University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: Primary aldosteronism (PA) is a common, treatable cause of resistant hypertension and kidney fibrosis but is vastly underdiagnosed. Limited evidence exists regarding screening rates and outcomes of screening for PA among patients with chronic kidney disease (CKD).

| Kaplan-Meier curve analyses for each outcome. a. All-cause mortality, b. ischemic stroke, c. severe bleeding, and d. MACE.

TH-PO218
Survival Benefit of Anticoagulation in Patients with ESKD and Atrial Fibrillation
Soo yeon Choi, Jun Young Lee, Donghui Shin, Jae seok Kim, Byoung Geun Han. Yonsei University Wonju College of Medicine, Wonju, Republic of Korea.

Background: Prevalence of atrial fibrillation (AF) in patients with end stage kidney disease (ESKD) is high and increasing; however, current evidence is insufficient and conflicting regarding oral anticoagulant (OAC) use in patients with ESKD and AF.

Methods: A retrospective cohort study of patients diagnosed with AF after ESKD was conducted using the Korea National Health Insurance System Database from January 2007 to December 2017.

Results: Compared with OAC nonuser OAC user were associated with lower risk of all-cause death (hazard ratios (HR) 0.71; 95% confidence interval (CI) 0.58-86), ischemic stroke (HR 0.63; 95% CI 0.43-92), and MACE (HR 0.76; 95% CI 0.59-0.98) without increased risk of severe bleeding (HR 1.58; 95% CI 0.99-2.52). Patients used direct OAC showed significantly lower risk of all-cause death (HR 0.44; 95% CI 0.28-0.69), ischemic stroke (HR 0.36; 95% CI 0.13-0.99), and MACE (HR 0.42; 95% CI 0.22-0.79) than those of OAC-nonuser, but no association with severe bleeding (HR 0.26; 95% CI 0.04-1.90).

Conclusions: In patients with ESKD and AF, OACs were associated with reduced all-cause death, ischemic stroke, and MACE risks.
Methods: In a national cohort of US Veterans diagnosed with hypertension and followed from January 2000 to December 2021, we identified patients with new indications for PA screening (i.e., hypertension with hypokalemia or resistant hypertension). We evaluated rates of PA screening and results of screening among those with and without CKD (eGFR <60 vs. ≥60 ml/min/1.73m²) using Cox regression, adjusted for age, sex, race, systolic blood pressure, heart rate, insurance status, smoking, substance abuse, homelessness, cardiovascular disease, obstructive sleep apnea, and diabetes.

Results: A total of 457,395 patients met inclusion criteria, among whom 73,747 (16%) had CKD at the time of developing a new indication for PA screening. Those with CKD were older (mean 72 vs. 61 years) and had higher serum potassium levels (4.2 vs. 4.0 mEq/L) and higher prevalence of diabetes (42% vs. 30%) and cardiovascular disease (25% vs. 18%) compared to those without CKD. In the overall cohort, 7,427 (1.5%) patients underwent PA screening, among whom 1,068 (14%) had biochemical evidence of PA. Patients with CKD were 55% more likely to undergo PA screening than those without CKD (adjusted HR 1.55, 95% CI 1.44-1.67), which was similar across all CKD stages. Among those who underwent PA screening, biochemical evidence of PA was similar in patients with and without CKD (adjusted HR 0.92, 95% CI 0.75-1.12). Patients with CKD had similar rates of adenolactenectomy but were less likely than those without CKD to be appropriately treated with a mineralocorticoid receptor antagonist (adjusted HR 0.86, 95% CI 0.78-0.94), excluding patients with serum potassium >4.5 mEq/L.

Conclusions: In a national cohort of Veterans with indications to undergo PA screening, those with CKD were more likely to undergo PA screening and had similar rates of PA compared to those without CKD, but were less likely to receive appropriate treatment with a mineralocorticoid receptor antagonist. Overall, rates of PA screening among all groups were exceptionally low.

Funding: Other NIH Support - NHLBI

TH-PO220
Salt Sensitivity and Hypertensive Nephropathy: A Link to Be Discovered Francesca Tonelli, Luca D'Urban, Marco Simonini, Lorenza Citterio, Laura Zagato, Paolo Manunta, Chiara Lanzani, IRCCS Ospedale San Raffaele, Milano, Italy.

Background: Sodium sensitivity (SS) is a change in blood pressure (BP) depending on Na+ intake, 30% of population has it. Either a salt load test or a sodium dietary protocol can be used to stratify the population into 3 groups based on BP variation: sodium sensitive (-1.3084 ml/min microalbuminuria. Genetic polymorphism analysis has been executed.

Methods: We analyzed data collected from the follow-up (FUP) of 127 subjects with a new diagnosis of hypertension, categorized by their profile through acute salt load test. We analyzed the kidney damage by annual decline of eGFR and development of proteinuria. SNPs located in genes related with Na+ metabolism, aldosterone synthesis and kidney tubular Na+ reabsorption are related to this phenotype.

Methods: We analyzed data collected from the follow-up (FUP) of 127 subjects with a new diagnosis of hypertension, categorized by their profile through acute salt load test. We analyzed the kidney damage by annual decline of eGFR and development of proteinuria. Genetic polymorphism analysis has been executed.

Results: No differences in the decline of eGFR are observed among the groups (-1.3084 ml/min ± 0.16 vs. 0.372). SR subjects seem to be more prone to develop earlier microalbuminuria (2.10.808, p= 0.005) even with an adequate BP control (P-Anova SBP 0.766; P-Anova DBP 0.856). An inverse correlation exists between pressure-natriuresis ratio and decline in eGFR (R -0.194 p= 0.016). Polymorphism in CYP11B2 (0.72 OR p=0.045) and NEDD4L (0.74 OR p=0.027) are protective against eGFR decline. ADD3 polymorphism (3.73 OR p= 0.049) is a risk factor for development of microalbuminuria. KL (0.15 OR p=0.034), PKD and TRPC6 (p-Value 0.037, p-Value 0.009) polymorphism are protective factor against microalbuminuria.

Conclusions: SR patients are more at risk of developing hypertensive nephropathy earlier than other groups; steeper pressure natriuresis ratio is involved in quicker decline in renal function possibly accelerating development of hypertensive nephropathy. Further studies with larger sample and standardization in salt sensitivity test are needed to translate this knowledge into clinical setting.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Statewide Burden of CKD due to Hypertension (HTN) from 1990 to 2019 in the United States: Analysis for the Global Burden of Disease Study

TH-PO223

Rohan Gajjar,1 Hardik Desai,2 Bijin Thajuddeen,1 Sahas Reddy Jitta,4 Shasank Rachapudi,3 Jobby John,3 Abhiraj Patel,1 Viswaja Koppama,1 John H Stroger Jr Hospital of Cook County, Chicago, IL; 1Gujarat Adani Institute of Medical Science, Bhuj, India; 2Banner University Medical Center Tucson, Tucson, AZ; 3Mercy Hospital St Louis Area, Saint Louis, MO; 4Kurnool Medical College, Kurnool, India; 5Dr Somervell Memorial CSI Medical College and Hospital, Thiruvananthapuram, India; 6Our Lady of Fatima University College of Medicine, Valenzuela City, Philippines; 7Mayo Clinic Stroger Jr Hospital of Cook County, Chicago, IL; 8Mayo Clinic

Background: CKD due to HTN ranks as the 2nd leading cause of death among all causes of CKD in United States (US). We sought to assess the burden of CKD due to HTN within the US.

Methods: Using Global Burden of Disease methodology, prevalence, incidence, death, and disability-adjusted life year (DALYs) of CKD due to HTN assessed by age, sex, year from 1990-2019 for all resident in US.

Results: The prevalence has shown a steady increase over the years, with the total number of cases rising from 1.5 million (95% uncertainty interval [UI]: 1.4-1.7 million) in 1990 to 2.8 million (95%UI:2.6-3.1 million) in 2019. Simultaneously, the number of deaths has tripled, from 13,960 in 1990 to 43,329 in 2019. The highest Annual Percentage Change (APC) in the age-standardized mortality rate (ASMR) was found in West Virginia(101%), Iowa(95%) and Minnesota(93%). For the ASIR, the highest rates were seen in Utah and California, both at 11%, with Iowa at 10%. The ASDR revealed West Virginia(87%), Iowa(81%), and Kentucky(80%) as the areas with the highest burdens.

Conclusions: CKD attributed to HTN has shown a rapid increase across the US, given the substantial APC in prevalence rose by 86%. From 1990-2019, the DALY numbers and the age standardized DALYS per 100,000 population caused by CKD due to HTN increased by 171% and 57%, respectively.

Representation of Real-World Adults with CKD in Clinical Trials Supporting Blood Pressure Treatment Targets

TH-PO224

June Li,1,2 Jaejin An,3,4 Mengjiao Huang,1 Matt M. Zhou,1 Maria E. Montez-Rath,2 Fang Niu,5 John J. Sim,6 Alan C. Pao,5 Vivek Charu,5 Michelle Olden,1,2 Manjula Tamara,1,21 VA Palo Alto Geriatric Research Education and Clinical Center, Palo Alto, CA; 2Stanford University School of Medicine, Stanford, CA; 3Kaiser Permanente Southern California Department of Research & Evaluation, Pasadena, CA; 4Kaiser Permanente Bernard J. Tyson School of Medicine, Pasadena, CA; 5Kaiser Permanente Southern California, Pasadena, CA; 6Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA; 7VA Palo Alto Health Care System, Palo Alto, CA; 8Stanford University Department of Pathology, Stanford, CA.

Background: Little is known about how well trial participants with CKD represent real-world adults with CKD. We assessed the population representativeness of clinical trials supporting the 2021 Kidney Disease: Improving Global Outcomes blood pressure (BP) guidelines in real-world adults with CKD.

Methods: We identified two real-world population of patients with CKD who met the guideline definition of hypertension based on use of antihypertensive medications or a sustained systolic BP ≥120 mm Hg in 2019 in the Veterans Health Administration (VA) and Kaiser Permanente of Southern California (KPSC). We applied the inclusion and exclusion criteria from three BP target trials, the Systolic Pressure Intervention Trial, the Action to Control Cardiovascular Risk in Diabetes trial, and the African American Study of Kidney disease, to estimate the proportion of adults with a systolic BP above the guideline recommended target of <120 mm Hg and the proportion who met eligibility criteria for 1st trial.

Results: We identified 503,480 adults in VA and 73,412 adults in KPSC with CKD and hypertension in 2019. We estimated 79.7% in the VA population and 87.3% in the KPSC population had a systolic BP ≥120 mm Hg; only 23.8% (95% CI: 23.7% - 24.0%) in the VA and 20.8% (95% CI: 20.5% - 21.1%) in KPSC were trial-eligible. BP trials were representative of <15% of adults with CKD and diabetes, age <50 years, or stage 4 CKD. More than 50% of trial-ineligible adults met a exclusion criteria.

Conclusions: Fewer than one in four real-world adults with CKD and hypertension were represented in major BP target trials. A large proportion of adults who are at risk for cardiovascular morbidity from hypertension and susceptible to potential adverse treatment effects still lack relevant treatment information.

Funding: NIDDK Support

Table 1. Percentage of real-world adults with chronic kidney disease and hypertension in the VA and KPSC resources in 2019 with BP trials supporting the 2017 Kidney Disease: Improving Global Outcomes blood pressure (BP) guidelines.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>VA</th>
<th>KPSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number with Hypertension</td>
<td>503,480</td>
<td>73,412</td>
</tr>
<tr>
<td>Blood pressure guidelines (recommended target, %)</td>
<td>≥90</td>
<td>≥90</td>
</tr>
<tr>
<td>ACE/ARB use, %</td>
<td>52.5</td>
<td>52.5</td>
</tr>
<tr>
<td>ACCO/CCO/CO use, %</td>
<td>10.4</td>
<td>10.4</td>
</tr>
<tr>
<td>ACCO/CCO/CO use, %</td>
<td>10.4</td>
<td>10.4</td>
</tr>
<tr>
<td>AACE guideline, %</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Use of trial-eligible, %</td>
<td>10.4</td>
<td>10.4</td>
</tr>
<tr>
<td>Use of trial-eligible, %</td>
<td>10.4</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Percentage of real-world adults who meet eligibility criteria of blood pressure trials in the VA and KPSC.

Blood Pressure Control Before and After the Updated 2017 Guidelines in Patients with Proteinuric Kidney Disease

TH-PO225

Donald J. Weaver,1 Nathaniel Putnam,2 Bruce M. Robinson,2 Eloise Salmon,2 Elaine S. Kamel,1 Sharon G. Adler,1 Richard A. Lafayette,1 Susan F. Massengill,3 Zubin J. Modil,4 Kidney Research Network, 5Levine Children’s Hospital, Charlotte, NC; 6University of Michigan, Ann Arbor, MI; 7University of California Los Angeles, Los Angeles, CA; 8Stanford Medicine, Stanford, CA; 9Cedars-Sinai Medical Center, Los Angeles, CA.

Background: We hypothesized that the stricter 2017 ACC/AHA Task Force hypertension (HTN) guidelines led to improved blood pressure control (BPC) in patients with proteinuric renal disease after 2017.

Methods: Data from existing electronic health record documentation for each patient up to May 1, 2022 was extracted on adult patients (≥18) from the Kidney Research Network multi-center electronic health record registry of patients with glomerular disease. Baseline diagnosis of HTN was defined using blood pressure measurements, ICD-9/10 codes, and medication records. BPC was defined as BP < 120/80 for ≥75% of follow-up records, excluding baseline diagnosis. Follow-up was split into two eras,
Hypertension and CVD: Clinical - I

Figure 2. Odds of reaching blood pressure control in hypertensive glomerular disease

Conclusions: In adjusted analyses, BPC improved modestly after 2017. However, BPC in patients with proteinuric CKD remains poor, especially when compared to more recent stricter recommendations. Future analysis with greater follow-up time, and using the most contemporary data possible, are needed to understand opportunities to do more to achieve greater BPC in this population.

TH-PO226

A Multicentre Audit of Standardised Office Blood Pressure Measurement in Ireland

Eithne M. Nic an Righ,1 Anees Anees,2 Lynn Redahan,3 Yvonne M. O'Meara,4 Frank Ward,5 Denise M. Sadlier,1 Mater Misericordiae University Hospital, Dublin, Ireland; Tallaght University Hospital, Dublin, Ireland.

Background: Hypertension is a common comorbidity of chronic kidney disease (CKD) and increases the risk of cardiovascular disease, end-stage kidney disease and death. The KDIGO 2021 Clinical Practice Guideline on the Management of Blood Pressure in CKD recommends a target systolic blood pressure (BP) target <120 mmHg in adults with CKD. Importantly, the guideline distinguishes between routine and standardised office BP measurement with the latter more likely to be an accurate measure of BP. In this study, adherence to standardised office BP measurement was assessed in busy nephrology outpatient clinics in two hospitals.

Methods: The KDIGO guidelines describe eighteen criteria to achieve standardised office BP measurement (e.g. patient sitting relaxed ≥5 mins, avoidance of caffeine/ tobacco in 30 minutes prior to BP measurement, position of BP cuff). Adherence to these criteria was prospectively assessed by direct observation of BP measurements. Basic demographics and BP data from patients attending nephrology outpatient appointments in two Dublin teaching hospitals were collected electronically. Adherence to 18 criteria was assessed using descriptive statistics. This audit is now expanding to include cardiology clinics as well as a questionnaire to assess patient awareness of hypertension.

Results: From January 2022–2023, 308 patients were recruited. Of the 18 criteria assessed, 6 had an adherence of ≥ 90% and 5 criteria had an adherence of <10%. Areas with poorest compliance included supporting the arm during BP measurement 18.2% (n=56), averaging ≥2 readings 0.3% (n=1) and noting the time antihypertensive medication was last taken 2.3% (n=7). Measurement of BP in both arms at the initial visit was not carried out for any patients. The mean BP was 136/72 mmHg and Systolic BP <20 mmHg was achieved in 22% (n=33) patients. Clinical practice was similar across both sites other than a statistically significant difference in practice: informing patients of their BP verbally (90.3% vs 12%, P <0.001) and in writing (100% vs 1.9%, p <0.001).

Conclusions: Current clinic BP measurement does not meet the definition of standardised office BP measurement as outlined by KDIGO. However, simple changes to clinical practice could be implemented through education to significantly improve BP measurement as a more accurate measure of treatment response.

TH-PO227

Exploring the Spectrum of Blood Pressure Associations with CKD: The International 24-Hour Aortic Blood Pressure Consortium (i24ABC)

Sola Aouw Bahous,1 Thomas Weber,2 Chadia S. Haddad,1 Pascale Salahem,3 Alejandro De La Sierra,4 Antonio Argyris,5 Bernhard Hametner,6 Christopher C. Mayer,7 Daniel L. Piskorz,8 Dimitrios Terentes-Prinzlott,7 Emanuel Giddula,9 Eugenio Girolami,10 Gary D. Hartzler,11 Giacomo Pucci,12 Jacques Blacher,13 Kazuomo Kari,14 Maria Lorenzo Muiesan,15 Mohnsen Agharazi,16 Piotr Jankowski,17 Sabine Perl,18 Siegfried Wassertheurer,14 Yi Zhang,19 Stefan Orter,19 Athanasia Protogerou.20 The International 24-Hour Aortic Blood Pressure Consortium (i24ABC).1 Lebanese American University School of Medicine, Byblos, Lebanon; 2Klinikum Wels-Grieskirchen GmbH, Wels, Austria; 3Ethniki Kαι Kapodistriaka Panepistimio Athenon Iatriki Scholae, Athens, Greece; 4Universität de Barcelona Facultat de Medicina i Ciencies de la Salut, Barcelona, Spain; 5Universidad Cardenal Herrera-CEU, Valencia, Spain; 6Aristoteleio Panepistimio Thessalonikis Scholae Epistemon Ygeias, Thessaloniki, Greece; 7The University of Iowa, Iowa City, IA; 8Universiteit Jagiellonski w Krakowie Collegium Medicum, Krakow, Poland; 9Ethniki Kαι Kapodistriaka Panepistimio Athenon, Athens, Greece; 10University degli Studi di Perugia, Perugia, Italy; 11Hotel-Dieu de Paris, Paris, France; 12Universita degli Studi di Brescia, Brescia, Italy; 13Universite Laval, Quebec, QC, Canada; 14Austrian Institute of Technology GmbH, Wien, Austria; 15Shanghai Tenth People's Hospital, Shanghai, China; 16Istituto di Cardiologia Sanatorio Britannico SA, Santa Fe, Argentina; 17Ethniki Kαι Kapodistriaka Panepistimio Athenon, Athens, Greece; 18Jichi Ika Daigaku, Shimotsuke, Japan; 19Medizinische Universitat Graz, Graz, Austria.

Background: Chronic kidney disease (CKD) has emerged as a significant public health concern. The kidneys are primarily exposed to pulsatile rather than steady hemodynamics, which complicates the bidirectional relationship between CKD and hypertension. We aimed to explore relationships between blood pressure (BP) parameters and renal function in a pooled dataset from 21 centers worldwide.

Methods: The dataset included clinical and hemodynamic information. All participants underwent office BP measurements, in addition to 24-hour ambulatory BP monitoring (ABPM) with the same validated automated brachial oscillometric device (Mobil-O-Graph, I.E.M., Germany) using a transfer function for central pressure, and mean/diastolic pressure calibration. Renal function was estimated using the CKD-EPI equation and subjects classified into the 6 eGFR categories following the KDIGO 2021 guideline.

Results: We included 5204 subjects, 46.1% females, with a mean age of 60.8 ± 13.9 years. Diabetes was noted in 14.7% and hypertension in 70.3% of subjects, 76% of whom were on antihypertensive therapy. The mean eGFR was 88.5 ± 19.9 mL/min/1.73 m². More than half of the participants (56.5%) had a normal or high eGFR (G1) and only 1.9% had a severely decreased eGFR (G5). The prevalence of hypertension increased progressively across GFR categories with 95.7% of subjects in G5 vs. 67.7% in G1 (p<0.001) with hypertension. Diastolic BP tended to decrease (p=0.001) and SBP to increase (p=0.001) with decreasing eGFR. These associations were consistent for both brachial and central values, and for office and ABPM measurement techniques. Systolic reverse dipping status was independently associated with decreased eGFR after adjustment for gender and age, and irrespective of hypertension status (β=1.74, p=0.004).

Conclusions: CKD is associated with adverse hemodynamic changes, both at the brachial and the aortic level, and in office and out-of-office measurements, indicative of arterial stiffening.
pCRS were less than high school education [1.82 (1.21, 2.73)], history of CVD [1.48 (1.02, 2.12)], diabetes [1.83 (1.40, 2.36)], and higher serum creatinine and albumin to creatinine ratio (ACR) was measured from urine. CKD was defined as eGFR < 60 ml/min/1.73m² or ACR ≥ 30 mg/g. Change in eGFR and log ACR were defined as the difference in each measure between V1 and V2. To estimate the association between LE8 score with change in eGFR and log ACR, we used linear and generalized linear models adjusted for follow-up time, baseline demographics, smoking status, and clinical factors. All analyses accounted for HCBS/SOL complex survey design.

Results: Among 1,284 Hispanic/Latino participants with CKD at V1, mean age was 48.6, 57.2% were women, and mean LE8 was 61.1 (SE: 0.7). Over an average of six years of follow up, the mean eGFR declined by 1.73m² per year and log ACR declined by 0.60 per year. Multivariable-adjusted models, for each 10-unit increment (improvement) in LE8 score, eGFR declined by 0.99 less (95% CI: -1.97, -0.02) and log ACR declined an additional 0.15 (95% CI: 0.06, 0.28) between V1 and V2.

Conclusions: Among diverse US Hispanics/Latino adults with CKD, greater LE8 score (better CV health) was associated with modest but statistically significantly lower declines in eGFR and greater improvements in log ACR over six years.

Funding: NIDDK Support

TH-PO231

Ideal Cardiovascular Health and CKD Progression in Hispanic Adults

Magdalena Madero,1 Ana C. Ricardo,2 Ana K. Fernandez Yépez,3 Eunice Carmona,3 Karen Sacal Saba,1 Jose M. Alvarez Vallejo,1 Sara Cabrera Castelán,1 Ana L. Ramírez Santamaría,2 Natalie Meza,3 Claire T. Larkin,3 Celestín Missikpode,2 James P. Lash.1,4 Instituto Nacional de Cardiología Ignacio Chavez, Mexico, Mexico;5 Universidad de Illinois Chicago, Chicago, IL.

Background: The American Heart Association developed the Life’s Simple 7 metric to promote cardiovascular health. We evaluated the association of this metric with chronic kidney disease (CKD) progression among Hispanic individuals with CKD.

Methods: We conducted a prospective observational cohort study of 663 adults with CKD enrolled in the Mexico and Hispanic Chronic Renal Insufficiency Cohorts (HCRC and MCRIC), with entry estimated glomerular filtration rate (eGFR) 20-70 ml/min/1.73m².

Ideal levels of Life’s Simple 7 (score range 0-14) were the following: nonsmoker; body mass index <25 kg/m²; ≥150 minutes/week of physical activity; healthy dietary pattern (high in fruits and vegetables, fish, and fiber-rich whole grains; low in sodium and sugar-sweetened beverages); total cholesterol <200 mg/dL; blood pressure <120/80 mm Hg, and fasting blood glucose <100 mg/dL. The primary outcome was CKD progression defined as 30% and 40% decline in eGFR from baseline. Cox proportional hazards regression analyses were used.

Results: At study entry, mean (SD) age was 56 (12) years, 238 (36%) were female, and 408 (62%) had diabetes. Mean (SD) baseline eGFR was 45 (17) ml/min/1.73m², and median (IQR) urine protein excretion was 0.6 (0.1-2.6) g/24 hours. The median (IQR) Life’s Simple 7 score was 7 (6-9) points, and 47% of participants had ideal or intermediate cardiovascular health (score 8-14 points). During a median follow-up of 3.4 years, there were 415 (63%) and 341 (51%) CKD progression events for 30 and 40% eGFR decline, respectively. In analyses adjusted for age, sex, education, and baseline eGFR and proteinuria, each point higher Life’s Simple 7 score was associated with 10-12% lower risk of 30% and 40% eGFR decline (HR, 95% CI: 0.90,0.85-0.94 and 0.88,0.84-0.92, respectively).

Conclusions: In this cohort of Hispanic adults with CKD, the prevalence of ideal cardiovascular health was high. Higher Life Simple 7 score was associated with reduced risk for CKD progression.

TH-PO232

Cardiorenal Clinic: The Experience of Patients with CKD and Cardiovascular Disease

Sebastian Consuegra-Flores,1,2 Fernando A. Cuellar-Gonzalez,1,2 Mauricio Arvizu Hernandez,1,3 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; 1TecnoMedico de Monterrey - Campus Ciudad de Mexico, Ciudad de Mexico, Mexico.

Background: The coexistence of CKD and CV disease poses significant challenges in patient management. CV disease is the leading cause of mortality among CKD patients. This study aims to describe the establishment of a specialized cardiology nephrology clinic and report the initial and follow up results.

Methods: Since 2022, the cardiology nephrology clinic has been established, providing the care of a nephrologist, cardiologist, nephrologist fellows, medical students, and a nutritionist. Together, we conduct simultaneous clinical evaluations of patients using ultrasound (VEXU) and bioimpedance. The clinic aims to enhance care, optimize pharmacological and non-pharmacological management, reduce hospitalizations, slow disease progression, and ultimately improve patient outcomes.

Results: 50 patients completed one year follow-up, 30 (60%) were male, mean age of 43.8±13.5 yrs. The baseline and outcomes of the patients are presented in Table 1.

Conclusions: The establishment of a specialized cardiology nephrology clinic offers comprehensive management of patients with CKD and CVD. The clinic aims to reduce the risk of complications and improve long-term prognosis for these patients. In addition, nearly all of these patients have experienced successful outcomes, including effective management of their comorbidities and the utilization of appropriate medications and overall clinical improvement. As a result, patients experience an enhanced quality of life.
TH-PO233

Influence of Baseline Depressive Symptoms on the Effect of Blood Pressure (BP) Intervention on Cognitive Outcomes in the SPRINT Trial


Background: We examined the hypothesis that baseline depressive symptoms might modify the effects of BP control on cognitive outcomes.

Methods: We used data from SPRINT, an RCT that tested the effects of SBP goal <120 vs. <140 mmHg on cardiovascular and cognitive outcomes. Based on Patient Health Questionnaire (PHQ)-9, we defined 3 groups: no (score 0), minimal/mild (score 1-9), moderate/severe (Scores 10-27) depressive symptoms. We examined interactions of baseline PHQ9 groups and SBP intervention on adjudicated cognitive outcomes of mild cognitive impairment (MCI) or probable dementia (PD).

Results: Among 8487 SPRINT participants included in the analysis, the three baseline PHQ9 groups were 34.6%, 57.9%, 7.3%, respectively. There were 1243 MCI events and 322 PD events. As shown in Table 1, BP intervention lowered the risk of MCI/PD, more so with baseline depression.

Conclusions: Intensive SBP control resulted in decreased hazard of developing MCI/PD and presence of baseline moderate/severe depression was associated with significant increase in hazard of developing PD and PD/MCI. Nonetheless, there was no evidence that the effects of BP intervention on cognitive outcomes were modified by baseline depressive symptoms.

Funding: NIDDK Support

Table 1

<table>
<thead>
<tr>
<th>Depressed symptom</th>
<th>Delta SBP</th>
<th>Delta % antihypertensives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>140 (14.4, 15.2)</td>
<td>0 (0, 0, 0.4)</td>
</tr>
<tr>
<td>Mild</td>
<td>140 (13.6, 14.9)</td>
<td>0.7 (0, 0.6, 1.5)</td>
</tr>
<tr>
<td>Moderate/Severe</td>
<td>80 (5.6, 12.4)</td>
<td>0.6 (1.6, 0.5)</td>
</tr>
</tbody>
</table>

TH-PO234

Depressive Symptoms and Achieving Blood Pressure (BP) Goals in the Systolic Blood Pressure Intervention Trial (SPRINT)


Background: We examined the hypothesis that depressive symptoms might result in lower adherence to systolic BP intervention (SBP goal < 120 vs. < 140 mmHg) in a post-hoc analysis of SPRINT data.

Methods: Based on baseline depressive symptoms assessed by the Patient Health Questionnaire (PHQ-9), 9 scores, we defined depressive symptom groups as no (score = 0), minimal/mild (score =1-9), moderate/severe (score = 10-27) depressive symptoms. We used mixed effects models to relate baseline PHQ9 groups to post-randomization delta SBP (achieved standard arm SBP - achieved intensive arm SBP and delta number of antihypertensives).

Results: In the 9340 included SPRINT participants, achieved SBP by baseline PHQ9 groups in standard and intensive arms are presented in Fig 1. Delta SBP and delta antihypertensives are presented in Table 1.

Conclusions: Moderate/severe depressive symptoms were associated with less separation of achieved SBP in SPRINT. Addressing depressive symptoms might be important to achieve adherence to interventions.

Funding: NIDDK Support

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

Underline represents presenting author.
Trends of Blood Pressure Control in CKD Among US Adults: Findings during the period 2017-2020 (Table 6). The % of individuals with self-reported hypertension or taking BP medications was 66, 69, and 86%, respectively (p value<.0001). Although the number of BP medications prescribed increased significantly across time (Table), a significant % of individuals with CKD and hypertension had systolic BP 130-139 mm Hg (17%) or a diastolic BP 37 (23%) during the period 2017-2020 (Figure).

Conclusions: The number of individuals with CKD noted to have hypertension has increased significantly over time. Although there has been a significant increase in the number of BP medications prescribed, a considerable number of individuals with CKD still did not meet their BP goal.

Funding: Other NIH Support - NHLBI

<table>
<thead>
<tr>
<th>Number of BP medications</th>
<th>2011-2014</th>
<th>2015-2016</th>
<th>2017-2020</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8,185,709 (28)</td>
<td>8,405,170 (27)</td>
<td>8,344,185 (28)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>2</td>
<td>5,304,534 (18)</td>
<td>5,290,751 (21)</td>
<td>11,384,859 (36)</td>
<td>&lt;.0001</td>
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<tr>
<td>≥3</td>
<td>2,766,509 (9)</td>
<td>2,313,501 (7)</td>
<td>6,205,776 (17)</td>
<td></td>
</tr>
</tbody>
</table>

% in systolic BP categories over time

TH-PO237

An Interesting Presentation of Unilateral Renal Artery Stenosis Swee Ping Teh,1 Ivan Wei Zhen Lee,1 Jia Min Chua.1 1Sengkang General Hospital, Singapore, Singapore; 2Ministry of Health Holdings Pte Ltd, Singapore, Singapore.

Introduction: Renal artery stenosis is uncommon, however, the prevalence has increased in the presence of hypokalemia and severe hypertension. We report a spontaneous dissection of the renal artery resulting in unilateral ischaemic nephropathy and secondary hyperaldosteronism.

Case Description: A 52-year-old Chinese Male was referred for the evaluation of hypertension and symptomatic hypokalemia (2.4 mmol/L). 24-hour urine potassium (K+) was 74 mmol/day suggestive of urinary loss. There was no history of diuretic use. Cortisol post 1mg ONDST was 25 nmol/L, excluding Cushings syndrome. Serum aldosterone was elevated (29 ng/dL (~21)) and plasma renin activity was not suppressed (5.4 ng/ml/h (2.9-10.8)), suggesting secondary hyperaldosteronism. Doppler ultrasonography of the renal arteries showed an atrophied left kidney with poor visualization of the proximal segment of the left renal artery with tardus parvus waveform. CT angiography showed near complete occlusion at the origin of the left renal artery with significantly reduced opacification distally and an atrophic left kidney suggesting chronic dissection with thrombosis. The right renal artery was normal. DMSA scan showed left kidney contributes to 5% and the right kidney contributes to 95% of the total kidney function.

He was started on Valsartan 40mg OD and spironolactone 12.5mg OD later. His blood pressure was well controlled. Potassium supplementation was reduced from 3.6g/day to 0.6g/day while maintaining normal K+, stable serum creatinine of 119nmol/L, eGFR 58ml/min/1.73m2 and urine albumin/creatinine ratio of 2.7mg/mmol.

Discussion: We present an interesting case of unilateral RAS, likely from a chronic dissection of the left renal artery causing secondary hyperaldosteronism. Familial etiologies of renovascular hypertension include atherosclerosis or fibromuscular dysplasia. Upon reviewing his medical history, we noted that he presented with left flank pain a year ago, and was treated for pyelonephritis. CT KUB then revealed normal-sized kidneys. We postulate that spontaneous dissection could have happened then, resulting in left renal artery stenosis and secondary hyperaldosteronism. Initiation of RAAS blockade resulted in the reversal of the effects of hyperaldosteronism and glomerular hyperfiltration, as evidenced by the reduction in potassium supplementation, albuminuria, and BP control.

TH-PO238

Resistant Hypertension with Recurrent Flash Pulmonary Edema in the Setting of Bilateral Renal Artery Occlusion Korin Karabulut, Boston University, Boston, MA.

Introduction: Resistant hypertension is defined as elevated blood pressure despite three different classes of anti-hypertensives and warrants thorough investigation to rule out underlying secondary causes. Renal artery occlusion is an uncommon pathology, which can lead to severe kidney damage and can present with non-specific symptoms such as hematuria, acute kidney injury, uncontrolled hypertension.

Case Description: 49-year-old male with past medical history of unprovoked pulmonary embolism, recurrent flash pulmonary edema, hypertension, stage 4 chronic kidney disease with nephrotic range proteinuria who presented with breathlessness, back pain and claudication symptoms. On presentation, he was found to have hypertensive emergency with flash pulmonary edema, requiring nitroglycerin infusion and mechanical ventilation. Initial laboratory tests were remarkable for hypokalemia, elevated creatinine, 4 g/dl plasma uric acid on dipstick and microscopic hematuria. Anti-PLA2r, ANCA, serum and urine metanephrines were unrevealing. Patient had prior renal biopsy showing collapsing glomerulopathy with chronic renal thrombotic angiopathy. As the patient was hemodynamically stabilized, secondary causes for hypertension were investigated. Renal doppler ultrasound was performed, showing abnormal aorta thrombosis at the level of junctional infrarenal segments with bilateral occlusion of renal arteries. These findings furthermore confirmed with MR-Angiogram and renal nuclear scans. Given the life debilitating claudication symptoms, the patient underwent right axillolibral bypass.

Discussion: Recurrent flash pulmonary edema and resistant hypertension should raise suspect for renovascular hypertension and potentially renal artery occlusion. Renal artery occlusion is a rare finding and can be seen in patients with trauma, endothovascular interventions, atherosclerosis, thromboembolic events and possibly underlying hypercoagulability. After ruling out lupus anticoagulants, antiphospholipid panel, Factor Leiden V, homocysteine, trauma and we concluded that the renal artery occlusion was due to atherosclerotic plaque by pathologic. While the treatment is on case-on-case basis, recanalization was pursued for our patient with resolution of claudication symptoms but no significant improvement of kidney functions.

TH-PO239

Primary Hyperaldosteronism Secondary to Right Adrenal Hypoplasia Nonfunctioning Left Adrenal Adenoma Elucidated by Adrenal Vein Sampling Adam Tuchinsky,1 Sundus Sardar,2 Abdel-Rauof M. Akkari,3 Umar Farooq,2,3 Nasrollah Gahramani.2,3 1UPMC Pinnacle Littitz, Littitz, PA; 2Penn State Health Milton S Hershey Medical Center, Hershey, PA; 3Penn State College of Medicine, Hershey, PA.

Introduction: Primary hyperaldosteronism includes two main subtypes namely idiopathic hyperaldosteronism(also termed bilateral adrenal hyperplasia) and unilateral aldosterone-producing adenoma, managed with aldosterone antagonists or adrenalectomy, respectively. Aldosterone renin ratio (ARR) has emerged as a significant parameter as compared to plasma aldosterone concentration (PAC), thus identifying need for adrenal vein sampling (AVS) or further exclusionary tests including imaging, the solitary utility of which without AVS may result in unwarranted adrenalectomy. Our case demonstrates the importance of AVS and elaborates the context that needs to be applied to plasma renin and aldosterone levels.

Case Description: A 68-year-old male with history of type 2 diabetes, coronary artery disease status post stenting 15 years ago, hyperlipidemia, and GERD, was referred for refractory hypertension, requiring carvedilol 25mg twice a day, doxazosin 2mg twice a day, hydrochlorothiazide 50mg daily, isosorbide mononitrate 30mg daily, losartan 100mg daily and spironolactone 50mg daily. Workup revealed microalbuminuria, normal serum potassium, bicarbonate, free metanephrines, renin, elevated aldosterone level of 40.1ng/dL, and elevated ARR of 44.6. Renal duplex ultrasound negative for renal artery stenosis. Patient had prior renal biopsy showing collapsing glomerulopathy with chronic renal angiographic thrombosis. As the patient was hemodynamically stabilized, secondary causes for hypertension were investigated. Renal doppler ultrasound was performed, showing abdominal aorta thrombosis at the level of junctional infrarenal segments with bilateral occlusion of renal arteries. These findings furthermore confirmed with MR-Angiogram and renal nuclear scans. Given the life debilitating claudication symptoms, the patient underwent right axillolibral bypass.

Discussion: Recurrent flash pulmonary edema and resistant hypertension should raise suspect for renovascular hypertension and potentially renal artery occlusion. Renal artery occlusion is a rare finding and can be seen in patients with trauma, endothovascular interventions, atherosclerosis, thromboembolic events and possibly underlying hypercoagulability. After ruling out lupus anticoagulants, antiphospholipid panel, Factor Leiden V, homocysteine, trauma and we concluded that the renal artery occlusion was due to atherosclerotic plaque by pathologic. While the treatment is on case-on-case basis, recanalization was pursued for our patient with resolution of claudication symptoms but no significant improvement of kidney functions.

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

Underline represents presenting author.
Discussion: PAC may be challenging to interpret due to many influencing factors, hence PAC is emerging as a beneficial parameter to delineate the initial diagnosis of primary hyperaldosteronism. Our case also emphasizes the utility of cortisol corrected PAC laterization ratio in these cases. While adrenal vein sampling may appear counterintuitive, it is prudent to consider AVS for confirmation prior to adrenalectomy.

TH-PO240
Lessons Learned in Determining Unilateral vs. Bilateral Intervention in Bilateral Renal Artery Stenosis
Amanda Abi Doumet, Ruchir D. Trivedi, UConn Health, Farmington, CT.

Introduction: Renal artery stenosis (RAS) is defined as a narrowing of one or both renal arteries. It is most frequently caused by atherosclerosis and less frequently by Fibromuscular Dysplasia (FMD) and other vascular abnormalities. Although RAS due to FMD is successfully treated with balloon angioplasty, such intervention is not as promising in atherosclerotic RAS. We present a case of a patient with bilateral RAS with successful balloon angioplasty of only the left renal artery.

Case Description: A 46-year-old male with a history of hypertension and CKD stage IIIb presented with headaches and blurry vision. His BP was severely elevated at 209/153. His creatinine was elevated at 2.1 (baseline of 1.7). He was admitted for hypertensive emergency and underwent a workup for secondary causes of hyperaldosteronism. Aldosterone/ Renin ratio was 11.8/8.5 (1.4). Renal ultrasound duplex revealed a right kidney of 8.5 cm and left kidney of 11.4 cm, ostium of the right kidney was unable to be visualized and left renal artery systolic velocities were elevated. Renal angiography revealed critical mid-segment left RAS and right ostial RAS. A stent was placed in the left renal artery and the patient was started on Aspirin and Clopidogrel. Kidney function and blood pressure improved thereafter.

Discussion: RAS has many cardiovascular implications including resistant hypertension, CKD, and cardiac destabilization syndromes to name a few. Although the mainstay of treatment is medical therapy, some patients do benefit from stenting, such as those with hemodynamically significant atherosclerotic RAS and recurrent heart failure, refractory ACS, refractory hypertension, or progressive CKD due to bilateral or solitary ARAS. Although our patient had evidence of bilateral RAS, we concluded that the hemodynamically significant stenosis was that of the left renal artery. Since the left kidney was larger, we theorized that the primary stenosis was in the right kidney which led to compensatory hypertrophy of the left kidney and points to the relatively acute development of left RAS, explaining the patient’s acute presentation. Improvement in kidney function and BP after stenting the left renal artery further supports that conclusion. More studies are needed to identify which patients will benefit most from stenting, based on clinical presentation and assessment of hemodynamic significance of RAS.

TH-PO241
Preeclampsia Superimposed on Secondary Hypertension in the Setting of Fibromuscular Dysplasia
Alejandro Valdesuso,1 Eric S. Kerns,2 Landmark Medical Center, Woonsocket, RI; 3Rhode Island Hospital, Providence, RI.

Introduction: Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic disorder of medium-sized vessels that leads to arterial stenosis. Most affected vessels are the renal and internal carotid arteries. When to pursue endovascular treatment is not always clear.

Case Description: The patient is an 18-year-old female who had recently given birth presented to the nephrology clinic for evaluation of uncontrolled hypertension possibly related to fibromuscular dysplasia. The patient was first seen to have hypertension at an emergency department when she was 10 weeks 4 days pregnant. At that time, her blood pressure was 157/107 and proteinuria was 3+ on urinalysis. The pregnancy was complicated due to fibromuscular dysplasia (FMD) and her blood pressure was not well controlled.

Discussion: The patient had hypertension before 20 weeks gestation and proteinuria was first detected at 32 weeks 3 days, making this case one of chronic hypertension that progressed to preeclampsia with severe features. This patient meets criteria for angioplasty since she appears to have bilateral FMD and her blood pressure is not well controlled on as many as 3 antihypertensives. Cure rate of endovascular treatment appears to fall markedly with age. Curing hypertension in her case is preferable in view of her history of preeclampsia with severe features and the patient’s desire to become pregnant again.

TH-PO242
Sex Differences in the Risk of Uncontrolled Hypertension: Variation over the Life Course
Wan-Jin Yeo,1 Aditya L. Surapaneni,2 Josef Coresh,3 Shoshana Ballew,2 Bige Ozkan,2 Pascal Schlosser,3 Morgan Grams.2 NYU Langone Health, New York, NY; 3Johns Hopkins University, Baltimore, MD.

Background: Recent studies suggest that sex differences in uncontrolled hypertension (HTN) may vary by age.

Methods: We evaluated the prevalence of HTN and uncontrolled HTN in middle-aged (visit 2) and older-aged (visit 5) men and women of the Atherosclerosis Risk in Communities (ARIC) Study, assessing the associated risk of death and kidney function decline (defined as a 40% decline in eGFR). We looked at whether sex differences in older age could be explained by differences in chronic kidney disease (CKD), coronary heart disease (CHD), obesity, or by anti-HTN medication prescription patterns or adherence.

Results: Among 14,261 participants attending visit 2 (mean age 57), the prevalence of hypertension was 36% in both men and women. Among those with hypertension, the prevalence of uncontrolled hypertension (defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) was higher in men (51%) than in women (44%). Among 6398 participants attending visit 5 (mean age 76), the prevalence of hypertension was similar in both men and women (76% and 74% respectively). Among those with hypertension, the prevalence of uncontrolled hypertension was higher in women (41%) than in men (33%). Both controlled HTN and uncontrolled HTN were risk factors for mortality for visit 2 participants (HR 1.3, 95% CI [0.8, 1.3] and HR 1.5 [1.3, 1.6], respectively), with higher risk associated with uncontrolled HTN in women compared with men (p=0.003). Among those attended visit 5, both controlled hypertension and uncontrolled HTN were risk factors for kidney function decline (HR 1.2 [1.0, 1.5] and HR 1.6 [1.4, 1.9], respectively), with no difference by sex. Among visit 5 participants, controlled HTN and uncontrolled HTN were not significantly associated with mortality, but were strong risk factors for kidney function decline (HR 1.2 [1.0, 1.4] and HR 3.8 [1.8, 6.5], respectively) with no sex difference. Differences in uncontrolled HTN by sex at visit 5 was not explained by differences in CKD prevalence, CHD, obesity, anti-HTN medication prescription patterns (prescription, classes, and number), or anti-HTN medication adherence (defined as having at least one detectable antihypertensive medicine in urine).

Conclusions: Uncontrolled HTN shows sex differences which vary by age, with implications for mortality and kidney function decline.

Funding: NIDDK Support

TH-PO243
Trends in Hypertension Recognition, Treatment, and Control Between 2011 and 2019 Among Adults with CKD in the Veterans Health Administration
Joshua D. Martinez,1 I-Chun Thomas,2 Maria E. Montez-Rath,2,3 Alan C. Pao,2 Enrica Fung,1 Vivek Charn,1 John J. Sim,1 Jacin An,1 Michelle Odden,2,1 Manjula Tamur02,3,1 Stanford University, Stanford, CA; 2VA Palo Alto Health Care System, Palo Alto, CA; 3Kaiser Permanente Southern California, Pasadena, CA.

Background: Hypertension frequently accompanies chronic kidney disease (CKD) as etiology and sequelae. We examined contemporary trends in hypertension treatment and control in a national sample of adults with CKD.

Methods: We evaluated serial 5% cross-sectional samples of adults with CKD between 2011 and 2019 in the Veterans Health Administration (VHA). We defined CKD as a sustained estimated glomerular filtration rate (eGFR) value <60 ml/min/1.73m2 or a urine albumin-creatinine ratio (UACR) ≥30 mg/g.

Results: We examined 238,748 adults with a mean age of 72 years, 96% of whom were male. The age-adjusted proportion of adults with controlled BP declined from 78.0% in 2011 to 72.9% in 2019 (p-value for linear trend <0.001). Between 2011 and 2019, among adults with BP above goal, the age-adjusted proportion with a diagnosis of hypertension declined from 97.1% to 94.3% (p-value for linear trend <0.001), the age-adjusted proportion who did not receive antihypertensive treatment increased from 18.8% to 21.6% (p-value for linear trend <0.001), while the age-adjusted proportion who received three or more antihypertensive medications decreased from 41.8% to 36.3% (p-value for linear trend <0.001). The age-adjusted proportion of adults who received angiotensin converting enzyme inhibitors or angiotensin receptor blockers declined from 65.0% to 59.7% (p-value for linear trend <0.001); the age-adjusted proportion of adults who received thiazide-type diuretics declined from 24.1% to 20.0% (p-value for linear trend <0.001).

Conclusions: Among adults with CKD treated in the VA, the proportion with controlled BP has declined over time, coinciding with fewer prescriptions for antihypertensive medications.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO244

Proteomics of Myocardial Fibrosis in Advanced CKD
Chenyu Liu,1 Liangliang Zhang,1 Scott E. Janus,2 Robert J. Gaivin,3 Sudha K. Iyengar,1 Aparna Padiyar,1 Mahboob Rahman,1 Sanjay Rajagopalan,1 Sadeer Al-Kindi,1 Anne M. Hamil,1 Jeffrey R. Schelling,1 Mirela A. Dobre,1 1Case Western Reserve University, Cleveland, OH; 2University Hospitals, Cleveland, OH; 3Cleveland Clinic, Cleveland, OH.

Background: We used a large-scale, high-throughput DNA aptamer-based discovery proteomic platform to identify circulating biomarkers of myocardial fibrosis (MF) in advanced chronic kidney disease (CKD).

Methods: We evaluated 26 living kidney transplant (KT) recipients (age 53±16 years, 44% women, dialysis vintage 24.3±20 months) and 21 KT waitlisted participants (age 55±14 years, 58% women, dialysis vintage 23.2±17 months) who underwent proteomic profiling (SomaScan v.4.1) at study baseline. Living KT group had MF assessed by non-contrast cardiac magnetic resonance T1 maps prior to and 9 months post KT. Waitlisted group had T1 maps at baseline and 9 months follow-up. Plasma levels of 6472 proteins were assessed and related to baseline and change in T1 maps using DSEq2, adjusted linear regression, spike and slab regression, and Firth’s bias-reduced logistic regression models. PathfindIR and STRING-db v11.5 enrichment analyses were used to explore pathways.

Results: Among 126 proteins associated with baseline T1 maps, 43 remained significant after adjusting for clinical covariates (false discovery rate [FDR] adjusted p<0.05). Of these, 10 proteins were consistently selected across a large proportion of resampling iterations (~60%), with macrophage colony stimulating factor-1 (M-CSF1), displaying the greatest retest reproducibility (80%). Compared to waitlisted, KT recipients had a significant reduction in T1 maps at 9 months (79.2% vs 38.9% participants, p=0.043). Though FDR adjustment attenuated the association, greater baseline M-CSF1 was associated with decreased T1 maps in KT recipients (OR 2.53, 95%CI: 0.85, 14.11) and lower baseline M-CSF1 associated with increased T1 maps in waitlisted participants (OR 0.35, 95%CI: 0.07, 1.08). Plasma M-CSF1 levels by ELISA highly correlated with SomaScan values, and confirmed the inverse correlation with T1 maps.

Conclusions: Kidney transplantation was associated with a reduction in myocardial fibrosis measured by T1 maps. Plasma M-CSF1 was inversely associated with T1 maps and may serve as a prognostic, and potentially mechanistic biomarker, conferring a protective effect against myocardial fibrosis in advanced CKD.

Funding: Other NIH Support - NHLBI

TH-PO245

Relative Blood Volume Monitoring Using Crit-Line and Hospital Admissions: A Retrospective Analysis of over 25,000 Patients Across 330 Dialysis Clinics
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Background: Relative blood volume (RBV) monitoring may help guide fluid management, but real-world data on its use and potential impact on hospital admissions in chronic hemodialysis is limited. We aimed to compare hospital admissions among Fresenius Kidney Care (FKC) clinics with high utilization of RBV and propensity score matched (PSM) clinics not using RBV.

Methods: All data was retrospective, de-identified, and collected as part of routine clinical care and spanned 7/1/22-12/31/2022. RBV was conducted using Crit-Line (CLc; CLc+HR, in a Clip) devices integrated into 2008T dialysis machines. 165 FKC clinics with high utilization of RBV (HI-RBV; >90% of HD treatments used RBV) were PSM matched (PSM) clinics not using RBV.

Conclusions: HI-RBV clinics had fewer hospital admissions for all-cause (8%) and fluid-related (14%) hospital admissions and hospital days (113 days per 100 py) when compared to PSM clinics without RBV. PSM clinics experienced a trend toward lower 30-day readmissions among HI-RBV vs NO-RBV (25.5% vs 27.3%, p=0.049).

Funding: Commercial Support - Fresenius Medical Care

Figure 1. Predicted H trajectories (red lines) for measured profiles (black circles) during 20 treatments for 10 patients.
TH-PO247

Estimation of Absolute Blood Volume in Hemodialysis Patients Using Bioimpedance Spectroscopy

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Background: Measurement of absolute blood volume (ABV) during hemodialysis is essential to understand the relationship between the rates of vascular refilling and ultrafiltration. However, ABV is usually measured with dilution methods that are impractical in clinical routine. We evaluated whole body bioimpedance spectroscopy (wBIS) as an alternative approach.

Methods: Extracellular (ECV) and intracellular (ICV) volume were estimated using published equations (Moissl, Physiol Meas 27:921-933, 2006) based on wBIS measurements (Hydra 4200). Lean tissue mass (LTM) and adipose tissue mass (ATM) were calculated by a body composition model (BCM) (Chamney, Am J Clin Nutr 85:80–89, 2007). Reference blood volume (ABV_Rx) was measured by tracer dilution (Daxor BVA-100 analyzer, Daxor Corp., New York, NY, USA). Multiple regression and Bland-Altman analyses were used to determine the relationship of ABV with BCM and wBIS models, respectively.

Results: Data from 12 subjects (3 females, 53.8±15.2 years, pre-HD weight 85.6±19.7 kg) were analyzed. Pre-HD ECV (19.0±1.36 L), ICV (23.0±5.96 L), LTM (46.78±13.97 kg) and ATM (36.86±18.53 kg) were calculated, while ABV_Rx (5.58±1.20 L) was measured before HD. The BCM model (ABVBCM = 1.028+0.023*ATM+0.078*LTM) comprised LTM and ATM as independent variables (Fig. 1). The wBIS model (ABVwBIS=0.711+0.141*ICV+0.085*ECV) comprised ECV and ICV as independent variables (Fig. 2). ABV_Rx correlated with ABVBCM (R²=0.84, p<0.0001) and ABVwBIS (R²=0.84, p<0.0001). Since the head and parts of the feet and hands had not been measured by wBIS, the y-intercept in both regression models conceptually represents an estimate of the blood in these body parts.

Conclusions: Estimation of ABV by both ABVBCM and ABVwBIS models correlate with the reference method. Despite the small sample size, utilizing such simple body parts.

TH-PO249

Pulmonary Congestion Management Guided by Lung Echography in Hemodialysis: When and How?

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Background: Assessment of pulmonary congestion (PC) by lung ultrasonography (LUS) may help its management in hemodialysis (HD) patients, and better defining the dry weight (DW). We inspected the best moment to perform LUS in HD, and then applied a LUS guided DW adjustment approach.

Methods: Prospective randomized study: 18 HD patients, preceded by an observational phase: B-lines score (BLS: 8-sites method) and echocardiography were obtained before and after the first 2 HD sessions of the week. Total body volume using Bio-electrical Impedance Analysis (BIA) was measured besides serum NT-pro BNP levels. Circulating markers of inflammation (soluble urokinase Plasminogen Activator Receptor [suPAR] and soluble Suppression of Tumorigenicity 2 [sST2]) were measured.

Results: Patients were then randomized into: an active group where DW was reduced by 500 g in case of BLS > 0.54 zone measured after HD2 (every 2 weeks), and a control group where DW was modified only according to standard of care. Same measurements were repeated a month later.

Conclusions: BLS pre-HD1 (16.5 ± 5.33) and post-HD1 (15.3 ± 6.63) were elevated as pre HD2 (16.2 ± 5.26) and post-HD2 (13.6 ± 5.83). BLS was not affected by inter-dialysis interval (68h vs 44h). BIA was correlated to BLS only before HD2 (P= 0.007). BLS and the systolic cardiac function (left ventricular ejection fraction) were correlated only after HD2 (P=0.046). NT-ProBNP levels and BLS were correlated before both sessions (P=0.004, P<0.001). Cardiac diastolic function was correlated to BLS before HD1 (P=0.002) and after HD2 (P<0.034). Mean levels (± SD, ng/ml) of suPAR (7.88 ± 3.07 and 7.78 ± 3.02) remained high (N= 4 ng/ml), while sST2 levels reached 2-fold the upper normal value (27.4 ± 17.8). At day 30, a significant reduction in BLS was obtained before (17.4 vs 8.5, P<0.0001) and after (13.3 ± 5.0, P<0.001) HD in the active group, whereas no difference was found in controls.

Conclusions: Pulmonary congestion is common in HD patients even after reaching their dry weight is not systematically correlated to volume status or cardiac function. Chronic inflammation may be involved in PC pathophysiology. The best moment to estimate pulmonary congestion degree by lung ultrasound is after the 2nd HD session of the week, and a step by step DW adjustment guided by LUS may significantly and safely reduce PC.

Funding: Government Support - Non-U.S.
TH-PO250

Legacy Effect of a Lung-Ultrasound Intervention on the Risk for Death and Cardiovascular Events in Dialysis Patients

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Background: In the “Lung water by Ultra-Sound Guided Treatment (LUST) to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy” trial (NCT02310061), this treatment strategy was not more effective than usual care strategy in improving the primary end point of the study over two years. Since robust long-term effects of intensive haemodialysis in the frequent haemodialysis trial, we designed a post-trial, observational analysis extended up to 4.4 years.

Methods: We included in this analysis 315 HD patients. In patients in the active arm of the trial (n=157) ultrafiltration prescription was guided by lung US, while in the control arm (n=158) ultrafiltration was prescribed on the basis of standard clinical criteria. After the trial, patients were followed-up for 2 additional years, but no intervention was applied (observational phase). Since fluid volume is higher in men than in women, by protocol we tested the effect modification of male sex on the response to the lung-US intervention.

Results: Among the 315 HD patients, 223 (71%) were males. During the long-term observation (up to 4.4 years), the combined event occurred in 88 patients (56%) in the active arm and 100 (63%) in the control arm. Like in the LUST trial, the 16% risk reduction registered in the observational extension of the trial failed to achieve significance (HR: 0.84; 95% CI: 0.63-1.12, P=0.23). Sex emerged as a robust moderator. [P for effect modification 0.02] of the effect of the lung US intervention on the combined end-point. Indeed, the intervention produced a 35% risk reduction in men [HRmen: 0.65, 95% CI: 0.46-0.93, P=0.02] but not in women [HRwomen: 1.40, 95% CI: 0.84-2.34, P=0.20].

Conclusions: In an observational extension to 4.4 years of the LUST trial, the treatment strategy guided by lung-US was associated with a 35% reduction of the risk of the combined end-point of the trial in men while no such an effect emerged in women. These results are in keeping with biological knowledge indicating that in the hemodialysis population, men have higher fluid volume and cardiovascular risk than women.

TH-PO251

Volume Status Assessed by Physical Examination Correlates with Lung Ultrasound Findings in Patients with CKD

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Background: Volume overload is common in patients with chronic kidney disease (CKD), predominantly in dialysis patients. Volume assessment by physical examination (PE) may be subjective, therefore more accurate methods are necessary. Lung ultrasound (LUS) is one method used to accurately diagnose dry weight in dialysis patients. We aimed to assess LUS accuracy compared to PE in the range of CKD stages.

Methods: A prospective single center study. Hemodialysis (HD), peritoneal dialysis (PD) and CKD 1-5 patients were enrolled. PE was performed prior to LUS to evaluate signs of volume overload. Lung findings (crackles, pleural effusion) were reported as present or not, peripheral edema was graded 0-4. HD patients were examined twice, pre and post dialysis. LUS was performed by inspection of 12-zones. Each zone was assigned 0 points for less than 2 separated B-lines, 1 point if more than 3 B-lines were observed, 2 points when multiple B-lines with coalescing lines were documented and 3 points in cases of pulmonary consolidation. Accordingly, exam scores could range from 0, indicating a normal exam, to 36, indicating worst congestion possible. Results of PE and LUS were compared.

Results: Among 175 participants, 112 were HD patients, 18 PD and 45 CKD 1-5 patients. Higher LUS scores correlated with presence of lung crackles (OR=1.16 (1.10-1.23) p=0.01) and pleural effusion (OR=1.17 (1.11-1.23) p=0.01). There was a significant correlation between LUS score and peripheral edema (Figure 1), and an inverse correlation between room air saturation and LUS score (r=0.143, p=0.017). In HD patients weight differences before and after dialysis (delta weight) were compared with LUS score difference before and after dialysis (delta score). There was a linear correlation between delta weight and delta score (r=0.225, p=0.013).

Conclusions: LUS correlates significantly with PE findings in volume overload assessment in a broad spectrum of CKD patients.

Funding: Private Foundation Support
Absolute Iron Deficiency, Coronary Artery Calcification, and Mortality in Dialysis Patients

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Background: It is reported that iron-deficiency is associated with hypercoagulability and stroke by upregulating transferrin (Tang X. Circ Res. 2020;127:651). We studied the associations among iron deficiency, coronary artery calcification and mortality in patients on dialysis.

Methods: We included 230 patients with predilation online hemodiafiltration and 76 on hemodialysis. The Agatston coronary artery calcium score (CACS) and clinical data, such as transferrin saturation (TSAT), ferritin, hemoglobin, mean corpuscular hemoglobin (MCH), serum albumin and C-reactive protein (CRP) at baseline, were assessed. Kaplan-Meier survival analyses and Cox proportional hazard models were used to assess patients’ survival. Logistic regression analyses were used to determine related factors for absolute iron deficiency (TSAT ≤20% and ferritin concentrations ≤100 ng/mL).

Results: In all patients (n=306), age, dialysis duration and diabetes prevalence were 65±12 years, 76 (38-142) months and 42.5%, respectively. During 3 years, 52 all-cause deaths and 34 cardiovascular (CV) deaths occurred. Patients with absolute iron deficiency (n=102) showed significantly lower TSAT (13±4% vs 30±10%) and ferritin (34±23 vs 109±49 ng/mL) and MCH (28±5 vs 32±2) pg concentrations, but significantly higher CRP concentrations than patients without absolute iron deficiency (n=204) (P<0.05). Age, sex, dialysis duration, prevalence of diabetes and serum albumin concentrations were not significantly different according to the presence of absolute iron deficiency. Absolute iron deficiency was significantly related to the CACS (P<0.05). Patients with absolute iron deficiency had a significantly lower Kaplan-Meier survival rate for 3-year CV death than patients without absolute iron deficiency (82.2% vs 90.9%; log-rank test, P<0.05). However, there was no significant difference in survival for 3-year all-cause death between the two groups. After adjusting for age, sex, diabetes, dialysis duration, serum albumin, C-reactive protein and hemoglobin, absolute iron deficiency was a significant predictor for 3-year CV mortality (hazard ratio: 2.08, P<0.05), but not for 3-year all-cause mortality.

Conclusions: Absolute iron deficiency is a significant predictor for the CACS and CV mortality, but not for all-cause mortality in patients on dialysis.

Funding: Private Foundation Support

Coronary Artery Calcification Is Associated with Low Kt/Vurea and TH-PO254

Sonoo, Kenichi,1 Yoshiko Nishizawa,2 Toshiki Doi,3,4 Aiko Okubo,3,4 Kenichiro Morii,1,2 Kazuomi Yamashita1, Koji Usui1, Kenichiro Shigemoto,1 Takao Masaki,1 Iryo Hoin Ichiyokai Harada Byoin, Hiroshima, Japan; 4Iryo Hoin Ichiyokai Harada Byoin, Hiroshima, Japan; 1Hiroshima Daigaku Byoin, Hiroshima, Japan.

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Conclusions: Absolute iron deficiency is a significant predictor for the CACS and CV mortality, but not for all-cause mortality in patients on dialysis.

Funding: Private Foundation Support

Association Between Magnesium, Erythropoietin Resistance, and Mortality: The Japanese Dialysis Outcome and Practice Pattern Study (J-DOPPS) Study

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Background: Limited data are now available to evaluate the relationship between serum magnesium level, anemia, and mortality in the dialysis population.

Methods: Using data from the Japanese Dialysis Outcomes and Practice Patterns Study (J-DOPPS) phases 5 and 6, we analyzed the association between serum magnesium (s-Mg) levels and the erythropoietin resistance index (ERI) as the primary outcome. To estimate the longitudinal relationship, a mixed-effect model was used with ERI at each 4-month period as the dependent variable, quintiles of s-Mg at the previous 4-month period as the independent variable. We also examined the all-cause and cardiovascular disease (CVD)-related deaths as secondary outcomes by Cox regression with quintiles of s-Mg at baseline.

Results: Of the 4776 participants in J-DOPPS, 1650 were included in the analysis. The median of s-Mg at baseline was 2.5 mg/dL. A significant linear association of s-Mg with ERI (p for trend < 0.001) was revealed (Figure). The highest quintile of s-Mg was significantly associated with lower incidence of all-cause mortality (Table) and deaths due to CVD events compared to the middle (reference) quintile.

Conclusions: We observed that lower s-Mg levels subsequently induced higher ERI and that mild higher s-Mg levels predicted good rather than poor outcomes in Japanese dialysis patients. Adjustment of s-Mg levels may be proposed as a new strategy at low cost and risk to reduce the risk of premature mortality.

Funding: Commercial Support - Kyowa Kirin Co, Ltd.

Relationship between the all-cause deaths and serum magnesium.

Outcomes: Mg quintiles (mg/dL)/Baseline quintile (100 PYC). Cox analysis HR (95%CI): Adjusted analysis HR (95%CI).

All-cause deaths Q1 (2.1-2.3) 5.1 0.90 (0.63, 1.27) 0.60 (0.41, 1.08)
Q1 (2.2-2.3) 6.1 1.20 (0.81, 1.78) 1.23 (0.81, 1.88)
Q2 (2.4-2.5) 7.4 1.43 (0.99, 2.06) 1.4 (0.99, 2.0)
Q3 (2.6-2.7) 4.1 0.86 (0.52, 1.20) 0.93 (0.54, 1.62)
Q4 (2.8-2.9) 2.8 0.80 (0.52, 1.26) 0.80 (0.41, 1.55)

Mg, magnesium; Pys, person-years; HR, hazard ratio; CI, confidence interval.

Figure 1. Relationship between erythropoietin resistance index (ERI) and quintiles of serum magnesium (Mg). Point estimates and 95% confidence intervals of between-group comparison with Q3 as the reference are presented.

Anticoagulant and Antiplatelet Use and Risk of Serious Bleeding Events Among PDOPPS and DOPPS Patients Receiving Peritoneal or Hemodialysis, 2009-2022

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Background: Risk of serious bleeds among patients receiving dialysis is higher than the general population and may increase with the use of oral anticoagulant (OAC) and antiplatelet therapies (APT). The rate of bleeding in patients on OAC and APT between dialysis modalities is not well reported.

Methods: Using data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) (PDOPPS 2012 and PDOPPS 2014-2022), we examined all-cause mortality and APT use among patients receiving hemodialysis (HD) or peritoneal dialysis (PD) and present event rates of bleeding events that led to death or inpatient hospitalization, per 100 person-years, stratified by dialysis type, and use of OAC or APT.

TH-PO253

TH-PO254

TH-PO255

TH-PO256
Results: Overall, 27,612 received HD and 5,288 PD. OAC (9% vs. 4%) and APT (10% vs. 7%) use was higher among patients receiving HD vs. PD, and ~99% of all OAC use was warfarin. In both modalities, the rates of non-fatal, fatal bleeding events and hospitalizations due to any bleed or GI bleed were higher for patients prescribed (vs. not) OAC and APT (Table). First hospitalization bleeding rates occurred 2 and 3 times more often among HD patients and PD patients using OACs (compared to not), respectively. Those using APTs were observed to have a 25% (HD) and 40% (PD) increase (compared to not) in first hospitalization rate. The same trend was observed for recurrent hospitalizations due to any bleed and fatal bleeds.

Conclusions: OAC and APT use was >10% in both populations. Serious bleeding rates were higher among patients prescribed OAC and APT regardless of dialysis modality and differences in bleeding rates between treatment groups were larger among PD patients. Results underscore the need for strategies to reduce bleeding in patients on dialysis requiring anticoagulation, including novel agents with improved safety profiles.

Funding: Commercial Support - Merck and Co., Inc.

TH-PO257
Hemoglobin (Hgb) Variability and Target Range in Hemodialysis (HD) Patients
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Background: Based on randomized controlled trials in CKD patients (pts), in the US, a hgb target range between 10 to 11 g/dL is the mandated. Retrospective studies have shown lower hospitalization and death rates with higher hgb, and a higher risk of death with increased hgb variability. We investigated in this retrospective cohort study of incident HD pts receiving erythropoietin stimulating agent (ESA), the association between all-cause mortality hazard ratio (HR), hgb variability and level.

Methods: We studied a cohort of incident HD pts initiated with a long-acting ESA (Micrera; Vifor) within the first 90 days. In pts with at least twelve hgb values over the 6-months baseline period we quantified mean hgb and variability, as either standard deviation (sd) or slope of a linear model, as metrics. We built proportional hazard models including both mean and variability metrics to predict HR over the following 18 months, adjusted for race, sex, age, diabetes, serum albumin and phosphorus. We then built spline functions to depict HR in a bivariate fashion as a function of baseline mean hgb level and variability.

Results: We studied 64,042 pts out of 517,860 pts in Fresenius Kidney Care clinics. A range between 10.5 and 12.5 g/dL associated with the lowest HR when accounting for variability at lower and higher levels of mean hgb. Limitations of retrospective research apply. Adequately powered and designed experimental studies are needed.

Funding: Commercial Support - Vifor Fresenius Medical Care Pharma Ltd

TH-PO258
Using Machine Learning to Construct a Predictive Model for Hemoglobin in Maintenance Hemodialysis Patients
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Background: Constructing prediction models of hemoglobin concentration by machine learning method, to assist clinicians to make clinical decisions in order to achieve individualized and precise treatment for maintenance hemodialysis (MHD) patients with renal anemia.

Methods: The medical records of maintenance hemodialysis patients from January 1, 2021 to January 1, 2023 in Sichuan Provincial People’s Hospital were included. Demographic characteristics, test results, medication orders were included to constructed the prediction models. Selection of characteristic variables were mainly based on previous published articles, and all medical data were derived after desensitization. Data were randomly divided into training set (80%) and test set (20%) after desensitization, filling, deletion and other preprocessing. Ten machine learning methods (Linear Regression, K-Nearest Neighbor Regressor, Support Vector Regression, Ridge Regression, Lasso Regression, XGBoost Regressor, Random Forest Regressor, AdaBoost Regressor, Gradient Boosting Regressor, Bagging Regressor) were used to construct prediction models. Model performance was assessed by comparing the difference between predicted and true values and by fitting with internal validation.

Results: The medical records of 495 patients were finally included. The study included 56% male with a median age of 60 years old. The patients’ dry weight was 58.7±11.3 kg and their weight before dialysis was 61.3±11.6 kg. In terms of laboratory results, the patients had a hemoglobin level of 10.9±6.18 g/L, a serum albumin level of 40.8±14.9 g/L, serum ferritin of 210.3(130.0–359.4) mg/L and an average transferrin saturation level of 26.2±17.3 %.

Conclusions: The machine learning-based hemoglobin prediction model of MHD patients can be used to predict the hemoglobin concentration to a certain extent, which can contribute to the individualized and precise management of anemia in maintenance hemodialysis patients.

Funding: Clinical Revenue Support

TH-PO259
Dynamic Predictions of All-Cause Mortality in Incident Hemodialysis Patients with Extended Joint Models Adjusting for Albumin Trajectory and Competing Risks
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Background: Joint models (JM) provide individual patient dynamic risk predictions based on the association between longitudinal biomarkers and mortality. We explore extensions to JM methodology performed for the first time with hemodialysis (HD) clinical trial data.

Methods: We evaluated the association of albumin with all-cause mortality in incident HD patients followed over 8 years in the Initiating Dialysis Early And Late trial. To account for skewness/outliers in albumin, novel JM with mixed effects sub-model with skew-normal, skew-t and skew-error errors were compared with conventional JM under normal distribution. Furthermore, we adjusted for the competing event of transplantation using Weibull cause-specific hazards. The dataset (N=315 patients) was randomly split into training dataset (3/4, N=236) for model fitting and validation dataset (1/4, N=78) to infer predictive performance. We obtained 12-month individual patient survival predictions from all JM at cut-offs 1, 1.5 and 2 years utilizing albumin trajectory and baseline risk factors.

Results: A median of 12 albumin records per patient with 24% and 19% event rates for death and transplantation ensured coverage of all 12 joint models. Albumin hazard ratio (HR) remained robust (0.89 to 0.90), 0.88 vs 0.79-0.83, 0.86-0.90 vs 0.84-0.88, 0.96-0.97 vs 0.96-0.97) across all distributional models for albumin. Prediction performance of all JM surpassed classical Cox model with baseline albumin (AUC = 0.71, 0.77, 0.93). Results were confirmed by a simulation study.

Conclusions: Our first clinical implementation of the joint models indicates its great potential for dynamic personalized survival prediction. Robustness of estimates to deviations from normality and higher predictive accuracy when adjusting competing events contribute to JM superiority over the classical Cox approach.

Funding: Commercial Support - Baxter Healthcare Corporation

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Real-Time Dual Prediction of Intradialytic Hypotension and Hypertension Using an Explainable Deep Learning Model

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Background: Intradialytic hypotension (IDIH) and hypertension (IDIHTN) are associated with poor outcomes in hemodialysis patients. However, there is currently no real-time predictive model for dual outcomes. This study aims to develop an explainable deep learning model using a sequence-to-sequence-based attention network to simultaneously predict IDIH and IDIHTN.

Methods: Electronic health records of 11,110 hemodialysis patients were utilized, comprising 302,774 sessions. The data was divided into training (70%), validation (10%), and test (20%) sets using randomization. IDIH-1 was defined as nadir systolic blood pressure (BP) <90 mmHg, IDIH-2 as a decrease in systolic BP ≥20 mmHg and/or a decrease in mean arterial pressure ≥10 mmHg, and IDIHTN as an increase in systolic BP ≥10 mmHg within 1 hour. The temporal fusion transformer (TFT)-based model was developed and compared with other machine learning models, including recurrent neural network, light gradient boosting machine, random forest, and logistic regression, in terms of model performance measured by receiver operating characteristic curve (AUCROC) and area under the precision-recall curves (AUPRC).

Results: The TFT-based model outperformed other models with AUCROCs of 0.953 (0.952–0.954), 0.892 (0.891–0.893), and 0.889 (0.888–0.889) for predicting IDIH-1, IDIH-2, and IDIHTN, respectively. The AUPRCs of the TFT-based model for the outcomes were higher compared to other models. Key predictors included age, previous session, systolic BP, and elapsed time.

Conclusions: The developed TFT-based model enables real-time prediction of both IDIH and IDIHTN while providing explainable variable importance.

Effect of Antioxidants on Oxidative Stress, Endothelial Dysfunction, Inflammatory Markers, and Carotid Intima Media Thickness in Maintenance Hemodialysis and Renal Transplant Patients

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Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in dialysis patients. Various non-traditional factors have been proposed for the increased incidence of CVD. N-acetylcysteine (NAC) serves as an antioxidant, acts on atherosclerosis and also improves the endothelial function. This study was designed to assess the effects of three months of NAC therapy on oxidative stress, endothelial dysfunction, inflammatory markers and carotid intima media thickness in maintenance hemodialysis and renal transplant patients.

Methods: Doppler was done to assess endothelial function by flow mediated dilatation (FMD) of the brachial artery and carotid arterial intima media thickness (cIMT). Brachial artery was imaged during reactive hyperemia (endothelium-dependent), flow-mediated dilatation, FMD) and during nitroglycerine-mediated dilatation (NMD, endothelium-independent). Oxidants (Melondialdehyde, MDA) and antioxidants (Total Antioxidant Status) were measured. NAC 1200 mg was given in two divided doses for three months. Parameters were repeated after three months of NAC therapy.

Results: 220 hemodialysis, 135 renal transplant patients were enrolled. Hemodialysis patients had higher serum homocysteine level which was significantly reduced after three months of NAC (25.7±3.86 vs 13.9±3.01 μmol/L after NAC, p<0.001). At baseline they had a high hsCRP (85.6±1.01 mg/dl) which reduced significantly (02.1±0.43 mg/dl, p<0.001) after NAC. CIMT was significantly reduced after three months of NAC (0.49±0.12mm). FMD of brachial artery endothelium was impaired at baseline (0.34±0.07mm, 0.69±0.21%), significant improvement after 3 months of NAC (0.41±0.11mm, 10.12±2.86%), p<0.001). Elevated baseline oxidative stress markers (MDA) compared to levels after NAC (16.2±1.30 vs 9.9±3±94 mmol/L, p<0.001). Antioxidant status was significantly low at baseline (1.03±0.21 mmol/L) compared to antioxidant status after NAC (1.41±0.24 mmol/L, p<0.01). Similar findings were seen in the post renal transplant patients.

Conclusions: CKD patients have endothelial dysfunction and oxidative stress which begins early, progresses during dialysis and persists after renal transplantation. With three months of therapy, NAC significantly reduces the oxidative stress, inflammatory markers and improves the endothelial function.
TH-PO264
Citrate-Acidified Dialysate Requires Less Heparin Use Without Affecting Mineral Metabolism Negatively
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Background: Heparin is used to prevent clotting in hemodialysis, but may cause bleeding, thrombocytopenia, and skeletal complications. Citrate-acidified dialysate (CAD) compared to acetate-acidified dialysate (AAD) may improve hemodynamic stability and reduce inflammation. Citrate has calcium complexing properties in regional anticoagulation, yet its use may affect mineral metabolism negatively. We studied the effect of a dialysis bath with low concentrations of citrate on heparin use and mineral metabolism.

Methods: 207 prevalent ESRD pts. (182 with high flux dialysis (HD), 25 with post dilution hemodiafiltration (HDF)) were followed for 48 weeks after switching from AAD (3mmol/l acetate) to CAD (0.8 mmol/l citrate, 0.3 mmol/l acetate; MTN, Germany). We monitored heparin consumption, potassium, pH, THP, phosphate, magnesium, and calcium as well as side effects.

Results: The cohort comprised 127 males and 81 females, mean age 71.6 years (range 25 – 95). Mean treatment time was 254 minutes per session (range 180 – 00) and mean blood flow at baseline 360 ml/min (range 250 – 420) vs. 254 minutes (range 180-300) and 370 ml/min (range 240-420) at 48 weeks. Mean initial heparin dosage per session was 5171 IU (95%CI 4836-5507) in HD and 6720 IU (95%CI 5920-7520) in HDF. This could be reduced step by step to a mean of 2985 IU (95%CI 2722-3246) in HD and 3375 IU (95%CI 3029-3723) in HDF after 48 weeks. CRP was higher (p=0.05) in HD pts than in HDF pts. at start. It increased during the observation in HD (8.0 vs. 15.0, n.s. after 48 weeks), but not in HDF (CRP start 2.7mg/l vs. 4.2mg/l after 48 weeks, n.s.). In neither group magnesium, calcium, phosphate, pH, THP nor KT/V changed significantly. During the observation period 7 pts. (3.4%) were intolerable to CAD, 11 withdrew for unknown reasons (5.3%), 11 pts. (5.3%) left the clinic, 1 patient switched to CAPD (0.5%), 3 (1.4%) were transplanted and 32 died (15.3%).

Conclusions: Under CAD heparin-dosing could be reduced markedly. This may be beneficial for the patient and reduce treatment costs. Long-term treatment with a low-concentration CAD was well tolerated and did not exacerbate secondary hyperparathyroidism. Further long-term studies are ongoing to assess effects on calcification, morbidity, and mortality.

TH-PO265
To Study the Clinical and Biochemical Outcomes of Citrate-Based Dialysate in Hemodialysis Compared with Bicarbonate-Based Dialysate in a Tertiary Care Hospital
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Background: The study to compare the effects of Citrate-based dialysate with Bicarbonate-based dialysate on systemic haemodynamics, dialysis efficiency, serum calcium, phosphate and bicarbonate levels.

Methods: The study was conducted in 25 ESRD patients undergoing HD with bicarbonate dialysate initially for period of 3 months followed by citrate dialysate for 3 months. Parameters were recorded at start, 3 months of HD with bicarbonate dialysate and HD with citrate dialysate at 6 months. Predialytic, intradialytic and postdialytic BP was recorded at each HD session. The mean of all BP readings was calculated for both groups. The clinical and lab parameters Kt/V, calcium, phosphate and bicarbonate levels were compared among both groups

Results: The mean Predialytic SBP in bicarbonate is 153.84 ± 18.60 mmHg, in Citrate dialysate is 140.24 ± 16.63 mmHg(p<0.001), mean Predialytic DBP in bicarbonate is 87.16 ± 10.75 mmHg, in citrate dialysate is 79.96 ± 8.63 mmHg (p<0.001). The Intradialytic SBP and DBP were lower in pts.undergoing citrate vs bicarbonate.

The mean Intradialytic SBP in bicarbonate is 148.56 ± 15.50 mmHg vs 135.92 ± 15.29 mmHg in citrate(p<0.005). The mean Intradialytic DBP in bicarbonate is 84.12 ± 12.02 mmHg vs 75.92 ± 8.94 mmHg in citrate(p<0.006). The mean Postdialytic SBP in bicarbonate is 145.56 ± 17.50 mmHg vs 129.24 ± 15.46 in citrate(p<0.003). The mean Postdialytic DBP in bicarbonate is 82.40 ± 10.77 mmHg vs 74.20 ± 7.04 mmHg in citrate(p<0.00)1

The mean Kt/V in bicarbonate is 1.2 ± 0.06 vs 1.33 ± 0.06 in citrate (p value<0.001).

The mean calcium level in bicarbonate is 9.03 ± 1.03 mg/dl vs 8.51 ± 0.97 mg/dl in citrate(p<0.07), the phosphate in bicarbonate dialysate is 5.53 ± 1.04 vs 4.76 ± 1.72 in citrate (p value<0.06).

The mean HCO3 level in bicarbonate dialysate is 16.08 ± 1.39 vs 17.75 ± 1.34 in citrate dialysate(p value<0.001)

Conclusions: Citrate dialysate can be good alternative for the standard bicarbonate based dialysate as it provides significant advantages in improvement in Pre, Intra And Postdialytic BP, better dialysis efficiency, improved acid base balance and lower phosphate levels.

TH-PO266
The Association of Dialysate Bicarbonate with Cardiac Arrhythmia in the Monitoring in Dialysis (MiD) Study
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Background: Sudden death accounts for half of all cardiovascular-related mortality among patients receiving maintenance hemodialysis (HD) and occurs more frequently on days that patients undergo HD. Higher dialysate bicarbonate (DBIC) may predispose to alakalemia and arrhythmogenesis. We tested if higher DBIC is associated with cardiac arrhythmia, and if this is modified by serum bicarbonate (SBIC).

Methods: Using data from the Monitoring in Dialysis study, we analyzed session-level data over a 12-month period from 66 patients with implantable loop recorders (ILR). We fit logistic regression and negative binomial mixed effects regression models to assess the association of DBIC with the presence and frequency of reviewer confirmed arrhythmia (RCA) events (ILR identified or patient marked event in which a manual review of the stored ECG tracing confirmed the presence of atrial fibrillation, supraventricular tachycardia, sinus tachycardia with rate >130 beats per minute, ventricular tachycardia, asystole, or bradycardia) in the intra- and inter-dialytic period.

Results: Mean age was 56 ± 12 years, 70% were male, 53% were Black, and 35% were Asian. There were 9,718 RCA events over 3,655 HD sessions. There were fewer RCA episodes associated with DBIC<35 compared to 35 mg/dL in unadjusted and adjusted models (IRR 0.45 (0.27, 0.75) for DBIC<35 at 48 weeks; aIRR 0.54 (0.30, 0.97), respectively). Otherwise no associations between DBIC and arrhythmia were identified. No results were modified by the inclusion of SBIC in the model.

Conclusions: We observed a lower frequency of RCA with higher DBIC, contrary to our original hypothesis. Within RCA, a majority of events were atrial arrhythmia. Validation of these findings in larger studies is required, with further need for interventional studies to explore the optimal DBIC level.

Funding: NIDDK Support

TH-PO267
Dialysate Buffer in Hemodialysis: Effect of Practice Patterns on Serum PTH

Background: We report the analysis of 3 dialysate (D) acidic buffers on serum PTH in 4 dialysis units in Paris (France) area.

Methods: Data from prevalent hemodialysis (HD) patients (pts) treated in 4 units were collected in the 4th quarter 2022 and analyzed with Kruskal-Wallis and stepwise logistic regression tests. The biology lab is common to the 4 units. PTH was assessed using Architect ICT PTH assay.

Results: The 529 pts were 64 y.o. with 35% females, dialysis vintage: 47 months, Charlson index: 10. The acidic buffers were acetate (30.7%), hydrochloric acid (HCl) (35.7%) and citric acid (citrate) (33.6%). Pts on acetate were significantly younger (59 years) versus 67.5 years on HCl and citrate (p<0.001), with a lower Charlson index (9 versus 10 (p<0.001). Pts on HCl had significantly lower serum PTH levels; serum magnesium was significantly lower in citrate group; calcium, phosphate, native vitamin D were not different (Table 1). Muscle cramps during the dialysis were found in 10.2% (citrate), 8.5% (HCl) and 6% (acetate, p<0.027). The D calcium is reported in Table 1. The proportion of pts on calcimetics and active vitamin D did not differ between groups. Factors associated with a PTH >612 pg/ml were age (≥0.012, p<0.04), acetate buffer (0.065, p<0.001) and calcimetic prescription (0.76, p<0.001). Conversely, only dialysis vintage was associated with a PTH < 130pg/ml (0.07, p=0.0066).

Conclusions: The use of citrate D in this cohort was not associated with a higher PTH compared to pts on acetate or HCl. The large prescription of D calcium at 1.65 mmol/l in the citrate group may have helped to avoid low ionized calcium. Higher muscle cramps and less magnesium levels were associated with use of citrate D and confirmed in this cohort. Dialysis with citrate or HCl are possible alternatives when avoiding acetate buffer is wanted. Increasing D magnesium to avoid cramps remains to be studied.
Hemodialysis: Volume, Metabolic Complications, Clinical Outcomes

**TH-PO268**

**Asymptomatic Heartbeat Irregularities (AHbI) During Hemodialysis (HD) Are Associated with Decreased Short-Term Survival**

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**Background:** Intradialytic AHbI are not well defined and are of unknown significance.

**Methods:** Beat-to-beat systolic blood pressure (SBP) and interbeat interval (IBI) were monitored during regular HD sessions in 83 age-matched patients (Pt). AHbI were defined as a10 irregular beats on a4hr recording. Hemodynamic variability indices were assessed using Finometer device and Beatscope software.

**Results:** AHbI were detected in 25 Pt (AHbI (+)). The representative clinical, laboratory and hemodynamic data in AHbI (+) and in Pt with regular beats (AHbI(-)) are listed in Table 1. There were no statistically significant differences between groups regarding the proportion of diabetes, hypertension, ischemic heart disease, SBP, intradialytic hypotension, PTH level or ultrafiltration rate. Kaplan-Meier analysis showed a significant decreased survival at 2y in AHbI (+) (Figure 1).

**Conclusions:** 1. Intradialytic AHbI are associated with cardiovascular risk factors and a higher plasma phosphate level, suggesting a link between mineral metabolism and heart disease. 2. In AHbI (+), diminished post HD plasma potassium change combined with decreased IBI and increased sdCO suggest a tendency to hemodynamic instability leading to higher mortality. The nature and the long term effects of the AHbI remain to be further explored.

Table 1.

<table>
<thead>
<tr>
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<th>AHbI (+) (n=25)</th>
<th>AHbI (-) (n=58)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>History of smoking (%)</td>
<td>37.60</td>
<td>19.75</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>63.80</td>
<td>63.14</td>
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<tr>
<td>Plasma creatinine (mg/dl)</td>
<td>17.20</td>
<td>17.10</td>
</tr>
<tr>
<td>Plasma glucose (mg/dl)</td>
<td>7.90</td>
<td>7.90</td>
</tr>
<tr>
<td>Lipoprotein(a) level (%)</td>
<td>3.20</td>
<td>3.20</td>
</tr>
<tr>
<td>IBI (ms)**</td>
<td>191.32</td>
<td>191.32</td>
</tr>
<tr>
<td>sdSBP (mmHg)**</td>
<td>83.12</td>
<td>83.12</td>
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<tr>
<td>SBP:DBP ratio**</td>
<td>0.70-1.5</td>
<td>0.70-1.5</td>
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</tbody>
</table>

* Predialysis: ±mean±SD; **Median (interquartile range); ***sd (standard deviation); DBP: diastolic blood pressure; CO: cardiac output.

Figure 1. Patients in normal, low, and high platelet groups from 15 countries and areas, A/NZ is for Australia and New Zealand, GCC is for Gulf Cooperation Council (6 countries)

**TH-PO270**

**Clinical Burden and Management of Hyperkalemia in Hemodialysis Centers in China: A Multicenter Retrospective Study (Visualize-HD)**

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**Background:** Hyperkalemia (HK) is associated with sudden cardiac death in patients on maintenance hemodialysis (mHD). We aimed to examine HK prevalence, serum potassium (sK) management practices, and mortality data in Chinese HD centers.

**Methods:** Visualize-HD (NT05020717) was a retrospective survey conducted in 31 Chinese administrative divisions. Patients aged 18 years who were on mHD for ≥3 months were eligible. HD centers were grouped as having high or low HK (sK ≥5.0 mmol/L) prevalence based on median values. Outcomes were analyzed over 3 years. The primary outcome was risk factors associated with HK prevalence. Secondary outcomes included risk factors associated with HK management, sK management practices, and mortality risk factors associated with mortality.

**Results:** A total of 50,983 patients from 231 centers were included. The age groups 18–44, 45–64, 65–74, and ≥75 years accounted for 18.7%, 46.5%, 23.0%, and 11.8% of patients, respectively; 59.2% were male. Most patients had a dialysis vintage of <5 years (62.2%), used 2.0 mmol/L dialysate potassium (91.8%), were on three times weekly dialysis (68.0%), and had a sK test once every three months (53.9%). Over half of the cohort (55.2%) received renin-angiotensin-aldosterone system inhibitors and 7.7% received potassium-binding drugs. HK occurred in 40.8% of patients; 20.4%, 8.7%, and 3.2% had sK ≥5.5, >6.0, and ≥6.5 mmol/L, respectively. Higher HK prevalence was associated with a higher proportion of patients with hyperphosphatemia and lower proportions of elderly patients and those with hypalbuminemia at the HD center level (all P < 0.05). The 3-year cumulative mortality rate was 21.3%. Over one-third of deceased patients (36.7%) had HK based on their last sK tests. Centers with high vs low HK prevalence had higher mortalities (all-cause: 21.9% vs 20.7%; cardiovascular: 13.5% vs 11.5%, both P < 0.05).

**Conclusions:** HK is prevalent in Chinese HD centers and is associated with risk factors. Chinese HD centers with higher HK prevalence had increased mortality rates. Long-term sK control is important for improving survival in patients on mHD. Yet, potassium-binding drugs are underused.

**Funding:** Commercial Support - AstraZeneca
TH-PO271
Readmission after Gastrointestinal Bleeding Hospitalization in Dialysis Patients
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Background: Gastrointestinal bleeding (GIB) is the most common bleeding event in patients on chronic dialysis, and oftentimes leads to hospitalization. The outcomes associated with hospitalization for a GIB are unknown. The INSPIRE collaborative group assessed all-cause hospital readmission rates after a GIB hospitalization among a nationally representative sample of dialysis patients in the United States.

Methods: We used data from adult dialysis patients who had a GIB hospitalization between Jan-2018 to Mar-2021. GIB hospitalizations were defined from primary, secondary, or tertiary discharge diagnosis codes (Zhao et al., AHQR 2006). All-cause readmission rate considered hospitalizations within 30 days from an index GIB hospitalization.

Results: Among a population of 405,530 patients, there were 19,663 GIB hospitalizations during follow up and 5,196 all-cause readmissions (26.4%) within 30 days of the index GIB hospitalization. On average readmissions occurred within 16.3 days of the index GIB hospitalization. Patients with a GIB hospitalization typically had one readmission event (n=4,365), yet a small proportion of patients had multiple readmissions during follow-up. Readmission rates after a GIB hospitalization were highest for younger patients between 18-44 years old, and those with an unknown or black race (Figure 1).

Conclusions: The 30-day all-cause readmission rate after a GIB hospitalization was 26%, and appeared to be highest among younger patients of a black race or those who were missing data on race. These findings act as a benchmark for the nephrology community. Future adjusted analyses are warranted to confirm the results and should consider morality and competing events of death within 30 days of an index GIB hospitalization.

Funding: Commercial Support - Fresenius Medical Care

TH-PO272
Left Ventricular Global Longitudinal Strain in Stable Stage 5 CKD Patients with Preserved Ejection Fraction Predicts Cardiovascular Events and Mortality After Dialysis Commencement
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Background: Early detection of subclinical cardiac dysfunction offers opportunity of timely intervention, especially before vulnerable transition from advanced CKD to ESKD. We previously found absolute left ventricular global longitudinal strain (GLS) <15% is predictive to mortality in dialysis patients with preserved ejection fraction (EF), while it’s still inconclusive whether the systolic function evaluated by GLS before hemodialysis commencement (HDC) is applicable to predict post-dialysis outcome in clinic stable CKD5 patients.

Methods: In this longitudinal prospective observation across HDC, we aimed to predict the post-dialysis cardiovascular outcome with pre-dialysis GLS. The CKD5 patients who had long-term HDC before 2020 were enrolled to post-dialysis outcome follow-up. Inclusions were EF>50% and eligible GLS within 2 years before HDC; main exclusion was frequent admission. The primary outcomes were post-dialysis major adverse cardiovascular events(MACCE), and secondary outcome was all-cause mortality(ACM).

Results: 201 among 242 stable CKD5 patients reached HDC, and 108 with eligible GLS were enrolled. Median duration from examination to HDC was 5.39 months. Median follow-up was 1458 days. GLS>15% is independent predictor of MACCE (HR 2.34[1.11-4.91][p<0.025*] and ACM(HR 2.97[1.18-7.49][p<0.021*]). GLS as continuous variable is independent predictor of MACCE(HR 0.80[0.82-1.00][p<0.040]*) and ACM(HR 0.84[0.73-0.95][p=0.007**]). The incremental diagnostic values contributed from GLS>15%(p<0.025*) or GLS<15%(p=0.042*) were significant in nested Cox models but LVEF (Figure).

Conclusions: LV subclinical systolic dysfunction, assessed by GLS<15% within previous 2 years before HDC, predicted post-dialysis MACCE and ACM in clinically stable patients having their HDC.

TH-PO273
Effectiveness of Heart Rate Variability for Predicting Intradialytic Hypotension in Chronic Hemodialysis Patients
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Background: Intradialytic hypotension(IDH) is a common complication during hemodialysis reported to occur in 20-30% of hemodialysis sessions. According to a recent meta-analysis, IDH based on nadir 90 criterion was reported to have the highest association with the patient survival rates. The heart rate variability(HRV) test is a non-invasive and simple method to measure autonomic nervous system activity. To date, no studies have demonstrated the usefulness of the HRV test in predicting IDH based on nadir 90 criterion. This study was aimed to elucidate the usefulness of the HRV test in predicting the occurrence of IDH.

Methods: This study was a multi-center prospective observational study. A total of 70 patients were enrolled in this study. Blood tests, echocardiography, and body composition measurement results were collected, and HRV test was performed for 24 hours during non-hemodialysis period. And then, a total 12 hemodialysis sessions were monitored. The patients were divided into the IDH group and non-IDH group. HRV index model was developed by a multivariate logistic regression analysis. The predictive value of IDH occurrence was analyzed through area under the receiver operating characteristic curve(AUROC) value.

Results: Among the nadir 90 criterion, 37 patients were placed in the IDH group, and 33 patients in the non-IDH group. Considering that the HRV test is affected by the lifestyle, data of night-time(00:00-04:00) was used. Standard deviation of normal-to-normal interval(SDNN), root-mean-square of successive differences(RMSSD), normal-to-normal interval<50ms(NN50), count, percentage of NN50 count(NN50), total power(TP), very low frequency(VLF), low frequency(LF), high frequency(HF), and LF/HF ratio, which are parameters of the HRV test, were analyzed to develop a HRV index model. The AUROC value for IDH occurrence (even in one session) of the developed HRV index model was 0.77. The AUROC value for frequent IDH occurrence (in more than 10% of sessions) was 0.803. A high HRV index (>0.544) was observed as an independent risk factor after adjusting for several other confounding factors(odds ratio 6.137, P<0.011).

Conclusions: The HRV test can be used as a useful tool to predict IDH. This is the first study to demonstrate the usefulness of the HRV test in prediction of the IDH occurrence according to the nadir 90 criterion.

TH-PO274
Changes of Hemodynamic Parameters over a Single Treatment Week in Patients Undergoing Chronic Intermittent Hemodialysis
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Background: Using ultrasound dilution, hemodynamic parameters such as access flow or cardiac output can be measured non-invasively and repeatedly during hemodialysis (HD). No data are available on the changes of these parameters within one week of treatment with long and short dialysis intervals.

Methods: In a prospective cohort study, various hemodynamic parameters were determined in n=44 prevalent HD patients over 4-hour-HD and HD3 monitor (Transonic). Measurements were taken hourly on the first HD day of the week, on the
Results: The median AF was 1.1 L/min (interquartile range 0.8-1.7) at the beginning of the HD and did not change during HD. The values were unchanged on the following HD days. The median CI was 3.2 (2.7-3.9) L/min/m² body surface area at the beginning of the first HD and CI continuously decreased to 85% of the baseline value during the HD (p<0.001). The CI recovered to baseline by the second HD and decreased to a median of 82% of baseline at the end of a session of HD (p<0.001). The same pattern was found at the third HD. Median TEF was 53% (46-64) at the start of the first HD of the week and remained constant across all HD treatments. Medians of the central hemodynamic parameters CVBI and TEDVI were 19 (16-25) and 10 (8-12) mL/kg body weight, respectively, at the beginning of the first HD and were lowered significantly by 13% and 9%, respectively, at the end of the first HD. The same pattern was found at the third HD. Median CI was significantly lower before the beginning of the third HD than before the first HD. Systolic and diastolic blood pressure as well as heart rate showed a course parallel to that of the CI.

Conclusions: HD treatment compromises cardiac index that recovers regularly and reversibly within the treatment week. Central overhydration is highest after the long interval and decreases as the week progresses.

TH-PO275
Risk Factors for Inpatient Mortality in Patients with CKD Hospitalized with Infections due to Multidrug-Resistant Organisms: A Nationally Representative Study
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Background: The CKD population, especially those with end-stage kidney disease (ESKD) on hemodialysis (HD), has higher rates of infections and more exposure to multidrug-resistant organisms (MDRO). However, few studies have evaluated the risk factors for mortality among CKD patients hospitalized with MDRO infections.

Methods: We extracted data from the 2020 national inpatient sample, the largest nationwide inpatient database in the US, for adults (age ≥18 years) with diagnosis of CKD (non-dialysis dependent CKD) and HD on MDRO infections (methicillin-resistant Staphylococcus aureus, vancomycin-resistant Enterococcus, multidrug-resistant gram-negative bacilli and Clostridioides difficile) by ICD 10 codes. The primary outcome was inpatient mortality. We compared the baseline characteristics and constructed multivariable logistic regression models adjusted for socio-demographics, comorbidities, and hospital characteristics to determine the risk factors for inpatient mortality.

Results: There were 49,624 and 15,075 admissions with MDRO infections among patients with CKD and ESKD, respectively. The mean age was 72.5 vs. 63.3 years, females 49.1% vs 47.2%, and White patient accounted for 73.0% vs. 48.9% in CKD vs ESKD group, respectively. Inpatient mortality was higher in ESKD patients compared to CKD patients (9.5% vs 12.1%). Older age and worse comorbidity scores were associated with increased risk of death in both groups. Black patients had higher risk of inpatient mortality compared to White patients (OR 1.40; 95% CI 1.14-1.71) in the CKD but not ESKD group. In the CKD group, hospital characteristics including large bed size, Northeast location, and government ownership were associated with higher risk of death, while in ESKD group, private-investor hospitals had higher mortality.

Conclusions: Inpatient mortality is higher in ESKD compared to CKD patients hospitalized with MDROs. Risk factors for mortality were older age, more comorbidities, and among those with CKD, Black race. Hospital-level risk factors include size, region, and ownership. Further studies should investigate structural, social, and dialysis-related factors on risk of inpatient mortality in CKD and ESKD patients hospitalized with MDRO infections.

TH-PO276
Factors Influencing Pre- and Post-Dialysis Central and Peripheral Blood Pressure in Dialysis-Dependent Veterans: A Single-Center Study
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Background: Central aortic blood pressure (BP) is more reflective of cardiovascular health than peripheral BP. While it is hypothesized, central BP monitoring which detects minute changes in vessels is not suitable for dialysis patients due to stiff vessels, data on pre and post dialysis variations between central and peripheral BP is non-existent. We aimed to study the differences between pre and post dialysis central and brachial BP in patients and identify factors influencing any differences.

Methods: All patients receiving hemodialysis at Hines VA Hospital were approached between December 2021 and March 2022. Pre and post dialysis central aortic and brachial BP were obtained using ACTOR technology. Data collected included demographic characteristics, prescribed dialysis time and achieved ultrafiltration (UF). Mixed effects model was used for statistical analysis.

Results: A total of 51 patients participated in the study. Baseline characteristics are shown in Fig 1. Average difference of 2.6 mmHg is noted between pre and post dialysis brachial and central aortic systolic BP readings, post dialysis readings being higher than pre dialysis readings (Fig 2) after controlling for age, BMI, ethnicity, history of smoking, diabetes, hypertension, peripheral vascular disease and coronary artery disease. Every 1 liter increase in UF is associated with a 1.35 mmHg difference in brachial vs. central aortic systolic BP.

Conclusions: In our single center study of veteran male dialysis population, for every liter of UF achieved, a 1.35 mmHg difference is noted in post dialysis brachial and central aortic systolic BP.

TH-PO277
Exposure to Elevated Temperature Is Associated with Elevated Risk for Cardiovascular Disease (CVD) Outcomes and Mortality Among Hemodialysis Patients in the United States
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Background: Ambient temperatures have increased due to climate change in many parts of the world. Adaptation and resilience to changing conditions is particularly concerning among individuals with chronic kidney disease, due to loss of renal function which impacts regulation of thermoregulatory mechanisms. The aim of this study is to assess the effect of heat on mortality and health care utilization among US hemodialysis patients.

Methods: We conducted a retrospective time-series analysis (2011-2016) of daily mortality, hospital admission, and emergency department visits identified in the United States Renal Data System. Daily volume of mortality, hospitalization and event-related emergency department visits, comparing 99th percentile vs. 50th percentile daily temperatures. Larger effects were observed for cumulative lagged exposure three-days prior to the outcome and for Southwest and Northwest climate regions.

Results: Overall, daily ambient temperature increase is associated with elevated risk for both mortality and health care utilization among hemodialysis patients. The rate ratios for all-cause mortality and daily temperature was 1.07 (95% CI: 1.03-1.11), 1.17 (1.14-1.21) for fluid disorder-related hospital admissions, and 1.19 (1.16-1.22) for cardiovascular event-related emergency department visits, comparing 99th percentile vs. 50th percentile daily temperatures. Larger effects were observed for cumulative lagged exposure three-days prior to the outcome and for Southwest and Northwest climate regions.

Conclusions: Heat exposure is associated with elevated risk for mortality and health care utilization among this vulnerable population. Furthermore, the effect appears to be potentially cumulative in the short-term, and varies geographically. Disclaimer: this abstract does not represent EPA policy nor USRDS position.
Predictors of Hospitalization in Adolescents and Young Adults with ESKD
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Background: Treatments for end-stage kidney disease (ESKD) include in-center dialysis, home dialysis, and transplant. Adolescents and young adults (AYA) are at increased risk for difficult disease course. Identification of risk factors for hospitalization may lead to changes in management.

Methods: We performed a secondary analysis of data in the US Renal Data System (USRDS). Included subjects were 16-24 years old at dialysis start 2010-2015 and had no previous history of kidney transplant. The combined outcome is time to first hospitalization. Analysis was by Cox proportional hazard modeling.

Results: Of the 4658 eligible subjects, 57% were male, 65% were white, and they had a mean age of 20.7 years (Table 1). Participants were followed for a median of 2.7 (2.6, 2.9) years during which there were 1963 hospitalizations. Multivariable Cox proportional hazards showed female sex, non-Hispanic ethnicity, dialysis catheter use, diabetic kidney disease, and lack of insurance were associated with increased risk of first hospitalization (Table 2).

Conclusions: Both demographic and potentially modifiable dialysis-related factors are associated with increased risk of hospitalization in AYA with ESKD.

Table 1. Baseline Characteristics

Table 2. Multivariable Hazard Ratios.
TH-PO279

Optimal Caloric Requirements of Critically Ill Patients on Chronic Hemodialysis (CHD)


Background: The KDOQI 2020 nutrition guidelines do not address the energy requirements of critically ill CHD patients. This study determined the actual caloric needs of critically ill CHD patients.

Methods: This was a single-center, single-blinded, randomized control trial of 11 critically ill intubated pts admitted to the ICU. A Puritan Bennet Indirect calorimeter was used for the data collection on non-dialysis days or before starting hemodialysis while NPO or on enteral feeding or TPN matched for protein, fat & carbohydrates after reaching a steady state. All pts were randomized to either a 28 kcal/kg/day or a 38 kcal/kg/day after baseline NPO data was obtained the prior day. The data collected by the calorimeter were 8 hr machine averages and included VO2, VCO2, respiratory quotient, and energy expenditure. In addition, time-averaged glucose obtained every 4 hours was calculated. Finally, statistics were performed utilizing the Student’s T-test & ANOVA for paired data.

Results: A total of 11 pts were included, seven males & four females. The pts had a mean age of 39 ± 7 years. 8 out of the 11 patients completed all three days of the study. Four patients were under 60 years, two males and two females. two males and five females comprised the over-60 age group. The baseline REE for patients <60 years was 26.0 ± 4 kcal/kg/day, and for patients >60 years was 22.0 ± 2 kcal/kg/day despite sepsis in two patients in each group. REE for all NPO patients was 23.5 ± 4 kcal/kg/day and only 24.5 ± 4 kcal/kg/day, and 26.0 ± 3 kcal/kg/day for TPN days with 28 or 38 kcal/kg/day (p<0.05). Time-averaged glucose increased to a clinically significant level with both diets; 162 ± 30 mg/dL (p<0.05) for pts receiving a 28 kcal/kg/day diet and 159 ± 25 mg/dL (p<0.05) for a 38 kcal/kg/day diet.

Conclusions: Current KDOQI nutrition recommendations overestimate the energy expenditure of critically ill HD patients. Critically ill CHD pts should be fed 24-26 kcal/kg/day or have their EE measured by indirect calorimetry to receive proper nutrition and avoid overfeeding.

Funding: Clinical Revenue Support

TH-PO280

Mortality of Elderly Patients with AKI Undergoing Continuous Renal Replacement Therapy: Is Age a Risk Factor?

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Background: The incidence of elderly patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is increasing. There is little evidence on the difference of mortality rates according to age in elderly patients. This study aimed to evaluate the age effect and predictors for mortality in elderly patients with AKI requiring CRRT.

Methods: A retrospective analysis was performed in elderly patients with AKI who underwent CRRT. A total of 480 patients aged ≥65 years were stratified into three groups according to age: youngest-old (age 65-74 years, n=205), middle-old (age 75-84 years, n=217), and oldest-old (age ≥85 years, n=58). The 28-day and 90-day survival rates were compared between three groups and predictors for mortality were analysed.

Results: The 28-day and 90-day survival rates were not different between three age groups (P=0.156 and P=0.189, respectively). The oldest-old group did not show an inferior survival rate compared to the other two groups. For 28-day mortality, prothrombin time [hazard ratio (HR) = 1.37, 95% confidence interval (CI) = 1.01 – 1.88, P = 0.046] and urine output at the start of CRRT (HR = 0.999, 95% CI = 0.998 – 1.000, P = 0.012) and CRRT duration (HR = 0.89, 95% CI = 0.83 – 0.95, P = 0.001) were predictors. For 90-day mortality, mean arterial pressure (HR = 1.02, 95% CI = 1.00 – 1.05, P = 0.019), admission duration (HR = 0.97, 95% CI = 0.95 – 0.99, P = 0.001) and CRRT duration (HR = 0.96, 95% CI = 0.91 – 0.99, P=0.036) were predictors. The middle-old group or the oldest-old group did not exhibit higher risk compared to the youngest-old group for 28-day and 90-day mortality.

Conclusions: An older age was not a risk factor for mortality in elderly patients with AKI undergoing CRRT. This implicates the importance of active management and application of CRRT in critically ill elderly patients with AKI.

TH-PO281

Intradialytic Hypotension and Worse Outcome in Patients with AKI Requiring Intermittent Hemodialysis

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Background: Intradialytic hypotension (IDH) is a critical complication related with worse outcomes in patients undergoing maintenance hemodialysis. Herein, we addressed impact of IDH on death and other outcomes in patients with severe acute kidney injury (AKI) requiring intermittent hemodialysis.

Methods: We retrospectively reviewed 1,009 patients who underwent intermittent hemodialysis due to severe AKI. IDH was defined as a decrease in systolic blood pressure (SBP) of ≥30 mmHg, with or without a nadir SBP of <90 mmHg during the first session. The primary outcome was all-cause death, and transfer to the intensive care unit due to unstable status was additionally analyzed. Hazard ratios (HRs) of outcomes were calculated using a Cox regression model after adjusting for multiple variables. Risk factor of IDH was evaluated using a logistic regression model.

Results: IDH occurred in 449 (44%) patients during the first hemodialysis session. Patients with IDH had higher death rate (39.6%) than those without IDH (23%) (HR, 1.39 [1.09–1.78]). The rate of ICU transfer was higher in patients experiencing IDH (17%) than those without IDH (11%) (HR 1.46 [1.02–2.09]). Factors, such as old age, high SBP, high pulse rate, active cancer, cirrhosis, anemia, and hypoalbuminemia, were associated with an increased risk of IDH episode.

Conclusions: The occurrence of IDH is associated with worse outcomes in patients with AKI requiring intermittent hemodialysis. Therefore, careful monitoring of IDH is necessary in this patient subset.

TH-PO282

Antibiotics Dosing in Four-Hour Sustained Low-Efficiency Dialysis: A Retrospective Data Review

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Background: Sustained Low-Efficiency Dialysis (SLED) is characterized by a slower blood flow rate than intermittent hemodialysis (IHD). SLED is usually done over 12 hours, a shorter duration of 4-hour might spare more time for procedures in critical care units (ICU). However, antibiotics dosing is not well established in 4-hour SLED, and clinicians might prescribe antibiotics using IHD dosing in view of the shorter duration.

Methods: In this single-center study, we assessed the dosing practices and clinical outcomes of antibiotics among recipients of 4-hour SLED. In-hospital mortality and recovery from sepsis were compared between those who received SLED dosing versus IHD dosing, using Cox regression and Kaplan-Meier curves. P-value <0.05 was set to represent statistical significance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: A total of 107 patients who underwent 4-hour SLED and received at least one broad-spectrum antibiotic were identified between 1/06/2016 to 1/06/2020. Among them, 68% were male with a mean age of 68 ± 12 years. The majority of patients were from the Middle East (81%). Around 20% had positive urine cultures, 19% had positive blood cultures, and 10% had positive sputum cultures. The majority of 4-hour SLED recipients (84%) were prescribed antibiotics according to iHD dosing, while only 16% were prescribed SLED dosing regimens. The use of SLED-based recommended dosing in 4-hour SLED resulted in significantly higher sepsis recovery [76% vs. 42%, HR = 2.02, 95 CI (1.07-3.82), p=0.030]. Interestingly, the in-hospital mortality didn’t differ between the two groups.

Conclusions: Our findings suggest that patients undergoing 4-hour SLED are more likely to get prescribed antibiotics using iHD-recommended dosing, which resulted in worse clinical outcomes. These findings would encourage using SLED-recommended dosing for 4-hour SLED and might serve as the basis for future larger studies.

Figure 1. Kaplan-Meier curve of recovery from sepsis

TH-PO283
Clinical Factors Affecting Continuous Renal Replacement Therapy Circuit Survival
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Background: Continuous renal replacement therapy (CRRT) is an effective treatment for critically ill patients with acute kidney injury (AKI). However, CRRT circuit is frequently clotted due to anticoagulation failure, thus resulting in blood loss and reduced dialysis efficacy. The aim of this study is to investigate the clinical factors affecting CRRT circuit survival.

Methods: A total of 117 CRRT circuit cases from 102 patients were reviewed retrospectively. We collected clinical data and investigated the factors affecting (1) the time from CRRT start to first dialysis circuit clotting or (2) frequency of circuit exchange during CRRT operation.

Results: The average time to 1st clotting was 26.1 hours. In Kaplan-Meier estimation, AKI due to trauma was related to shorter CRRT circuit survival (p=0.016), while DIC condition was related to longer survival (p=0.061) (Figure 1). In multivariate Cox-regression analysis, it was confirmed that the higher filtration fraction (FF) is associated with shorter circuit lifespan, while the higher DIC score or corrected calcium level were associated with the longer circuit survival (Table 1). The average number of circuit exchange was 1.46. In multivariate linear regression test adjusted for age, FF, DIC score and RBC transfusion, it was shown that FF had the positive correlation with frequent circuit exchanges (β=0.272, p=0.026), while DIC score had the negative correlation (β=-0.287, p=0.019).

Conclusions: The study indicates CRRT circuit survival depends on factors related to intra-dialyzer condition such as FF or clotting tendency rather than severity of patients. Interestingly, our results suggest that consumptive coagulopathy due to DIC rather prevents circuit clotting. Low corrected calcium is also thought to be due to consumption as a clotting factor and therefore predict early CRRT circuit clotting.

| Table 1. Clinical factors contributing to early CRRT circuit clotting |
|---------------------|---------------------|---------------------|---------------------|---------------------|
| Factor              | Adjusted HR (95% CI) | P-value (95% CI)    |
| FF                  | 1.000 (0.988-1.012)  | 0.603 (0.601-0.605)  |
| DIC score           | 0.578 (0.294-1.132)  | 0.223 (0.220-0.225)  |

TH-PO284
Continuous Renal Replacement Therapy vs. Intermittent Hemodialysis: Outcomes of Critically Ill Patients with AKI
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Background: Acute kidney injury (AKI) is a commonly diagnosed condition in critically ill patients, which poses a significant risk of chronic kidney disease, end-stage renal disease, and dialysis dependence (DD). Renal replacement therapies, including continuous renal replacement therapy (CRRT) and intermittent hemodialysis (iHD), are often used to support AKI patients. Although each modality has benefits, results from studies of outcomes associated with each modality remain inconclusive.

Methods: This retrospective multicenter cohort study utilized the TriNetX, a global federated health research network, to access deidentified electronic medical records from multiple large healthcare organizations. The primary objective was to investigate the outcomes of critically ill patients with AKI who received either CRRT or iHD after propensity score matching. The study identified and compared a total of 1024 propensity score-matched AKI patients in each group from Jan 2012, 2016, assessing them for 30-day mortality and DD using odds ratio (OR), 95% confidence interval (CI), hazard ratio (HR), log-rank test, and Kaplan-Meier survival analysis. Additionally, the study identified and compared a propensity-matched subgroup of 195 patients on mechanical ventilation in each group, with platelet count < 100,000/mL and bilirubin > 6 mg/dL and assessed these outcomes.

Results: The study was conducted on two groups, CRRT versus iHD, each consisting of 1024 patients. The 30-day mortality rate was 537 patients in the iHD group, and 672 patients in the CRRT group [OR: 0.578; 95% CI: 0.743-0.860; HR: 0.692; 95% CI: 0.617-0.775; p=0.067]. DD was observed in 114 and 93 patients in the iHD and CRRT groups, respectively [OR: 1.254; 95% CI: 0.940-1.674; HR: 1.125; 95% CI: 0.855-1.480; p=0.150]. In subgroup analysis, 30-day mortality was reported in 100 and 110 patients and survival probability of 74.61% and 74.6% in the iHD and CRRT groups, respectively [HR: 0.851; 95% CI: 0.649-1.115; p=0.790]. DD was observed in 25 patients in both cohorts.

Conclusions: In the cohort of critically ill patients with acute kidney injury who were admitted to the intensive care unit and required renal replacement therapy, the choice of renal replacement therapy modality did not have a significant impact on either 30-day mortality or the development of dialysis dependence.

TH-PO285
Timing of Continuous Renal Replacement Therapy in Critically Ill Patients on Extracorporeal Membrane Oxygenation
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Background: To investigate the timing for continuous renal replacement therapy (CRRT) in critically ill patients undergoing extracorporeal membrane oxygenation (ECMO).

Methods: Clinical data were collected of critically ill patients who received ECMO combined with CRRT in the Intensive Care Unit (ICU) of Henan Provincial People’s Hospital from January 2017 to June 2021. According to the time to start CRRT after ECMO application, they were divided into early CRRT group or late CRRT group. The differences in baseline clinical data and mortality between the two groups were compared. Kaplan-Meier curves obtained with the log-rank test were plotted to demonstrate the differences in patients’ survival between the two groups. Cox regression analysis was used to explore the risk factors of death.

Results: A total of 122 patients were enrolled, while 96 patients (78.6%) died. The early CRRT group and late CRRT group included 100 cases (81.97%), 22 cases (18.03%), respectively. Compared with the late CRRT group, the early CRRT group had higher proportion of receiving ECMO treatment due to respiratory and cardiac arrest, proportion of ECMO with venous-arterial mode, APACHEII score, and SOFA score (all P<0.05). In contrast, ICU stay time, The mechanical ventilation time and ECMO application time were shorter (all P<0.05). Kaplan-Meier curve showed that there was no significant difference in cumulative survival between the two group (p=3.397, P=0.065). Time-Dependent Cox Regression Model showed that Early CRRT was a risk influencing factor for patient death [HR=Exp(3.642+1.177ln(n)); 95% CI 3.323–351.384; p=0.004]. Multivariate Cox regression analysis showed that early CRRT [HR=Exp(3.499+1.162ln(n)); 95% CI 2.123–516.029; p=0.013]; ECMO weaning failed (HR=3.470, 95%CI 1.986–6.061; P<0.001), high APACHEII score (HR=1.042, 95% CI 1.001–1.085, P=0.044) were risk factors for in-hospital death.
Conclusions: Early CRRT after ECMO treatment may have a greater effect on mortality in critically ill patients than the late CRRT. Failure of ECMO weaning and high APACHE II score were risk factors for in-hospital death.

Funding: Government Support - Non-U.S.

TH-PO286

The Timing of Renal Replacement Therapy in Patients with Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO): A Nationwide Observational Cohort Study in Japan

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Background: Acute kidney injury is a common complication in patients on VA ECMO, thus fluid management plays a crucial role during VA ECMO. Renal replacement therapy (RRT) is enabled by precise fluid management, but early initiation of RRT has not shown benefits in general critically ill populations. We hypothesized that early initiation of tight fluid control with RRT would be beneficial for VA ECMO patients. In this study, we aimed to determine the association of early initiation of RRT with clinical outcomes in patients on VA ECMO, using the Diagnosis Procedure Combination database, a nationwide claims database in Japan.

Methods: This is a cohort study of adult patients who underwent VA ECMO during hospitalization between 4/2018 and 3/2022. We excluded patients who initiated RRT on the day of VA ECMO initiation and patients with end-stage kidney disease. We performed propensity-score-based inverse probability weighting (IPW) to balance the factors and to compare outcomes between two groups: patients who initiated RRT within 48h of VA ECMO initiation (Early RRT group) and those who did not (Late RRT group). The primary outcome was in-hospital mortality and the secondary outcome was RRT dependence at discharge in survivors.

Results: Of 1,181 VA ECMO patients, 336 were in the Early and 845 were in the Late RRT groups. After IPW, the clinical factors between the groups were well balanced, including age, sex, the prevalence of cardiovascular disease (96.7 vs 97.8%), the total SOFA score on the day of VA ECMO initiation (10.4 vs 10.4), and its renal component (0.9 vs 0.9). The median time to initiate RRT from the start of VA ECMO was 0 (IQR 0-1) days in the Early and 5 (IQR 2-11) days in the Late RRT groups. Early RRT initiation was associated with increased in-hospital mortality (66.5 vs 53.6%; OR 1.7, 95%CI 1.3 – 2.3) and increased RRT dependence at discharge in survivors (12.7 vs 2.0%; OR 5.6, 95%CI 2.2 – 14.0).

Conclusions: In adult patients with VA ECMO, early RRT initiation was associated with increased in-hospital mortality and RRT dependence at discharge in survivors, suggesting that early RRT initiation may not provide advantages for this population. Further investigation is needed to explore causal inference and identify specific subpopulations that may benefit from early initiation of RRT.

TH-PO287

Treatment Time Loss and Its Association with Fluid Balance Gap and Hospital Mortality in Critically Ill Adults Receiving Continuous Renal Replacement Therapy

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Background: Even with CRRT, fluid balance goals are not always achieved. Renal replacement therapy (e.g., fluid balance gap measured as prescribed minus achieved) is associated with hospital mortality. It has also been suggested that CRRT downtime can impair fluid management. Herein, we aimed to examine patient-related risk factors for treatment time loss and its association with hospital mortality and fluid balance gap.

Methods: Retrospective cohort study of critically ill adults receiving CRRT. Percent fluid balance gap (%FBgap) was calculated as the percentage difference between fluid balance goal and fluid balance achieved, divided by fluid balance goal. Percent treatment time loss (%TTL) was defined as the percentage of CRRT downtime in relation to the total CRRT time. We performed a linear regression model with %FBgap as the dependent variable, and age, sex, SOFA score at ICU admission and start of CRRT, Charlson comorbidity index, and %FBgap as independent variables. Adjusting for these clinical parameters, we further conducted a logistic regression model to determine the independent association of %TTL with hospital mortality. The correlation and interaction between %FBgap and %TTL were also examined.

Results: We included 591 patients with a median age of 60 years [IQR 50-68] and median SOFA score of 11 [IQR 7-14] at ICU admission and 13 [IQR 10-15] at start of CRRT. The median CRRT duration was 72.3h [IQR 30.7-141.4] (total of 61,718h). On average, treatment downtime per patient was 4.7h, accounting for 4.5% of total CRRT. There was no significant correlation between %FBgap and %TTL (r = -0.011, p = 0.78). The multivariable model did not identify any patient-specific clinical parameters associated with %FBgap. The univariable model was not independently associated with hospital mortality (OR 1.02, 95%CI: 0.99-1.04) and there was no interaction between %FBgap and %TTL with hospital mortality (p interaction = 0.92).

Conclusions: In this cohort of critically ill adults undergoing CRRT, treatment downtime was accounted for 4.5% of total CRRT time. %TTL was not independently associated with hospital mortality or significantly correlated with %FBgap. Other factors beyond %TTL need to be investigated to optimize fluid management with CRRT.

Funding: NIDDK Support

TH-PO288

Interactions Between Intradialytic Central Venous Oxygen Saturation, Ultraltrafiltration Rate, and All-Cause Mortality in Maintenance Hemodialysis Patients

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Background: In hemodialysis patients, low central venous oxygen saturation (ScvO2) and high ultrafiltration rate (UFR) have been associated with adverse outcomes. Here we explore the interactions between ScvO2 and UFR in relation to all-cause mortality.

Methods: We conducted a retrospective study in maintenance hemodialysis patients with central venous catheters as vascular access. During a 6-month baseline period, Crit-Line (Fresenius Medical Care, Walltham, MA) was used to measure continuously intradialytic ScvO2. We defined patients with age, diabetes, and the kidney disease type associated with hospital mortality or significantly correlated with %FBgap. Other factors beyond %TTL need to be investigated to optimize fluid management with CRRT.

Methods: We included 5,231 dialysis sessions in 216 patients. The median ScvO2 was 58.8% and median UFR was 6.8 mL/kg.h. During follow-up, 44 patients (20.4%) died. Kaplan-Meier analysis (Figure 1A) showed that worst survival was observed in patients with lower ScvO2 combined with higher UFR (group 4). The same result was observed in univariate Cox analysis. In multivariate analysis with adjustment for age, sex, and diabetes, and UFR, this association was mitigated (Figure 1B).

Conclusions: Intradialytic ScvO2 is an important effect modifier that should be considered when interpreting the relationship between UFR and outcomes. In patients with higher intradialytic ScvO2, UFR may be better tolerated, and fluid overload can be prevented easier while imposing high UFR in patients with low intradialytic ScvO2 may worsen outcomes.

Funding: Commercial Support - Renal Research Institute

Figure 1A. Kaplan-Meier analysis of survival probabilities in the four subgroups of patients based on the level of ScvO2 and UFR above and below the median of 58.8% and 6.8 mL/kg.h, respectively.

Figure 1B. Crude and adjusted hazard ratios (HR) for all-cause mortality associated with ScvO2 and UFR levels below or above the median population. CI, confidence interval.

TH-PO289

Parathyroid Hormone Decrease During Sepsis Predicts Re-Hospitalization in Hemodialysis Patients

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Background: Hemodialysis patients are at significant risk for infections. Given our clinical observation of decreased Parathyroid hormone (PTH) levels during sepsis among hemodialysis patients suffering from secondary hyperparathyroidism, we aim to characterize PTH levels before and during infection and explore its clinical significance.

Methods: A retrospective observational study conducted in the nephrology department at the Galilee Medical Center, Israel, between 2020-2022. Hemodialysis patients suffering from sepsis were included. PTH levels at different time points were analyzed using Wilcoxon signed rank test. Multivariable logistic regression analyses were conducted to identify risk factors for rehospitalization and mortality (median follow-up: 12.3 months; range:19-35.5). Model 1 included Age≥65 years, gender, dialysis vintage≥4 years and diabetes. Model 2: Similar to model 1 plus C reactive Protein (CRP), neutrophil/lymphocyte ratio (NLR) and albumin during hospitalization. Model 3: Similar to model 2 plus partial PTH decrease compared to baseline PTH.

Results: 72 hemodialysis patients were included in this study. The median duration of hospitalization was 9 days (IQR: 7-15). 74% were re-hospitalized after discharge while 50% were re-hospitalized within 1.8 months (IQR 0.5-5.8). Infection was the most common rehospitalization diagnosis. The mortality rate during follow-up period was 17% (median survival time: 7.7 months (IQR: 3.7-11.9). As hypothesized, PTH levels significantly decreased during sepsis compared to baseline (p=0.001), with partial decrease of 29% (IQR 8%-49%). In the final model of the multivariable logistic regression analyses, several traditional risk factors were associated with rehospitalization risk: Age≥65 years: OR 5.3, p=0.034 and dialysis vintage≥4 years; OR 5.5, p=0.045. Interestingly, partial PTH decrease during infection was the most significant risk factor for rehospitalization (OR 12.6, p=0.013). In the final model of the multivariable logistic regression analyses for mortality, only diabetes had a borderline significance (OR 8.6, p=0.065).
Conclusions: In this hemodialysis cohort a significant decrease in PTH levels during HDF was the highest OR for re-hospitalization. Further multicenter, prospective studies are needed to validate and explore this association, mechanisms, and clinical implications.

TH-PO290
Association Between Sleep Quality and Cardiovascular Disease in Maintenance Hemodialysis Patients
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Background: Most patients on maintenance hemodialysis (MHD) have sleep disorders. Studies have shown that poor sleep quality is associated with a variety of diseases, such as diabetes, cardiovascular disease (CVD), and depression. However, few studies have investigated sleep quality in the population of Chinese patients on hemodialysis. This study aimed to analyze sleep quality in patients on maintenance hemodialysis (MHD), and assess the impact of sleep quality on their prognosis.

Methods: A total of 601 patients on MHD were prospectively included in this cohort study. Pittsburgh sleep quality index (PSQI) was used to evaluate the sleep quality of patients. The global PSQI score > 7 indicates that a person has poor sleep quality. Follow-up was conducted until December 31, 2022, with all-cause death and major adverse cardiovascular events (MACEs) as the endpoint events. Correlations between sleep quality and incidences of endpoint events were analyzed using Cox regression models.

Results: Of the 601 patients, 595 completed the PSQI assessment, with 278 (46.7%) having poor sleep quality. Patients in the PSQI>7 group were older (p=0.001) and had a higher proportion of comorbid cardiovascular disease (CVD; p<0.001) and diabetes (p=0.002). Years of education (p=0.028), diastolic blood pressure (p=0.002), and heart rate (p=0.005) were lower in the PSQI>7 group than in the PSQI≤7 group. The 595 patients were followed up for 3 (2.5-3.7) years, during which 116 (19.4%) died, 415 (69.8%) survived, 64 (10.8%) were lost to follow-up, and 115 (19.3%) experienced MACEs. After adjusting for confounding factors such as age, gender, dialysis age, and previous cardiovascular disease, the risk of MACE in patients with poor sleep quality was twice that of patients with good sleep quality (HR=2.077 (1.339, 3.097), p<0.001). There was no significant difference in the risk of all-cause death between the two groups (HR=0.851 (0.584,1.240), p=0.9).

Conclusions: The prevalence of poor sleep quality in patients on MHD was 46.7%. Poor sleep quality was an independent risk factor for MACEs in patients on MHD.

Funding: Government Support - Non-U.S.

TH-PO291
Comparison of Utilities Consumption Between Different Modalities of In-Center Haemodialysis
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Background: Water is scarce in different parts of the world, including the Kingdom of Saudi Arabia (KSA). Water consumption during hemodialysis (HD) is about 360 liters/patient/day (L/PD). Online haemodiafiltration (HDF) requires more water consumption (dialysate and replacement fluid) than HD/patient/week. Electricity production is interconnected with water usage. In KSA, Dialysis incidence is expected to increase on average by 5% yearly. This study quantifies local KSA utilities costs associated with in-center HD (ICH), including High-Flux HD (HF-HD), Expanded HD (HDx), and online HDF.

Methods: Under laboratory conditions and a set treatment protocol, consumptions were recorded for power (Watt-hours, Wh) and water (Liters, L). We gathered cost data from available resources: KSA National Water Company (NWCo) and Saudi Electricity Company (SEC). The results were tabulated in Microsoft Excel comparing HD modalities (HF-HD, HDx, and online HDF). We used single & double-pump dialysis machines (Baxter, Deerfield, IL, USA). Protocols for HF-HD, HDx, & HDF were derived from local expert opinion based on local practice. The cost of consumables & session provision per modality is assumed the same. The analysis considered the perspective of a single center with 30 dialysis beds running two shifts/day over 6 days/week at 100% capacity, caring for 120 patients/year.

Results: HDs water consumption is 3.5 (m) liters and electricity consumption is 50.4m Wh/center/year (same results for HF-HD). The total for HDF is 4.1m L & 60.2m Wh/year adjusting for confounding factors such as age, gender, dialysis age, and previous cardiovascular disease, the risk of MACE in patients with poor sleep quality was twice that of patients with good sleep quality (HR=2.077 (1.339, 3.097), p<0.001). There was no significant difference in the risk of all-cause death between the two groups (HR=0.851 (0.584,1.240), p=0.9).

Conclusions: The prevalence of poor sleep quality in patients on MHD was 46.7%. Poor sleep quality was an independent risk factor for MACEs in patients on MHD.

Funding: Government Support - Non-U.S.

TH-PO292

Background: The field of dialytic replacement modalities has seen advancements; however, interventional studies have produced dismal outcomes. The debate regarding the most beneficial outcome between hemodiafiltration (OL-HDF) and hemodialysis (HD) for dialysis patients remains open. This study aimed to compare clinical, biochemical, and quality of life (QoL) data between patients receiving HD and OL-HDF over a six-month follow-up period.

Methods: A prospective observational study was conducted involving 70 dialysis patients. The inclusion criteria included stable patients with a dialysis Kt/Varea greater than 1.2 who had received either HDF or HD three times per week for at least three months. Patients who had undergone renal transplantation, exhibited severe noncompliance, or had a history of cardiovascular events during the six months duration of the study were excluded. QoL was assessed using the dialysis symptom score over the six-month period, along with clinical and biochemical parameters. Both modalities had an intended HD treatment duration of 240 minutes, with a blood flow rate between 250-400 mL/min and a dialysate flow rate of 500 mL/min for both groups.

Results: Out of the 70 dialysis patients, 35 (19 males) were in the HD group, with an average age of 50.0±15.31 (range 41-60) years, and 35 (19 males) were in the OL- HDF group, with an average age of 50.3±11.44 years. Compared to the HD group, the HDF group showed significantly lower levels of inflammatory markers such as Beta 2-microglobulin (p < 0.001) and hs-CRP (p < 0.002), lower levels of phosphorus (p < 0.001), and higher hemoglobin (p < 0.001) over the six-month follow-up period. Patients in the HD group had higher mean symptom severity scores compared to those in the HDF group (40.97±12.24 vs. 24.11±5.03, p < 0.001). Single pool Kt/V, calcium, blood pressure control, and the amount of anti-hypertensive drugs required were similar in both groups.

Conclusions: Online hemodiafiltration may be a preferable option over conventional HD, which reduced inflammation, improved anaemia control, better phosphorus control, and improved dialysis tolerance with fewer symptoms. Further research is needed to determine the long-term effects of mortality and morbidity in dialysis.

TH-PO293
Predialysis Serum Albumin and Hemoglobin and the Risk of Intradialytic Hypotension Katherine Curtis, 1, 2 Sushrut S. Waikar, 3 Finnian R. McCausland. 1, 4 McCasland Lab. 1 Brigham and Women’s Hospital Department of Medicine, Boston, MA; 2 The George Washington University Milken Institute of Public Health, Washington, DC; 3 Boston Medical Center, Boston, MA; 4 Harvard Medical School, Boston, MA.

Background: Intravascular hypovolemia may predispose to intra-dialytic hypotension (IH), a common occurrence among patients receiving maintenance hemodialysis (HD). Intradialytic hypotension (IDH) is associated with an increased risk of hospitalization and mortality. Studies have shown that pre-HD albumin and hemoglobin were each independently associated with IDH, but only hemoglobin retained significance in a joint- model. The aim of our study is to examine the association of serum albumin and hemoglobin with IDH during an HD session and how the HDF group compared.

Methods: A prospective cohort study of patients included in the DaVita Biorepository (N=950). Pre-HD serum albumin, hemoglobin, and complete blood pressure (BP) data were available for n=938 patients and n=11,460 sessions. Random-effects Poisson regression models (adjusting for age, sex, race, access type, pre-HD systolic BP (SBP), session length, ultrafiltration, post-HD weight, diabetes mellitus, blood transfusion, previous ischemic heart disease, and peripheral vascular disease) were fit to examine the association of serum albumin and hemoglobin with IDH (defined as minimum SBP <100 if pre-SBP ≥100 or minimum SBP <90 if pre-SBP <160 mmHg).

Results: At baseline, mean age was 58 ±4 years and 44% were female. The mean pre HD albumin and hemoglobin were 3.5 ±0.5 g/dL and 10.8 ±1.0 g/dL, respectively. A total of 1,606 (14%) sessions were complicated by IH. Higher pre-HD serum albumin was associated with a 17% higher adjusted risk of IDH (IRR 1.17; 95%CI 1.00, 1.37). Higher HB (per g/dL) was associated with 6% higher risk of IDH (IRR 1.06; 95%CI 1.01,1.11). When both were considered in the same model, only hemoglobin retained significance (IRR 1.05; 95%CI 1.01, 1.10).

Conclusions: Higher pre-HD serum albumin and hemoglobin were each independently associated with IH, but only hemoglobin retained significance in a joint-model. Higher hemoglobin may thus serve as a widely-available biomarker to predict IH at an individual HD-session level.

TH-PO294
Impact of Dialysate Calcium Concentration on Bone Metabolism in Relation to Different Calcitremes Jyunichiro Hashiguchi, 1 Tomoya Nishino, 2 Satoshi Funakoshi. 1, 2 Nagasaki Renal Center, Nagasaki, Japan; 1 Nagasaki Daigaku Byoin, Nagasaki, Japan.

Background: In Japan, three types of calcitremes are currently approved to treat secondary hyperparathyroidism. However, the specific impact of these drugs on bone metabolism remains unknown. Furthermore, limited research is available on the potential influence of different dialysate calcium concentrations used during hemodialysis on the

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

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Calcimimetics exert significant effects on bone metabolism in addition to their ability to lower iPTH levels. However, this effect may vary depending on the concentration of calcium in the dialysate.

TH-PO295
Loss of Residual Kidney Function at One Year in Diabetic and Non-Diabetic Incident Patients Treated with Incremental Hemodialysis
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Background: Residual kidney function (RKF) is better preserved with incremental haemodialysis (I-HD) as compared to conventional thrice-weekly HD (TW-HD). Preservation of diabetes is associated with a faster decline of RKF in TW-HD. We aimed to analyze the RKF decline at one-year in diabetic versus non-diabetic patients initiating dialysis with I-HD.

Methods: We conducted an analysis of a prospectively assembled cohort in a single university centre including all adults initiating I-HD from January 2013 to December 2021. Outcomes were maintenance of incremental dialysis at one year and RKF decline at one year (or transition to TW-HD) according to the presence of diabetes.

Results: Of 264 patients who started hemodialysis, 93 initiated dialysis with I-HD of whom 30 were diabetics. At dialysis initiation, age, eGFR, comorbidity score, daily diuresis and area clearance (Kt/V) were similar between non-diabetic and diabetic patients. Transition to TW-HD occurred after a mean duration of 16 ±15 months and 11±10 months in non-diabetic and diabetic patients respectively (p=0.07). At one year, the percentages of non-diabetic patients and diabetic patients still on I-HD were 51% and 37% respectively. At one-year, non-diabetic and diabetic patients had a daily diuresis decline of 32 and 37% (p=0.07) and a Kt/V decline of 34 and 46% (p=0.01) respectively.

Conclusions: RKF decline is more rapid in incident diabetic patients versus non-diabetic patients treated with I-HD and its duration before transition to TW-HD is shorter in patients with diabetes. Nephrologists should be aware that transition to TW-HD could be faster in diabetic patients.

TH-PO296
Patiromer Efficacy to Reduce Episode Hyperkalemia in ESRD Patients: The PEARL-HD Study
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Background: Patients who have end-stage kidney disease (ESKD) maintained on hemodialysis (HD) are exposed to a high risk of cardiac arrhythmias, and this risk is augmented by periodic exposures to hyperkalemia (HK). Use of dialysate with a low potassium concentration may increase the risk of sudden cardiac death. Furthermore, HD patients carry a high pill burden, and it is unclear if prescription of an additional oral medication will reduce the frequency of episodic HK. The purpose of the study is to determine whether patiromer (P) administered daily will effectively reduce episodes of HK in ESKD patients who receive HD, and to explore whether P administration reduces the number of significant arrhythmia events.

Methods: This is a prospective, randomized, open-label trial. Eligible ESKD patients who were on thrice-weekly HD were screened from health records. A total of 33 patients were randomized 1:1 to P vs usual care. Patients randomized to P were administered the medication daily with breakfast or lunch in place of their prescribed phosphate binder, and the dose was titrated based on pre-HD serum potassium concentrations at start of weeks 1, 2, and 3. All participants received 7-day continuous cardiac monitors (CCM) at baseline and at week 4. A Mann-Whitney test was used to compare median number of HK episodes across groups. Fisher’s exact test was used to compare the probability of at least 1 HK episode.

Results: Of those randomized, one withdrew due to adverse symptoms, and one withdrew due to pregnancy. The mean age of randomized patients was 57 ± 50% were male, 79% were Black, 11% were Hispanic/Latino, and mean HD vintage was 6 ± 6. The P group had significantly lower median HK episodes compared to the control group (0 vs 3, p=0.06). Those in the P group were significantly less likely to have at least one HK episode compared to the control group (21% vs 71%; p=0.02). On the week 4 CCMs, 5 participants had ≥ 1000/24 hr premature ventricular contractions, 4 had ventricular tachycardia events, 3 had atrial fibrillation, and 0 had Bradycardia events, with no differences between the groups.

Conclusions: Patiromer administered orally once a day effectively reduces frequency of HK in ESKD patients who receive thrice-weekly HD. Larger studies are needed to determine whether patiromer reduces significant cardiac events.

Funding: Commercial Support - Vifor
Favorable Outcome of Combined Antihypertensive Agents for Patients Undergoing Hemodialysis

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Background: Various antihypertensive agents are currently available. Some of them, including angiotensin receptor blockers, not only lower blood pressure but also have a favorable effect on life prognosis. However, the pleiotropic effects of anti-hypertensive agents in patients undergoing hemodialysis remain unknown.

Methods: Patients undergoing hemodialysis during 2011 and 2012 at Nagasaki Renal Center were followed up until June 2021. Multivariate Cox regression analyses were conducted, including patients' demographic data, such as blood pressure and the number of antihypertensive agents received.

Results: A total of 339 patients (mean age: 67.3 years, 57% men, median dialysis vintage: 4.7 years) were included. The prescription ratios of angiotensin receptor blockers, beta-blockers, and calcium channel blockers were 41%, 19%, and 50%, respectively. According to the multivariable Cox regression analysis, angiotensin receptor blockers (Hazard ratio [HR]: 0.69, 95% confidence interval: 0.51–0.95, P=0.02) and calcium channel blockers (HR: 0.58, 95% confidence interval: 0.43–0.77, P<0.001) were associated with a better prognosis. Compared with patients who did not receive antihypertensive agents, patients who were prescribed one, two, and three or more antihypertensive agents showed an adjusted relative risks of death of 0.79, 0.59 (p=0.001), and 0.48 (p<0.001), respectively.

Conclusions: Our study showed that the number of antihypertensive agents received was negatively correlated with prognosis, indicating their pleiotropic effect. Therefore, physicians should combine antihypertensive agents to lower the blood pressure of patients undergoing hemodialysis to improve the prognosis.

Association of Erythropoiesis-Stimulating Agents with Peri-Dialytic Blood Pressure Parameters

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Background: Anemia is a common comorbid condition among patients with end-stage kidney disease (ESKD) requiring maintenance hemodialysis and is associated with morbidity and mortality. While recombinant human erythropoietin (rhEPO) revolutionized anemia correction, concerns existed about the development or worsening of hypertension. This study aims to understand practice patterns of erythropoiesis-stimulating agent (ESA) use in outpatient hemodialysis and associations of ESA use with hypertension (HT).

Methods: ESA administration at individual HD sessions was assessed from the DaVita Biorepository (n=950), a prospective cohort study consisting of clinical data and biospecimen collection. Unadjusted and multivariable Poisson and linear random effects models were used to assess the association of ESA use with HT. We adjusted for baseline demographics, blood pressure, and comorbidities. An exploratory analysis was conducted assessing associations of ESA use with HT after adjusting for baseline blood pressure.

Results: Mean age was 53 ± 22 years, 44% were females, and 38% were Black. Mean pre-HD SBP was 159 ± 28 mmHg. ESAs were administered in 97,172 of the 135,892 sessions (71.5%) sessions. Those with ESAs administered were younger, had higher UF volumes and longer HD sessions, higher pre-HD SBP, diabetes, PVD, and higher HB and ET-1. In fully adjusted models, we observed a 9% higher rate of Hyper0 (IRR 1.09; 95%CI 1.06–1.12 mmHg.) In exploratory models adjusted for HB + ET-1, this association was mildly attenuated (IRR 1.06; 95%CI 1.01–1.11 mmHg.) In fully adjusted models of peri-HD parameters, ESAs were associated with a higher natriuretic SBP (IRR 1.3; 95%CI 1.1–1.6 mmHg) with similar patterns of association noted for ESAs with post-HD SBP.

Conclusions: We observed an independent association between ESA administration and higher risk of Hyper0, and higher intradialytic SBP parameters. Future studies are warranted to better understand the mechanisms underlying these findings.

Funding: NIDDK Support

Hypotension at the Start of Dialysis Is a Risk Factor of Cardiovascular Mortality

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Background: In recent studies on hemodialysis (HD) patients, the association of Blood pressure at the start of dialysis and cardiovascular disease (CVD) morbidity is controversial. In a retrospective study, we aimed to investigate whether the pre-hemodialysis blood pressure levels predict CVD-related death.

Methods: The patients were followed up for up to 4 years. At baseline, demographic data, comorbidity data, physical examination results, and laboratory data were recorded for each patient. Pre-dialysis fasting blood samples were collected from arterial blood lines at the beginning of a week. We divided the study patients into 4 groups according to their systolic blood pressure at the start of dialysis in an ascending order: from the bottom 25th percentile (Q 1) to the top 25th percentile (Q 4). The Cox proportional hazards model was used to assess the association between blood pressure and the risk of CVD related death.

Results: A total of 132 outpatients treated at the Kohsaka Kamiyooji Jinesei Clinic in Yokohama and the Soubudai Niren Clinic in Kanagawa, Japan between December 2008 and July 2009 were enrolled. At the baseline, blood pressure at the start of dialysis was 147 ± 20 / 51 ± 5 mmHg. Among the 132 patients, there were 11 lethal events due to CVD. The risk of CVD death was significantly higher in the lowest systolic blood pressure patients (Q 1) than in highest blood pressure patients (Q 4) for 4 years (Kaplan-Meier curve, log rank P = 0.035). In the multivariate Cox regression analysis, low systolic blood pressure was found to be an independent risk factors for CVD mortality.

Conclusions: Hypotension at the start of dialysis is an independent risk factor of cardiovascular mortality.

A Single-Center Study of the Appropriate Timing of Chest X-Rays in Hemodialysis Patients

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Background: To determine dry weight, the most commonly used biocomposition and relative plasma volume (RPV) monitoring. However the cardiothoracic ratio (CTR) of chest PA is a common method of setting the dry weight. It is not clear when to perform chest PA. So chest PA is conducted at the convenience of patients and medical staff regardless of dialysis. We hypothesis that the CTR ratio before dialysis would be different from that when the appropriate dry weight was reached.

Methods: We analyzed 211 hemodialysis patients at our hospital from December 1 to 16, 2022. We took chest PA in patients before hemodialysis on Monday or Tuesday, the beginning of the week (Pre-HD ct ratio). When our patients had been considered euolemia and reached dry weight after hemodialysis during the week, we additionally performed a chest PA test and evaluated the ct ratio (Post-HD ct ratio). Using SPSS ver. 18, we compared the ct ratio of chest PA before and after dialysis. We analyzed the correlation between the difference in the ct ratio of chest PA and the difference between weight and dry weight at the time of the test.

Results: There was a significant difference between the Pre-HD ct ratio (0.51 ± 0.058) and the Post-HD ct ratio (0.49 ± 0.060, P < 0.005). The difference in the ct ratio of the chest PA was correlated with the difference between weight and dry weight. However, differences in ct ratio were not related to gender, age, primary disease, dialysis period, and previous RRT methods.

Conclusions: There was a difference in the ct ratio of chest PA before and after dialysis. As the patient’s weight approached the dry weight, the ct ratio of the chest PA decreased. We concluded that the appropriate time to administer chest PA was after the patient’s weight reached dry weight.

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Results: Apollo DB includes 543,169 patients, 4.6% Asia-Pacific (AP), 13.9% Europe, Middle East, and Africa (EMEA), 7.0% Latin America (LA), and 74.5% North America (NA). Select characteristics are shown by world region in Figure 1. Most patients are 45–64 years old (yo), yet more are 18–44 yo in AP & LA, while more are 65–74 & ≥75 yo in EMEA & NA. Hemodialysis is the most used modality, but peritoneal dialysis is common in LA (17.3%) and NA (13.2%). There were regional differences, such as higher urea removal in EMEA that commonly uses hemodialfiltration. The mean treatment time tends to be lower in NA and patients have a higher weight and are taller versus other regions.

Conclusions: In a first descriptive analysis, several regional differences were observed. These patient characteristics act as benchmarks for the nephrology community. Apollo DB offers opportunities for investigators to conduct global analytics and advance the state of the art.

Funding: Commercial Support - Fresenius Medical Care

TH-PO304

Characteristics of Global Dialysis Data from Multiple Providers in the New MONitoring Dialysis Outcomes (MONDO) Dataset

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Background: The MONitoring Dialysis Outcomes (MONDO) initiative is an academia-industry collaboration whereby providers can contribute data to an anonymized dataset used for joint research purposes. We present the characteristics of 20 years of longitudinal patient data contributed to the new MONDO dataset, which is now the most robust global dialysis dataset in the world.

Methods: Data from Jan 2000-Dec 2019 on 382 fields was captured longitudinally on 355,169 patients, 4.6% Asia-Pacific (AP), 13.9% Europe, Middle East, and Africa (EMEA), 7.0% Latin America (LA), 20% North America (NA), yet outpatient PD was more frequent in LA, while cycling PD was more frequent in NA. 11% of patients received a transplant. 42.5% died or stopped dialysis with some regional variability.

Conclusions: MONDO developed a new global research dataset to study dialysis outcomes, pathophysiology and risk prediction. MONDO is open to collaboration and contributions without geographic restrictions.

Funding: Commercial Support - Fresenius Medical Care

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

Underline represents presenting author.
Volumetric Accuracy Testing (VAT) of a Novel Patient-Centric Gravity-Based Automated Peritoneal Dialysis Cycler (GBC) vs. Conventional Pump-Based Cylinders (PBC)

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Background: Safe and effective APD cycler function requires volumetric accuracy of fill and drain (F/D) volumes to accurately calculate achieved ultrafiltration (UF) critical to clinical outcomes in PD. Volumetric accuracy in most contemporary APD cylinders is now pump, rather than gravity-based, partly due to unreliability of GBC load cells. However, PBCs contribute to device noise/sleep disruption and drain pain (up to 47% of patients) from high suction pressures. VAT of a low cost, novel, newly engineered GBC was performed to provide reliable F/D volumes was measured and values compared with conventional PBC and another recently marketed GBC. In a recent blinded study, features of the novel GBC were rated far more favorably by PD patients & RNs than those of conventional PBCs.

Methods: VAT was performed collecting volume from both a Sartorius laboratory simulator at a constant height and IPP measurements were repeated 8 times. Regression analysis determined the relationship between calculated and measured IPP. The height increment (\(\Delta h\)) was 5.08 cm; each step was maintained for 10 minutes. The coefficient of variation (CV% = 100*Mean/SD) of the IPP was obtained at each step. Regression analysis and Bland-Altman plots were performed to determine the relationship between calculated and measured IPP.

Results: Figures 1 & 2 show VAT results for Fill and Drain for 500ml & 3000ml F/D cycles at described bed heights. All 500ml Fills were within the required accuracy bounds of ±2%, all Drains were within the required accuracy bounds of ±3%. VAT for 3000L volumes for both Fill & Drain, 5 cycles of 500ml (total 30 F/D cycles) and 3 cycles of 3000ml (total 18 F/D cycles) were tested. VAT was calculated as (measured-actual)/actual x 100%.

Conclusions: Calculated IPP correlated (R\(^2\) = 0.98) with clinical outcomes in PD.

Funding: Clinical Revenue Support - Simergent LLC.

A Feasibility Study to Establish Dialysate Flow Characteristics in Peritoneal Dialysis to Associate Outflow Dysfunction

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Background: Peritoneal dialysis (PD) catheter dysfunction is the second leading cause of technique failure in PD after peritonitis. Failure to recognize this complication early result in technique failure. Dialysate flow characteristics have been measured in the past for modeling automated PD dwell and drain time for clearance of solute rather than catheter dysfunction. We hypothesize dialysate flow characteristics are associated with outflow dysfunction.

Methods: The study was a prospective observational study measuring dialysate flow characteristics in incident PD patients. Dialysate flow rates were measured by standardized method weighing the drained volumes every 5 minutes up to maximum of 30 min or complete drainage of fluid up to 3 times during Training. The catheter-related complications were recorded during the study visits and then monthly up to 6 months. Patient characteristics at study entry were summarized by mean ± SD and proportions. Repeated-measure Poisson regression was performed to analyze incidences rates during and after training.

Results: 21 patients were consented; 3 withdrew. 17/21 patients had completed flow record. The mean age at study entry was 53.3 ± 16.9 years and 58.8% were men. Two out of three training visits were used for analysis. The mean drain time for training visits (both sitting and reclined) was 179 ± 81 min. 52.9% and 64.7% of patients reported catheter related complications in training and follow up respectively. Drain pain was the most reported complication during training while catheter dysfunction was most common during follow up visits. SThe sitting total time ± 10 minutes from first training visit was associated with 83% lower risk incidences rates of complications in training (incidence rates ratio (IRR) = 0.17, CI - 0.050-0.581, P = 0.005). Catheter dysfunction in training was associated with complications during monthly visits (IRR =1.66, CI-1.01-2.73, P = 0.0477).

Conclusions: Our study established feasibility of measuring dialysate flow characteristics and reports PD catheter complication rate. The drain time ± 10 min is associated with reduced catheter related complications in training due to early intervention by the clinical staff. Catheter dysfunction in training increases the odds of complications during monthly visits.

Funding: Clinical Revenue Support


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Background: We performed two bench studies utilizing a PD simulator. One evaluated the accuracy and precision of IPP measurements by a pressure sensor integrated in a PD cycler, the second assessed the relationship between IPP and intraperitoneal volume (IPV) during volume exchange.

Methods: The first study was performed using a PD simulator filled with 2 liters of 2.5% dextrose dialysate (Fig.1). The IPP was monitored every 15 seconds by the Liberty Cycler (Fresenius Medical Care North America, Waltham, MA). The height (h) of the PD simulator was adjusted to increase in 6 steps and decrease in 5 steps. The height increment (\(\Delta h\)) was 5.08 cm; each step was maintained for 10 minutes. The change in pressure (\(\Delta P\)) is calculated as \(\Delta P=\rho g\Delta h\), where \(\rho\) (density of dialysate) and \(g\) (acceleration of gravity) were kept constant. The coefficient of variation (CV%) was calculated and measured IPP.

Results: Fig.2 shows the change in height (a) of the simulator and the concurrent increased and decreased in IPP (b) with the steps up and down. IPP correlated (R = 0.98, p<0.0001) with \(\Delta P\) in each step (c). IPPs were accurately and precisely measured with a smaller bias (0.34±0.87 cmH\(_2\)O) and CV (2.5±1.9 %). IPP correlated with IPV (Fig.3) during filling (R = 0.99, p<0.0001) and draining (R = 0.86, p<0.0003) respectively.

Conclusions: This bench study shows that IPP can be measured accurately and precisely by the pressure sensor integrated in the Liberty Cycler and that IPP measurements should be feasible, non-invasively and automatically performed using a PD cycler equipped with a pressure sensor. Given the importance of IPP changes during a PD treatment, the technique could be a valuable tool to dynamically assess IPP.
Background: Hemodialysis (HD) treatments in the United States (US) are typically delivered in a dialysis center. Home hemodialysis (HHHD) reduces costs to healthcare payors while providing more flexibility to patients with kidney failure. The Quanta® Dialysis System (Quanta Dialysis System) is a modern, user-friendly HD device. Whether it is equally safe and effective when operated by patients and caregivers in the US at home vs. healthcare professionals at a center is unknown. The purpose of this study is to determine non-inferiority of efficacy and safety of the Quanta Dialysis System in self-care HHHD vs. in-center HD.

Methods: This is a prospective study set in 12 sites in the US. Adult patients with kidney failure currently undergoing dialysis for ≥90 days were eligible. Enrollment began in November 2021 and continued during the Omicron wave of the COVID-19 pandemic. Participants received HD at their respective HHHD training centers for 4-8 weeks. They were then dialyzing, participating and caregivers trained to use the device at home. Once deemed competent by a nephrology care team, participants performed supervised HHHD during a transition week, then performed HHHD with a care partner for 8 weeks. The primary efficacy outcome is dialysis adequacy measured by mean standardized weekly Kt/V. The primary safety outcome is a composite of adverse events.

Results: As of April 2023, 23 patients were enrolled. The mean age was 55.5 ± 13.1 years, mean weight was 95.6 ± 20.4 kg, 10 (43.5%) participants were female, and 17 had 11 (73%) who achieved competency by the 5 years, mean weight was 95.6 ± 20.4 kg, 10 (43.5%) participants were female, and 17 (73.9%) patients had previously dialyzed with an HHD device. To date, 15 patients have transitioned from HHHD with the Tablo® Hemodialysis System is easy to use for patients with kidney failure in the US. As the final participants of the study, patients with kidney failure currently undergoing dialysis for ≥90 days were enrolled. Eligibility began in November 2021 and continued during the Omicron wave of the COVID-19 pandemic. Participants received HD at their respective HHHD training centers for 4-8 weeks. We have previously dialyzed with an HHHD device. To date, 15 patients have transitioned from in-center HD to HHD, including 11 (73%) who achieved competency by the 5th week of training. Eight patients have completed the study.

Conclusions: Data on successful completion of training suggests the Quanta Dialysis System is easy to use for patients with kidney failure in the US. As the final participants are projected to complete the study by August 2023, complete safety and efficacy comparisons between the use of the Quanta Dialysis System in HHHD vs. in-center HD will be reported at the time of presentation.

Funding: Commercial Support - Quanta Dialysis Technologies

TH-PO308

Characteristics of Tablo Home Hemodialysis Users in Medicare Fee-For-Service

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Background: The Tablo® Hemodialysis System was cleared for home hemodialysis (HHHD) use in March 2020, offering dialysis patients the first novel technology for HHHD since 2005. In the 2022 ESRD PPS Final Rule, the Centers for Medicare and Medicaid Services (CMS) designated Tablo a “substantial clinical improvement” over the incumbent technology based on increased treatment flexibility, higher treatment adherence, higher modality retention and improvement in patient quality of life. This designation made it eligible for Capital-Related Assets Transition add-on Payment for Innovative Equipment and Supplies (CRATPNIES). The methods: Using CMS Medicare FFS Limited Data Sets, we identified Tablo HHHD claims between Jan 1 and June 30, 2022, using HCPCS E1629, which was designated for billing the CRA CRATPNIES reimbursement. Importantly, CRATPNIES billing is not validated, so may capture the true Tablo HHHD population in Medicare FFS. We then summarized characteristics, including age, sex, race/ethnicity, and concurrent Medicaid enrollment, as well as treatment characteristics.

Results: Between Jan 1 and June 30, 2022, there were 53 patients who collectively had 1,830 billed Tablo HHHD treatments (Mean treatments per patient: 34.5; SD: 25.2). The mean (SD) age was 60.6 (15.5), with 51% age ≥65. Racial distribution was 28.3% Black, 49.1% White and 22.6% Other, and 34.4% of patients had concurrent Medicaid enrollment. A summary of the billed treatments shows a mean (SD) weight of 82.9 (20.8) kg, and a mean (SD) hemoglobin of 9.8 (1.4) g/dL. Vascular access type in use was 42% Catheter, 58% Fistula. Based on billed Tablo HHHD treatment volume, the total CRATPNIES add-on payments (assuming $25 per treatment) in the first half of 2022 are estimated to be $45,750.

Conclusions: This is a novel and early window into Tablo HHHD users and treatments in the Medicare FFS population and a first estimate of the CRATPNIES add-on payment. Thus far, the population appears to be more elderly and diverse, and with greater catheter dependence than the broader HHHD population. Additional research into Tablo HHHD adoption, utilization and outcomes in the Medicare population will be important for understanding and advancing home hemodialysis growth overall.

Funding: Commercial Support - Outset Medical

TH-PO309

Patient Reported Outcomes (PRO) Among Patients Receiving Home Hemodialysis (HHHD) with the Tablo® Hemodialysis System

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Background: The HOME Registry is an ongoing observational (“real world”) study of patients with kidney failure utilizing the Tablo® Hemodialysis System (Tablo) for home hemodialysis (HHHD). To date, relatively few studies have evaluated patient-reported outcomes among patients receiving HHHD.

Methods: We evaluated the first 55 patients on Tablo HHHD using an ePRO software at 1-, 3-, 6- and 12-month visits using: 1) Physical Health Composite (PHC) and 2) Mental Health Composite (MHC) scores from the Medical Outcomes Study Short Form 12 (SF-12), 3) insomnia total score from the Insomnia Severity Index (ISI). We employed mixed effects regression for repeated measurements, using specific covariance technology based on increased treatment flexibility, higher treatment adherence, higher modality retention and improvement in patient quality of life. As adoption continues to grow, we sought to characterize the first 500 users in the Tablo HHHD population.

Results: We collected user-reported demographics and geographic information from the first 500 Tablo HHHD users. Data include age, sex, race/ethnicity, employment status and Zip Code. Using Zip Code, we evaluated neighborhood characteristics such as Social Deprivation Index (SDI) and Rural status using RUCA 4+. Population characteristics are compared to similar data from the 2022 USRDS Annual Data Report, where feasible. The results are descriptive only using MS Excel. No statistical significance tests were performed.

Conclusions: Across the basic demographics of age sex and race/ethnicity, the Tablo HHHD population and USRDS HHHD appear to have similar characteristics with several favorable trends. The first 500 Tablo HHHD users vs USRDS HHHD are: • Slightly older: 35.2% vs 29.0%, Age 65+ respectively. • Slightly more racially/ethnically diverse: 45.6% vs 52.8% White, 19.5% vs 30.6% Black, 11.5% vs 3.0% Asian and 18.1% vs 11.1% Hispanic, respectively. • More unemployed, fewer retired: 33.5% vs 18.6% Unemployed, respectively.

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

Underlines represent presenting author.
Utilization of Extended Training Decay Periods to Evaluate Training Efficacy in Home Dialysis Devices

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Background: When conducting medical device usability testing, users perform tasks under representative use conditions. A “training decay” in the study is a defined time period between user training and user testing to allow for representative memory decay. FDA 2016 guidance emphasizes the training provided to test participants should approximate the training that actual users would receive including training decay. In practice, medical device manufacturers typically utilize a 1-hour training decay to simplify scheduling logistics. Real-world training decay for home hemodialysis (HHD) patients ranges from several hours up to nine days before their first-time independent use. Here we present the results of a usability validation study evaluating extended training decay on the safe and effective use of the Tablo Hemodialysis System.

Methods: A hybrid decay (HF) protocol was implemented with recruitment of 16 patient/care partner pairs (PCP) and 17 health care professionals (HCP). The HCP arm included 10 pairs without any prior HHD experience, and the HCP arm was composed of dialysis nurses and technicians. Each participant completed standard Tablo training, after which they experienced extended training decay periods ranging from 1 to 4 weeks. All participants then performed a simulated dialysis treatment (treatment setup, monitoring, and tear down) on Tablo. Task performance (use errors, close calls, and difficulties), subjective interviews and knowledge task assessments were recorded.

Results: The training decay averaged 16 days (min = 9 days, max = 28 days) for HCPs and 13 days (min = 6 days, max = 25 days) for patient/care partner pairs. Participants were able to complete all necessary tasks with minimal use error rates (0.32% and 0.65%), for HCPs and PCPs, respectively. Post testing, 100% of participants reported confidence in being able to use Tablo safely and effectively.

Conclusions: Objective evidence of effective training through HF validation is critical to ensuring safe use of home dialysis devices. Task performance from this study demonstrates the effectiveness of standard Tablo training in scenarios of extended training decay including and beyond actual use (up to 28 days). These results extend prior data on usability and confidence expectations Tablo for patients performing home hemodialysis.

Funding: Commercial Support - Outset Medical

Hybrid Dialysis in Peritoneal Dialysis Patients with Low Solute Clearance or Volume Overload: Two Years’ Experience


Background: ESRD patients on PD prefer this modality because it allows them greater flexibility related to timing, a better lifestyle, and fewer dietary restrictions compared to HD. With the reduction in residual renal functions, the largest applicable PD regimen might not be enough to achieve adequate solute clearance or fluid removal. In such circumstances, convincing some patients to shift completely to hemodialysis is critical to ensuring safe use of home dialysis devices. Task performance from this study demonstrates the effectiveness of standard Tablo training in scenarios of extended training decay including and beyond actual use (up to 28 days). These results extend prior data on usability and confidence expectations Tablo for patients performing home hemodialysis.

Funding: Commercial Support - Outset Medical

Urgent Start Peritoneal Dialysis (PD) as a Safe and Effective Dialysis Modality to Reduce the Dropout of Patients on Peritoneal Dialysis


Background: PD dropout became a major factor affecting the united PD program and created a new burden in the setting of limited HD slots. Our registry shows that almost 35-50% yearly for the last 3 years of patients who choose PD as a permanent dialysis modality and started temporary HD through Percath maturation of the PD catheter will change their mind and request to be kept on HD and removal of PD catheter even before starting PD training. Urgent start PD program started by keeping CKD 5 patients eligible to start PD on one vascular access (PD catheter) without Percath insertion and start Peritoneal dialysis 48hrs post PD catheter insertion. The safety and efficacy of the program were evaluated through monitor any mechanical complications and patient satisfaction besides our regular parameters such as volume status and electrolytes.

Methods: Identified CKD-5 patients during ED visits with an earlier plan for PD as a dialysis modality or having no plan. We evaluated the emergency and urgent need to start Renal replacement therapy. We created an Urgent Start PD pathway for those patients without the emergency need to start or who had an emergency need and became stable after starting HD through a temporary dialysis catheter. They were referred to vascular surgeons for PD catheter insertion after checking suitability and liability to Peritoneal dialysis. PD will start 48 hrs. after insertion. We enrolled sixteen patients from April 2021 till April 2023. A binary outcome (through April 2023), all of them were started on APD but the final PD model is decided after completing both APD and CAPD training. Body surface area was the main factor that affected APD Prescription. Frequent PD clinic visits were arranged to readjust the PD regimen and monitor mechanical complications, patient satisfaction, volume status, and electrolytes.

Results: Almost all patients were discharged with satisfactory conditions & accepted electrolytes without any mechanical complications and with fewer dates of admission after starting the new program.

Conclusions: Urgent start PD seems to be a safe, effective, and reasonable way to reduce PD dropout in addition to reducing cost and total days of hospitalization. We need a larger number of patients and a longer duration to generalize the findings of these observations.

Prevalence of Frailty and Symptom Burden in Patients on Staff-Assisted Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is a preferred modality for patients with clinical or psychosocial consideration, but self-care can be challenging for some individuals. Staff-assisted PD offers support for patients to start or remain on PD. This study aims to evaluate the physical, cognitive, and emotional status of patients receiving staff-assisted PD.

Methods: Patients who received staff-assisted PD by April 2023 were included. Physical function was evaluated by the Clinical Frailty Scale (CFS; score = 5 indicating frailty), and the Katz Activities of Daily Living (ADL) surveys. Symptom burden (physical and emotional), cognition, and patient activation were evaluated using the Integrated Palliative Outcome Score (IPOS)-Renal survey, the Quick Mild Cognitive Impairment Screen (QMCI), and the Patient Activation Measures (PAM)-13-item survey, respectively. Surveys were completed after initiation of assistance. Descriptive analysis was performed on completed surveys.

Results: A total of 72 patients received staff-assisted PD. CFS, ADL, IPOS-Renal, QMCI, and PAM were completed by 72 (100%), 51 (71%), 68 (94%), 42 (58%), and 46 (64%) patients respectively. Frailty was identified by the CFS survey in 28% of patients, and 29% of ADL respondents were dependent in at least one activity of these individuals. Of those who completed the IPOS-Renal survey, physical symptoms of moderate or worse severity were reported by 78% of patients, with weakness and poor mobility being the most common physical symptoms, while anxiety and depression at a moderate or worse severity was reported by 40% and 28% of the patients respectively. Mild cognitive impairment and dementia were identified in 15% and 28% respectively of those who completed the QMCI survey. Low activation (levels 1 and 2) was observed in 37% of patients.

Conclusions: Patients referred to staff-assisted PD experience significant physical and psychosocial challenges, underscoring the need for these programs to support home dialysis.
TH-PO316
Outcomes of Incident Peritoneal Dialysis Patients with Depressive Symptoms
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Background: In 2016, CMS introduced annual depression screening as a reporting measure under the QIP. For incident dialysis patients, screening surveys are typically administered by social workers in the fourth month of modality initiation. This study aimed to explore the outcomes related to depressive symptoms in a contemporary cohort of incident peritoneal dialysis (PD) patients.

Methods: A retrospective observational study was conducted on patients starting PD for the first time between January 2017 and December 2022 at dialysis units managed by a mid-sized U.S. non-profit dialysis provider. Those who completed the PHQ2 survey within 150 days after starting PD were followed for 365 days from the date of survey completion. A PHQ2 score equal to or greater than 3 was considered positive. Univariate and age- and sex-adjusted Fine-Gray models were used to examine the association between time to transfer to hemodialysis (HD) or death, and time to first hospitalization, while Poisson regression was used for rate ratios.

Results: A total of 2,215 patients were included. Mean age was 58.7 ± 15.9 years, with 38% being female. PHQ2 surveys were positive in 75 (3.4%) patients. During the follow-up period, 16.3% transferred to HD, 3.7% died, and 6.5% received a kidney transplant. Patients with a positive PHQ2 survey were found more likely to experience transfer to HD or death (hazard ratios (HR): 1.99; 95% CI: 1.33 – 2.97, and 2.02; 95% CI: 1.35 – 3.03 in the unadjusted and adjusted models respectively). The hospitalization event rate was 1.45 and 0.75 events per patient-year for those with positive and negative PHQ2 results, respectively (Rate Ratio (RR) 1.95, 95% CI: 1.53 – 2.45). Similarly, hospital days per year were 11.06 and 5.44 days per patient-year for the PHQ2 positive and negative patients, respectively (RR: 2.03, 95% CI: 1.87 – 2.20). Lastly, a higher hazard for time to first hospitalization was observed in those with a positive PHQ2 survey (HR 1.62, 95% CI: 1.14 – 2.31, and 1.62, 95% CI: 1.14 – 2.30).

Conclusions: Among incident peritoneal dialysis patients, depression symptoms are associated with increased risks of transfer to HD or death and of hospitalization. This represents a potentially addressable risk factor for poor clinical outcomes that may be amenable to intervention.

TH-PO317
Nurse-Assisted Home Hemodialysis with NxStage System One Portable Machine: An Experience in the Gulf Cooperation Council (GCC)
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Background: Home hemodialysis (HHD) is a renal replacement therapy applied to treat active, autonomous, and relatively healthy dialysis patients. NxStage System One, portable dialysis machine suitable for home setting. NAHHD is an innovative modality for patients providing freedom choice in dialysis therapy. Indications for NAHHD in the GCC is due to Limited Mobility, CVA, Fractures, Morbid Obesity, Intolerance to conventional HD, Infections, Mental Retardation, Psychiatric disorder. Here, at NAHHD treating mostly debilitated and frail patients with comorbidities at home and long term care facilities. Presenting clinical outcomes of Home Hemodialysis treatment, at HHD, service provider in the GCC.

Methods: The study includes 566 patients undergoing HHD treatment, for atleast more than 3 months and thus one year report of the health outcomes with portable HD machine at home was done. Estimated the HD adequacy and key performance indicators. The frequency and length of session, fluid volume calculated by dose calculator by NxStage, with target standardised Kt/V ≥2.1.

Results: The total number of 566 patients (X) on NxStage machine at home and at long term care facility were included in the study. Study group selected based on duration i.e., (X ≥3 months). Female- 52.65% and Male- 47.35%. The mean average age of the patients, 69.06 ± 14.63. The average comorbidities: 6.11± 3.45 (Min-2, Max-16). The vascular access: AVF- 25.27%, AVG- 3.53%, PC- 70.67%, AVF/PC- 0.53%. The yearly average of the biological parameters with HD adequacy are shown in Table 1. The annual mortality rate is 18.02%, as shown in Graph 1.

Conclusions: The results as shown states efficient and remarkable health outcomes. Moreover, the mortality rate of the HHD patients as compared to the US Renal Data System, shows better quality of therapy and retention in patients.

TH-PO318
Assisted Home Hemodialysis: A Game-Changer for Patients and Providers

Background: Home hemodialysis HD (HHD) offers autonomy, cost benefits, and better quality of life. Uptake of HHD is limited by patient motivation and cognitive and physical barriers. Assisted HHD (AHHD) is a new concept where dialysis team provides HD at home but it is limited due to financial and logistics restriction. We are reporting success and outcomes of our AHHD program in the State of Qatar.

Methods: A Retrospective study of all HD patients who are enrolled in AHHD program between 7/2021 to 2/2023. Inclusion mainly for elderly patients requiring ambulance transportation to the dialysis center. Primary objective was effectiveness and safety of AHHD and secondary objectives were cost effectiveness and quality of life.

Results: 85 patients enrolled in our AHHD program during study period with a mean follow up of 7 months (total 5968 HD treatments). Age was 71±10 years with 45% males. 13 patients and 2 patients returned to dialysis center. We had 8 incidents of HD catheter malfunction and 20 technical incidents resolved without affecting program flow. No reported significant access bleeding, falls or hypotension episodes. We found a significant decrease of 43% in hospitalization rates compared to 6-month pre-study period. The program proved to be cost-effective, resulting in a reduction of costs by 27%, primarily attributed to savings in ambulance transport expenses. Key performance indicators, including adequacy, anemia, and mineral and bone management were maintained. In a survey, patients and families expressed an extraordinary level of satisfaction, with rates exceeding 98% in all assessed categories.

Conclusions: We present our program for AHHD, designed for frail dialysis population. This initiative has yielded exceptional outcomes, substantial cost savings, exemplary safety measures, remarkable enhancements in quality of life, and an extraordinary level of patient satisfaction.
AHHD prevalence and mortality rate

**TH-PO319**

**Medication Management with Antihypertensive Agents and Associations with Peritoneal Dialysis Technique Failure in a Large, Retrospective Incident Cohort**

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**Background:** The first 90 days of peritoneal dialysis (PD) have high rates of PD technique failure (TF). Although many factors determine patients’ (pts) longevity on PD, only some are potentially modifiable. Proper management of antihypertensive medications (AH-M) is one modifiable factor that may help to control blood pressure and fluid balance. We aimed to assess the association between AH-M and PD TF at 90 days.

**Methods:** Adult, ESKD pts first prescribed PD at Fresenius Kidney Care (FKC) facilities between 2017-2019 were included. Deidentified data were extracted from the clinical data warehouse. Medication classification was conducted by clinical pharmacists. Case-mix adjusted Cox regression models were used to evaluate the associations between AH-M and PD TF. Subanalyses were conducted based on residual renal function (RRF).

**Results:** Pts included (n=22,908) were often treated with AH-M (91%). There was a trend toward any AH-M being protective of PD TF (HR: 0.85, p=0.06). However, certain AH-M subclasses had stronger associations than others (Table). Treatment with any diuretic (54% of pts) was associated with 17% lower technique failure rate (p=0.001) compared to no diuretic. Subclasses of diuretics were associated with lower TF (15% for loop diuretics and 18% for other diuretics). ACEi were associated with lower rates of PD TF (19%, p=0.0047), whereas remaining subclasses showed no association. There was no association with diuretics in the pts without RRF (Table).

**Conclusions:** In a large population of incident PD pts, we observed that several AH-M subclasses were associated with reduced rates of PD TF after controlling for many non-modifiable case-mix variables/confounders.

**Funding:** Commercial Support - Fresenius Medical Care

**TH-PO320**

**The Effect of Implementing a Dialysis Start Unit on Modality Decision Among Patients with Urgent Start Kidney Replacement Therapy**

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**Background:** Many individuals start dialysis in an acute setting with suboptimal pre-dialysis education. The dialysis start unit (DSU) is a program performing in-center hemodialysis (HD) in a separate space while providing support and education on chronic kidney disease and treatment options in the initial weeks of kidney replacement therapy. We aimed to assess the uptake of home dialysis therapies between 2013-2021 among patients who started acute inpatient HD at University Health Network, Toronto and underwent dialysis at the DSU.

**Methods:** This is a retrospective observational cohort study based on prospectively collected data. Patients’ demographics were obtained from electronic charts. In the DSU, all patients received dialysis modality education by a nurse educator, dedicated home dialysis nurses, and the allied health care team.

**Results:** During 2013-2021, 122 patients were dialyzed in the DSU and included in the study. Among those patients, 68 patients ultimately chose home dialysis (57 peritoneal dialysis and 11 home HD). Fifty-four patients continued in-center HD. Patients adopting home dialysis were less likely to have diabetes and hypertension as the etiology of kidney disease and more likely to have glomerulonephritis or vasculitis.

**Conclusions:** Dialysis modality education is implementable in advanced chronic kidney disease. Individualized education and care after urgent start dialysis can potentially enhance home dialysis choice and utilization.
Participation in a CKD Navigator Program Is Associated with Improved Quality of Dialysis Starts

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**Background:** Initiation of chronic dialysis is frequently accompanied by the use of central venous catheters, hospitalisation and need for in-center hemodialysis. Optimal start dialysis with a permanent access, in an outpatient setting and with the patient’s choice of modality is suggested to improve patient quality of life as well as reduce complications and cost. Education, coaching and monitoring of patients as they approach End-Stage Kidney Disease (ESKD) are proposed to increase the probability of optimal starts.

**Methods:** The University of Vermont Medical Center (UVMCC) began enrolling persons with an eGFR ≤ 20 ml/min/1.73m² in a CKD navigator program in November 2020. The program provides education, assessment, planning, coaching and monitoring. From November 2020 through April 2023, 270 patients were approached to participate, 180 agreed (67% engagement rate) and 127 had completed a plan for ESKD and were being monitored. During this same period, 141 UVMCC patients started dialysis, 33 of whom were followed in the navigator program. The 141 starts were assessed for a permanent access (PermAcc), outpatient location (OP) and whether they were in a home program (HOME) then grouped according to participation in the program (NAV) or not (NoNAV). Starts with the combination of PermAcc+OP and PermAcc+OP+HOME were also compared. The significance of differences between groups was assessed by Chi Square analysis with Yates correction when appropriate.

**Results:** For numerical results see findings in Table. Patients participating in the navigator program were statistically more likely to start with a permanent access and in a home program. Combinations of these characteristics with an outpatient start also were statistically more common in navigator participants. Starting dialysis in an outpatient setting as a single finding was not different between groups.

**Conclusions:** Although lacking randomization, this observational study supports the proposal that patient participation in a CKD navigator program improves the quality of dialysis starts.  

**Funding:** Private Foundation Support

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**TH-PO322**

Experience with Remote Monitoring of Automated Peritoneal Dialysis: The First 50 Patients in a Private Peritoneal Dialysis Program in Mexico

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**Background:** The benefits of remote monitoring (RM) of automated peritoneal dialysis (APD) have been established, the aim of this study is to describe the characteristics and outcome of the first 50 patients who were maintained in APD with RM, from November 2019 to February 2022 in a private peritoneal dialysis program in Mexico City. Also, we analyzed time and distance traveled savings for patients.

**Methods:** Retrospective cohort study. This was an observational study, describing the main clinical outcomes in our patients maintained in APD with RM.

**Results:** A total of 50 patients were admitted to the study. Their mean age was 62.5 years. Most patients lived in an urban setting. 2 patients were lost to follow-up. The main causes of end stage renal disease were diabetes mellitus (69%) and hypertension (20%). The basal frequency of clinic visits was 1 per month; During the study, 92% of the prescribed PD sessions were completed. Just 2% of prescribed sessions were interrupted, and 6% were missed treatments. The median lost dwelling time was 78 minutes per patient-month (range 0-366), the mean number of prescription changes was 3 (range 0-8). Among patients who had a change in prescription during the study, the main adjustment was an increase in infusion volume and time spent on treatment (57%). Icodextrin 7.5% was prescribed, 16% of the prescribed PD sessions. The leak rate was only 5%. Peritonitis rate was 0.36 episodes/patient-year, both episodes were caused by gram positive microorganisms. 1-year PD catheter migration rate was 30%, most catheters were placed by a variety of surgical techniques (65%). 1-year PD catheter patency rate was 75%.

Weekly Kt/V mean was 1.60 (±0.28). 1-year PD technique survival was 60 %, the main causes of PD technique failure were mechanical failure (35%) and infections (35%). Twelve patients died during the study, the main cause was infections 50% (COVID-19 25%). The distance traveled by patients was reduced by 534 km with a time saving of 804 min for patients.

**Conclusions:** APD with RM allows a better use of healthcare resources, helping to improve patients follow up and remote early prescription modifications. The main outcomes rates were similar than previously reported in similar countries. It is important to consider the COVID-19 pandemic impact on these results.

**TH-PO323**

Machine Learning for Identification of Near-Term All-Cause and Cardiovascular Death Among Patients Undergoing Peritoneal Dialysis

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**Background:** Although more and more cardiovascular risk factors have been verified in peritoneal dialysis (PD) populations in different countries and regions, it is still difficult for clinicians to accurately predict who will have cardiovascular events and when the cardiovascular events will occur and cause death. We developed and validated machine learning-based models to predict near-term all-cause and cardiovascular death.

**Methods:** Machine learning models were developed on the Peritoneal Dialysis Telemedicine-assisted Platform Cohort (PDTAP) of 7539 PD patients enrolled between June 2016 and April 2019, which was randomly divided into a training set and an internal test set by 5 random shuffles of 5-fold cross-validation, to predict of 3-month cardiovascular death and all-cause death. We chose objectively collected markers such as demographic characteristics, clinical characteristics, and laboratory, and dialysis-related variables to inform the models and assessed the predictive performance using a range of common performance metrics, such as precision, accuracy, and area under the curve (AUC).

**Results:** CVDformer model was used to predict 3-month cardiovascular death of PD patients. In the test set, CVDformer model had a precision of 87.96% - 89.45% and an accuracy of 86.10% - 88.74%. best than the LSTM model had 78.78% - 80.45% for precision and 76.53% - 79.12% for accuracy. The AUC was 0.88-0.90 in identifying the presence of near-term all-cause death and cardiovascular death using the CVDformer model.

**Conclusions:** We developed and used a novel combination of machine learning methods to assess the all-cause mortality risk and cardiovascular death risk in 3 months. The ability to identify the potential risks of all-cause and cardiovascular death with an inexpensive, widely available, and automatic procedure has important practical implications, particularly for the management of dialysis patients.

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

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TH-PO324
Computational Models of Peritoneal Dialysis
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Background: In silico models may play a vital role in improving patient-specific kidney replacement therapies. Recent advances in mathematical modeling include models of kidney physiology (e.g. regarding sex-specific differences, solute, drug and toxin transport and their interactions). Various models have been generated for peritoneal dialysis (PD) as well, but what lacks is a benchmarking of the different models on the same (pre-) clinical dataset. Here, we look at previously published models of PD and benchmark the efficiency of the models in predicting time-dependent evolution dialysate concentrations of six solutes.

Methods: Two mechanistic models (Graff, Öberg (modified for static dwell); this model is also modular and has been applied to automated PD and continuous flow PD) and two analytical models used in clinical practice and research (Garrard, Waniewski) were chosen. The four models, in combination, encompass various mechanisms that are essential to PD (diffusion, convection, lymphatics). The dataset consisted of data from multiple static dwells (n = 16) in uremic pigs. Each model was trained by fitting the dialysate solute concentrations (in a subset of the dwells) to predict the mass transfer area coefficient (MTAC) of each solute. With the fitted MTAC, we predicted the dialysate solute concentrations in the remaining dwells.

Results: The (modified) model by Öberg appears to be the optimal model in terms of low error in solute concentration predictions, applicability of the model to multiple datasets (with different initial dialysate concentration), physiological MTAC values and reasonable ultrafiltration values in pigs. Applying the modified Öberg model to the data obtained in the uremic pig experiments showed a good predictive accuracy (Figure 1). Notably, this model accurately predicted the effects of sodium sieving, whereas other models did not.

Conclusions: The modified Öberg model provided an accurate prediction of solute concentrations throughout a static dwell in uremic pigs.

Funding: Private Foundation Support

Figure 1: comparison of predicted data by the Öberg model with pig data.

TH-PO325
Robust Joint Models of Albumin and All-Cause Mortality in Incident Peritoneal Dialysis Patients: A Dynamic Predictions Perspective Adjusting for Competing Risks
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Background: Joint models (JM) allow investigation of association between longitudinal biomarkers and mortality in patients on peritoneal dialysis (PD) and provide individual patient dynamic risk predictions. Yet, deviations from JM assumptions in dialysis trial data and consideration of competing events remain unexplored.

Methods: We evaluated the association of albumin with all-cause mortality in incident PD patients followed over 8 years in the Initiating Dialysis Early And Late trial. To account for skewness/outliers in albumin, novel JM with mixed effects model with skew-normal, t and skew-t errors were compared with conventional JM under normal distribution. Furthermore, we adjusted for the competing events of transfer to hemodialysis and transplantation using Weibull cause-specific hazards. The dataset (N=114 patients) was randomly split into training data set (3/4, N=236) for model fitting and validation dataset (1/4, N=78) to infer predictive performance. We obtained 6-month individual patient survival predictions from all JM at cut-offs 1, 1.5 and 2 years utilizing albumin trajectory and baseline risk factors.

Results: A median of 9 albumin records per patient and a 35% death rate with median time-to-event of 4.5 years ensured convergence of all 16 joint models. Albumin hazard ratio of death remained robust (0.78 to 0.81), suggesting significant inverse relationship between albumin and death across all models. Longer follow-up improved the prediction accuracy of all JM in the validation dataset with competing events outperformed JM with survival only (area under the curve (AUC) ranges at 1, 1.5 and 2-years: 0.53-0.57 vs 0.52-0.55, 0.75-0.80 vs 0.75-0.77, 0.84-0.90 vs 0.82-0.88), regardless of the distribution assumption for albumin. Prediction performance of all JM surpassed classical Cox model with baseline albumin (AUC = 0.46, 0.70, 0.75). Results were confirmed by two simulation studies.

Conclusions: This first comprehensive JM in dialysis patients demonstrates utility for dynamic personalized survival prediction, with robustness of estimates to deviations from normality and higher predictive accuracy when adjusting for competing risks, and marked superiority to the classical Cox approach.

Funding: Commercial Support - Baxter Healthcare Corporation

TH-PO336
Random Forest Can Accurately Predict the Technique Failure of Peritoneal Dialysis-Associated Peritonitis Patients
Zi Li, Zhiyun Zang. Institute of Nephrology, West China Hospital of Sichuan University, Chengdu, China.

Background: Peritoneal dialysis associated peritonitis (PDAP) is a major cause of technique failure in peritoneal dialysis (PD) patients globally. The purpose of this study is to construct a risk prediction model which could accurately predict the technique failure in PDAP patients.

Methods: This retrospective cohort study included maintenance PD patients in our center from January 1, 2010 to December 31, 2021. Technique failure was defined as catheter removal, transfer to hemodialysis (HD) or peritonitis-related death. The risk prediction models for technique failure in PDAP patients were constructed based on five machine learning algorithms: random forest (RF), the least absolute shrinkage and selection operator (LASSO), decision tree, k nearest neighbor (KNN), and logistic regression (LR). And the internal validation was conducted in the test cohort.

Results: A total of 574 episodes of peritonitis during the 12 years were included in this study. The technique failure accounted for 23.69%, and the mortality rate was 4.00%. There were significant statistical differences between the technique failure group and the technique survival group in multiple baseline characteristics. The RF prediction model is the best able to predict the technique failure in PDAP patients, with the accuracy of 93.75% and AUC of 0.881. And the model had sensitivity and specificity of 77.14% and 99.08%, respectively.

Conclusions: RF prediction model could accurately predict the technique failure of PDAP patients, which demonstrated excellent predictive performance and assist in clinical decision making.
Modifiable Physical Factors that Influence Physical Function for People Receiving Peritoneal Dialysis

**Methods:** Adults receiving peritoneal dialysis underwent assessments for objective (Short Physical Performance Battery) and self-report (Short Form-36 Physical Function) physical function, cardiorespiratory fitness (six-minute walk), muscle strength (quadriceps, bicep, abdominal, hand-grip strength), physical activity (accelerometry) and sedentary behaviour (inclinometry) on three occasions over a 12-month period (baseline, 6-months, 12-months).

**Results:** Eighty-two participants (mean age 61.4 years) underwent assessments. All modifiable physical factors were predominantly moderate to strongly associated with physical function at baseline. Through the observation period, cardiorespiratory fitness had the strongest and most consistent influence with every metre conferring a 0.08-unit (p <0.01) and 0.01-unit (p <0.05) increase in self-report and objective physical function score, respectively. Temporal changes were observed for modifiable physical factors with significant mean changes in cardiorespiratory fitness (+9.8%), quadriceps strength (+5%), moderate-vigorous (+25.9%) and total (+16.2%) physical activity, and sedentary behaviour (+7.1%).

**Conclusions:** The results of this study indicate that cardiorespiratory fitness could be routinely monitored to detect risk of physical function decline and targeted through intervention to enhance physical function for people receiving peritoneal dialysis. Nevertheless, all factors should be considered when designing interventions to mitigate temporal changes and induce the numerous health benefits offered.
Illustrative Quotes

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<td>Feelings of isolation</td>
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<td>Ongoing psychosocial impacts</td>
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TH-PO330

Patient and Care Partner Perspectives of Psychosocial Issues While on Home Dialysis

Ayesha Anwaar,1,2 Vael F. Hussein,2 Karine E. Manera,3 Nicole J. Scholes-Robertson,3,4 Jenny I. Shen,4 Stanford University, Stanford, CA; 5Satellite Healthcare, San Jose, CA; 6The University of Sydney, Sydney, NSW, Australia; 7Harbor-UCLA Medical Center, Torrance, CA; 8Flinders University, Adelaide, SA, Australia.

Background: Home dialysis has many advantages but requires initiative from patients and care partners. Without proper support, patients run the risk of burning out. Previous studies show that emotional and social deficits are the major causes of burnout of PD patients. The study’s aim is to survey the prevalence and risk factor of burnout in PD patients and their caregivers in performing PD.

Methods: We conducted 5 focus groups and 3 semi-structured interviews of 18 adult English-speaking patients and 11 care partners with experience with home dialysis, 16 patients and the remainder were caregivers. Median PD vintage were 3.5 years. In the MBI questionnaire, 22 patients (21.8%) had a high exhaustion score; 9 cases (8.9%) had a high score of cynicism (>22.36). 63 patients (62.4%) had a high Professional Efficacy (>28.2). On the STAI questionnaire, the mean score for state anxiety was 35.5, and 24 patients (23.8%) reported severe anxiety; the average score for trait anxiety was 38.3, and 31 cases (30.7%) met severe anxiety.

Conclusions: In our PD patients, there was a high incidence of emotional exhaustion and severe anxiety but a high personal efficacy. However, after adjusting for PD operators, age, PD vintage, there was no significant correlation between these parameters and the scores in each questionnaire.

TH-PO332

The Effects of Negotiation on Discordant Home Hemodialysis Patients

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Background: Home hemodialysis (HHD) has demonstrated superior clinical outcomes, improved quality of life and enhanced treatment flexibility in comparison to 3days/week incenter HDs. Nonetheless, some patients are discordant to their dialysis prescription and require a negotiation program to maintain their normal lifestyle and ameliorate their illness behavior.

Methods: Retrospective single center observational study of all prevalent HHD patients at UHN (2018-2022). Demographic and clinical data were extracted from clinical charts. Negotiation was defined as weekly contact between nurses and patients by phone, email or clinical visit to discuss the importance of being concordant to treatment and adapting the length and schedule of dialysis to avoid clinical complications. Patients were defined as concordant, discordant with agreement with at least 75% of dialysis prescription and discordant for those skipping/shortening HHD sessions without prior agreement with the clinical team.

Results: From 94 patients, 33(35%) required negotiation:15(16%) were concordant patients with agreement and 18(19%) discordant patient. There were no demographic differences between groups. Patients requiring negotiation presents higher median time on HHD (7.6years vs 4.3years for concordant patients). Discordant patients tended to be younger and were less likely to be listed for kidney transplant (figure 1). There were no differences in hospitalisation/technique complications amongst the 3groups.

Conclusions: A third of HHD patients require negotiation to maintain their lifestyle and safety. Those patients requiring negotiation did not present with more hospitalisation or technique complications than concordant patients. We speculate that a negotiation
Measuring Mindset: Validation of the Health Mindset Scale (HMS) in Peritoneal Dialysis (PD) Patients

TH-PO334

Time Trends and Causes of Infectious Mortality Among Patients Starting Dialysis in Finland

Patrik Finne,1,2 Susanna Kinnunen,1 Jaakko Helve,1,3 Auni Junttilainen,4 Wisam Bittar,2 Ilkka Helanterä,4 HUS-yhtymä, Helsinki, Finland; 4Helsingin yliopisto, Helsinki, Finland; 4Finnish Registry for Kidney Diseases, Helsinki, Finland; 4Kuopion yliopisto, Kuopio, Finland; 4Kuopio yliopistollinen sairaala, Kuopio, Finland; 4HUS-yhtymä, Helsinki, Finland.

Background: Infections are the second most common cause of death among dialysis patients. Still, there is very scarce information on recent trends and causes of infectious mortality among dialysis patients. Our aim was to evaluate the development of mortality caused by infectious diseases during the past decades in the dialysis population in Finland.

Methods: All adult patients who started chronic dialysis treatment in Finland during 2000–2019 were included. The patients were identified from the Finnish Registry for Kidney Diseases, and followed until kidney transplantation, death, five years from start of dialysis or end of 2019. Cumulative incidence of death caused by infections was calculated and deaths due to other causes were accounted for as competing risk events.

Results: Altogether 9671 patients started dialysis of whom 75% commenced hemodialysis and 25% peritoneal dialysis. During the 5-year follow-up, 2956 (31%) patients received a kidney transplant, and 3692 (38%) dialysis patients died of whom 866 (23%) due to infections. The crude cumulative incidence of infectious death decreased steadily over five-year time periods during 2000–2019 (Figure). The hazard ratio of infectious death decreased continuously and was 0.50 (95% CI 0.39–0.61) for patients who started dialysis in 2015–2019 compared to 2000–2004. The most common causes of infectious death were septicemia (38%), pulmonary infection (36%), and peritonitis (8%).

Conclusions: Dialysis patients’ risk of dying due to infections has dropped by half since the beginning of the millennia. The reason for this development will need further studies.

Funding: Private Foundation Support

Impact of Glycemic Control on Technique Failure in Incident Peritoneal Dialysis with Diabetes: Focusing on Volume Overload

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Background: To date, diabetes mellitus (DM) has been regarded as a risk factor for ultrafiltration failure in peritoneal dialysis (PD). This study is aim to delineate whether glycemic control could contribute to the technique failure in PD patients with DM, especially in terms of volume overload.

Methods: We retrospectively analyzed data from 84 incident PD patients with DM. The study population consisted of 71 males and 13 females, with mean age 51.1 ± 16.0 years. At the time of data collection, 35 patients (41.7%) had diabetes mellitus type 1 and 49 patients (58.3%) had diabetes mellitus type 2. The cumulative incidence of technique failure was 38.8% at 3.0 years.

Results: Multivariate Cox regression analysis revealed that patients with a HbA1c level 8.0% had a significantly higher risk of volume overload-associated technique failure (HR 3.741, 95%CI 1.166–11.908, P=0.026) compared to counterparts particularly within the first two years (HR 6.760, 95%CI 1.413–32.331, P=0.017). Additionally, hypertension was found to be significantly associated with an increased risk of volume overload-associated technique failure (HR 10.021, 95%CI 1.236–81.260, P=0.033).

Funding: Private Foundation Support
Conclusions: Inadequate glycemic control (HbA1c > 8.0%) particularly during the first 2 years, and hypertension were found to be related with a volume overload-associated technique failure in dialysis patients undergoing PD. Funding: Veterans Affairs Support

Methods: In a retrospective study, we identified patients with body mass index (BMI) ≤ 35 from patients who initiated PD between 2014 and 2020 (n=99) at the University Hospital Home Dialysis Center. Charts were reviewed for clinical and laboratory variables to assess PD adequacy, technique, and patient survival. Date of last evaluation was March 2023.

Results: A total of nine patients (9%) had severe obesity with mean BMI 23.2±2.9 kg/m², age 47.8±12.6 years, and 44% were female. The cause of ESKD was Diabetes Mellitus in eight and IgA nephropathy in one patient. PD catheter was placed percutaneously in six and surgically in three patients. None of the patients had pericatheter leak or poor healing. PD training was initiated within 7.4±1.1 days after catheter placement. The initial prescription involved on average 4±0.5 cycles over 8.7±1.1 hr at night, total volume 9.0±1.2 lt and three patients had a last fill of 1.67±0.24 lt. Adequacy (both clinical and weekly kt/v<1.7 using actual/adjusted weight) was achieved in every patient using incremental PD. After an average of 17.7±6.8 months on PD, three patients transferred to hemodialysis (1 burnout, 1 prolonged hospitalization after cardiac surgery, 1 peritonitis with leak in the tunnel) and one moved to another PD facility. The remaining five patients continue to be on PD with a mean duration of 27.8±4.5 months. The latest prescription was 4.3±0.7 cycles over 9.2±1.2 hr at night, total volume of 11.1±2.6 lt and six had a last fill of 2.0±0.8 lt. Seven patients maintained the residual kidney function by the end of follow up. Peritonitis rate was 0.28 episode/pt-yr. Two patients had issues with slow drain and one with omental wrapping. Mean HbA1c was 7.8±2.3% and 7.1±1.3% at PD initiation and end of follow up, respectively.

Conclusions: Our experience demonstrates that PD is a viable option for long term therapy in patients with severe obesity. Further studies in a large population are needed to confirm our findings.

TH-PO338
Association Between Prediabetes and Cardiovascular Mortality in Patients Treated with Peritoneal Dialysis: A Retrospective Study from Southern China

Hu Qinghua, Qimei Luo, Xianrui Dou, Shunde Hospital of Southern Medical University, Foshan, China.

Background: The term prediabetes is used for individuals who have impaired glucose metabolism but the levels of glucose or HbA1c are not yet high enough to be diagnosed as diabetes. Prediabetes may already be associated with an increased risk of chronic diabetes-related complications in the general population. The present study was aimed to investigate the clinical impact of prediabetes on cardiovascular mortality in a population from southern China who received peritoneal dialysis(PD) treatment.

Methods: Patients who received PD treatment above 3 months between January 2004 and December 2021 from four center were enrolled. The clinical record from last time before PD treatment were collected as baseline data. Prediabetes was defined as impaired fasting plasma glucose (IFG) according to the definition of the World Health Organization (WHO-prediabetes:6.1-6.9mmol/L). The association of prediabetes with cardiovascular mortality was evaluated with multivariable Cox proportionate hazard analyses.

We further performed subgroup analysis stratified by baseline characteristics including age(≥47,≤47year), sex, smoking, hypertension status, PD vintage(≥2,≤4months), hemoglobin(≥83,≤83g/L), albumin(≥36,≤36g/L), serum potassium(≥2.0,≤2.0mmol/L).

Results: A total of 2045 PD patients were enrolled in this study. Of them, 545 were (26.7%) diagnosed as diabetes, 165(8.1%) were diagnosed as prediabetes according to IFG-WHO. During a median follow-up period of 42months, 178(8.7%) patients occurred cardiovascular mortality, of which 123(6.9%) patients were with cardiovascular mortality (HR 1.86, 95%CI 1.33-2.61, P=0.001). Among patients who did not have hypertension, HR was 1.47, 95%CI 1.04-2.08, P=0.02. Among patients who diagnosed as WHO-prediabetes, patients diagnosed as WHO-prediabetes was associated with an increased risk of cardiovascular mortality(HR 1.80, 95%CI 1.11-2.28) after adjusted for age, sex, smoking, hypertension status, PD vintage, hemoglobin, albumin etc. The inverse association between the prediabetes with cardiovascular mortality was stronger in patients without hypertension (P for interaction=0.013).


TH-PO339
Clinical Outcomes of Peritoneal Dialysis in Patients with Chronic Liver and Kidney Failure: A Single-Center Experience

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Background: Patients with Chronic Liver and Kidney Failure (CLKF) face severe complications and high mortality. Simultaneous Liver-Kidney Transplant (SLKT) is the ideal therapeutic option, but the dearth of organs leaves most patients dialysis-dependent. PD is often overlooked due to concern for elevated peritonitis risk, hyperalbuminemia, and poor transplant candidacy. However PD treatment may offer some patients the opportunity to resolve pre-existing hemodynamic problems. We present a single-center experience to provide evidence that PD should be considered in CLKF patients.

Methods: In this retrospective observational study, we included all patients with CLKF who initiated PD from 01/2006 to 03/2023. Medical charts were reviewed, and demographic/clinical data was retrieved. The primary clinical outcomes included mortality, PD complications, hospitalization rates, change in serum albumin from baseline, and SLKT candidacy. Censoring events were study period end, death, transfer to HD or to a different PD center, and SLKT.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
**Results:** Twenty-six patients with CLKF and mean age of 58 years initiated PD during the study period. The mean time on PD was 38.3 months. There were 18 episodes of peritonitis with a rate of 0.2 episodes per year. Nine patients died with an annualized mortality of 10.9%. Hospitalization rate was 0.95 per patient per year. Six patients received SKLT, 3 remain active on the waitlist. Four patients had technique failure with a permanent switch to HD. Mean serum albumin at the end of the observation period was 2.8 g/dl, a 12% decline from baseline ($p<0.05$). No patient needed therapeutic paracentesis for ascites while on PD.

**Conclusions:** To our knowledge, this is the largest single-center study on PD with CLKF patients. Our patients had a higher mortality, hospitalization, and peritonitis rates lower than the general PD population. Peritonitis episodes were more commonly from non-enteric pathogens suggesting a failure of aseptic PD technique rather than cirrhosis-related spontaneous bacterial peritonitis. The decline in serum albumin from baseline was more modestly statistically significant. Six patients received SKLT and 5 are active on the list, demonstrating PD can be a successful bridge to SKLT. Given excellent outcomes and effectiveness in ascites management, we propose PD as a first-line kidney replacement therapy option in patients with CLKF.

**TH-PO340**

The Effects of Objective Structured Clinical Examination on Home Hemodialysis Transition

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**Background:** Home hemodialysis (HH) augments quality of life and improves several clinical outcomes in patients with end-stage kidney disease. However, patients are required to learn a complex medical task and are obligated to demonstrate competency of training. We hypothesize that Objective Structured Clinical Examination (OSCE) is a feasible strategy to enhance training and improve patient and provider confidence.

**Methods:** From 2017 to 2021, 58 patients completed HH training at University Health Network. Each patient completed an OSCE for formative assessment and a final OSCE for summative evaluation. The OSCE comprised of 94 or 85 items, depending on vascular access. Targeted training was provided after the first OSCE on identified areas of improvement. 25 of 58 consented and completed an optional Likert Scale survey (1 to 10) assessing confidence in seven categories, as seen in Figure 1. These include three routine practices of ultrafiltration (UF) target, HH access, and machine set up followed by three advanced actions of alarm and complication management, and safety. A final item, readiness to go home, served as a global assessment. Patients and training nurses completed the surveys, scoring from 1 to 10, before and after each OSCE. Within subject differences were assessed by paired Student t test.

**Results:** The mean OSCE score increased from 96.2 (+/- 5.7) after the first OSCE to 98.2 (+/- 3.1) % after the second OSCE ($p>0.05$). The patient mean score for home readiness increased from 8.0 (+/- 1.8) after the first OSCE to 9.5 (+/- 1.0) after the final OSCE ($p<0.05$). Similar trends were observed from the nurse trainers, with their mean home readiness score increased from 6.6 (+/- 1.8) to 8.9 (+/- 1.1) ($p<0.05$) after the OSCE process. Individually, there was an increase in patient confidence in all categories. Confidence in ultrafiltration target, dialysis access, and machine setup improved by 0.68, 0.40, and 0.36 respectively ($p<0.05$). Confidence in advanced components including alarm troubleshooting, complication management, and safety increased by 0.84, 1.04, and 0.72 respectively ($p<0.05$).

**Conclusions:** We demonstrated that OSCE is an implementable training strategy, which is associated with increased home readiness and confidence scores in our patients and nurse trainers. We speculate that assurance of training may reduce patient burnout.

**Figure 1. Patient and nursing reported confidence scores.**

**TH-PO341**

Tumoral Calcinosis in a Patient with ESKD on Peritoneal Dialysis: A Diagnostic Dilemma

Kartik Kalita, Lakshma Sankar, Evan Norfolk, Geisinger Health, Danville, PA.

**Introduction:** Tumoral calcinosis is an uncommon complication of secondary hyperparathyroidism related to end-stage kidney disease (ESKD) with calcium and phosphate deposition in soft tissues, which is different from calciphylaxis characterized by microvascular calcification resulting in painful skin ulcers.

**Case Description:** A 42-year-old woman with history of ESKD on peritoneal dialysis (PD) for 6 years presented with severe multiple joint pain for 2-week duration. Home medications included losartan, cinacalcet and calcium acetate. Labs revealed phosphorus of 11 mg/dl (2.5 - 4.8 mg/dl); parathyroid hormone (PTH) of 1061 pg/ml (15-65 pg/ml). She was anemic and her most recent Kt/V was 2.3. On examination, she had tenderness in multiple proximal and distal interphalangeal joints on her hands, bilateral hip, and knee joints. Computed tomography (CT) pelvis with contrast showed calcified masses in soft tissue and periarticular region in bilateral hip consistent with tumoral calcinosis (Figure A, B and C – red arrows); direct extrinsic erosion of the right posterior proximal femoral diaphyseal cortex (Figure C – yellow arrow) and left hip acetalabulum. Given the severity of symptoms, she was transitioned to intermittent hemodialysis and received sodium thiosulfate infusions. Calcium acetate was switched to sevalamer. She received a kidney transplant 3 months later. On 10 month follow up, her symptoms resolved.

**Discussion:** The timeline for tumoral calcinosis can range from 17 - 84 months in PD patients. Treatment includes low phosphorus diet, non-calcium-based phosphorus binders, calcimetics, sodium thiosulfate and surgical options are parathyroidectomy for secondary or tertiary hyperparathyroidism. Nephrologists should be aware of this rare entity to provide appropriate care including patient education on medication adherence, if needed switching dialysis modalities to intensive hemodialysis (5 times per week) and surgical management. Studies have shown complete resolution of tumoral calcinosis after kidney transplant.

**TH-PO342**

Pantoea dispersa Peritonitis in a Patient on Peritoneal Dialysis

Yoshitsugu Oji, Mohamed Hassanein, Prakhar Vijayvargiya, Khaled Obeidat, Zackary Knott, Neville R. Dossabhow, The University of Mississippi Medical Center, Jackson, MS.

**Introduction:** Pantoea dispersa, a gram-negative bacterium belonging to the genus Pantoea, is commonly found in natural environments, including plants, soil, and water. While traditionally regarded as a plant pathogen, certain species have emerged as significant pathogens in humans, particularly in immunocompromised individuals. Here, we report a rare occurrence of Pantoea dispersa peritonitis in a patient on peritoneal dialysis (PD).

**Case Description:** A male in his mid-60s with end-stage kidney disease on PD presented with a two-day history of progressively worsening diffuse abdominal pain and cloudy dialysate effluent. Additional symptoms included chills, nausea, emesis, and diarrhea. Analysis of PD fluid revealed an elevated WBC (9797 cells/mm³) with neutrophil predominance (98%). We initiated empirical intraperitoneal (IP) antibiotic therapy using vancomycin and cefepime. PD fluid culture grew Pantoea dispersa from two separate samples. Susceptibility testing showed low minimum inhibitory concentrations (MIC) to all tested antibiotics including amoxicilnoglycides, trimethoprim/sulfamethoxazole, fluoroquinolones, and cephalosporins (cefoxitin was intermediate). Hence, the IP antibiotic regimen was changed to ceftazidime monotherapy. The patient reported significant improvement in abdominal pain by day 3, and repeat analysis of PD fluid on day 4 confirmed an excellent response to antibiotic therapy (WBC 113 cells/mm³). He was discharged with a plan to complete a 3-week course of IP ceftriaxone as outpatient.

**Discussion:** This case sheds light on the emerging significance of Pantoea dispersa as a pathogen in human infections, particularly in immunocompromised hosts including patients with end-stage kidney disease. Pantoea dispersa often exhibits multilag drug resistance, emphasizing the importance of susceptibility testing for optimal management. Notably, Pantoea agglomerans, a related species, has been reported as a rare cause of peritonitis in PD patients, with documented complications including ultrafiltration failure and encapsulating peritoneal sclerosis. However, the consequences of Pantoea dispersa peritonitis remain unclear. By presenting this case, we hope to enhance clinicians’ understanding and awareness of the potential pathogenicity of Pantoea dispersa, facilitating the establishment of effective management in similar clinical scenarios.

**TH-PO343**

Comprehensive Approach to Renal Education and Support: Methods and Outcomes

Sana F. Khan, Danielle Wentworth, UVA CARES - Comprehensive Approach to Renal Education and Support. UVA Health, Charlottesville, VA.

**Introduction:** The 2019 Advancing American Kidney Health Initiative aims to increase home dialysis utilization and improve access to kidney transplantation. In our approach to achieve these goals, we designed a quality initiative to provide comprehensive, patient-centered nephrology care for patients with high risk of disease progression.

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

Underline represents presenting author.
Case Description: This QI project started January 2021. High risk patients were identified by 3 criteria: eGFR < 30 ml/min or KFRE score < 20% at 2 years. Patients were contacted and offered enhanced education and support regarding modality choices & CKD progression. Patients were sequentially scheduled with an experienced nephrology NP, Social Worker, dietician and home dialysis nurse, with an additional NP visit to determine further education, enrollment in ESRD decision plan and tracking. Patient modality choices were subsequently relayed to primary nephrologists and documented in the EMR. Patient progress and gaps in coordination were discussed during quarterly list management meetings.

Our 2021 panel included 42 patients: age 65 years, GFR 16 ml/min, KFRE 53%.35% patients completed all 5 comprehensive visits.78% made decisions on preferred modality (33% HD, 40% PD, 21% undecided). 20 patients (47%) progressed to ESRD, with incident rates of PD 25% and HD 75%. 7% patients died prior to ESRD progression. 9 patients (45% of ESRD group) initiated RRT and were referred to home dialysis in hospital starts. 36% (n=8) of patients without progression to ESRD are on AVF/AVG placement, awaiting RRT initiation. Transplant status include 2 patients on the active, 10 inactive transplant lists. 23 referrals were closed due to patient ineligibility whereas 1 patient received a pre-emptive transplant. Development of a multidisciplinary high-risk nephrology care clinic at our institution resulted in attainment of improved rates of incident PD utilization, which surpassed national benchmarks. Significant number of our patients without ESRD progression are expected to have optimal start RRT with functioning AV access. Despite advanced care planning, 45% of our patients initiated RRT in hospital, demonstrating high complexity of care/disease burden of advanced CKD patients. Adoption of comprehensive care models for patients at increased risk for development of ESRD may lead to improved patient outcomes while also meeting national quality metrics.

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Although his transplant kidney came from a stone-former, he is not a stone former and has never had nephrolithiasis. We conclude that although being anephric may increase the risk of DAA, it can rapidly resolve with transplantation so the prognosis may not be as grave if transplant can be expedited.

TH-PO348
A Case of Cellulosimicrobium Peritonitis Associated with Peritoneal Dialysis
Kevin Bodker. Medical University of South Carolina, Charleston, SC.

Introduction: While peritoneal dialysis (PD) associated peritonitis is common, isolation of an uncommon organism can pose a clinical challenge. We present a case of PD peritonitis caused by the organism Cellulosimicrobium. A review from 2019 by Rivero et al found only 43 described cases of infection due to Cellulosimicrobium. Two-thirds of described cases were associated with an indwelling medical foreign body, and only 5 cases described associated with PD.

Case Description: A 71-year-old male presented with acute coronary syndrome and hypervolemia. Nephrology was consulted for PD management. During evaluation for coronary artery bypass graft (CABG) patient was transitioned from PD to Continuous Hemodialfiltration, requiring aggressive ultrafiltration. CABG was complicated by protracted cardiogenic shock. Unresolving shock and leukocytosis raised concern for concurrent sepsis, broad-spectrum antibiotics (vancomycin and cefepime IV) and infectious workup were pursued. PD fluids were consistent with peritonitis and cultures were positive for Cellulosimicrobium. Despite 10 days of vancomycin cultures remained positive. Persistent clinical instability delayed removal of PD catheter, which was removed on day 20. Patient was successfully transitioned to hemodialysis and remained without evidence of an ongoing infection at discharge.

Discussion: Despite vancomycin sensitivity in all previously described cases of infection attributed to this organism, two weeks of IV administration failed to clear the infection in our case. This is consistent with the five published cases of Cellulosimicrobium described in the literature (fig 1), where three out of five cases were considered antibiotic failure and required PD catheter removal. Depending on the clinical context, removal of PD catheter should be considered early in the treatment course of Cellulosimicrobium peritonitis given high rate of treatment failure.

TH-PO349
Delayed “Sweet” Hydrothorax Associated with Peritoneal Dialysis Hariharan Sud Natarajan, Bibi Maryam, Zahid B. Ahmad. OU Health, Oklahoma City, OK.

Introduction: Hydrothorax in Peritoneal Dialysis (PD) patients is diagnostically challenging, often attributed to volume overload, uremic effusion, or parapneumonic effusion. A pleuro-peritoneal leak is a rare complication, usually presenting within 30 days of PD initiation, predominantly in females. We present a case of delayed pleuro-peritoneal leak three years after PD initiation.

Case Description: A 48-year-old man with end-stage renal disease from PLQR-associated membranous nephropathy on automated peritoneal dialysis for 3 years presented with progressive dyspnea over 2 weeks. He had a recent admission for PD peritonitis 3 months ago. Examination revealed decreased breath sounds on the right side, crackles on the lower left lung fields, and pitting edema in both legs. A chest radiograph indicated a large right pleural effusion. Labs showed glucose of 69 mg/dL, elevated creatinine (21 mg/dL), elevated blood urea nitrogen (81 mg/dL), and elevated B-natriuretic peptide (1101 pg/mL), suggesting possible non-compliance with PD or PD failure. However, analysis of the pleural fluid sample revealed a protein concentration of 2.6 g/dL, creatinine of 22.1 mg/dL, glucose of 80 mg/dL, and lactate dehydrogenase of 162 IU/L, similar in composition to the dialysate fluid, consistent with a pleuro-peritoneal leak. Symptoms resolved upon discontinuing PD and switching to hemodialysis.

Discussion: Pleuro-peritoneal leak, also known as “sweet hydrothorax,” is a rare complication of PD and classically occurs within a month of initiating PD due to increased intra-abdominal pressure during PD fluid administration in patients with diaphragmatic defects. Our patient’s delayed presentation is unique and may be linked to prior peritonitis and weakened diaphragmatic tissue. Prompt identification is crucial, as treating other causes of hydrothorax can worsen the leak. A pleural fluid to serum glucose ratio >1.0 and elevated creatinine levels close to dialysate composition indicate a leak, confirmable with Peritoneal Scintigraphy or CT/MR Peritoneography. Temporary transfer to hemodialysis often promotes healing, while chemical pleurodesis, surgical repair, or permanent transfer to hemodialysis are options if conservative measures fail. Our case highlights the possibility of delayed presentation after peritonitis and underscores the importance of timely identification.

TH-PO350
Diagnosing Scrotal Wall Edema in a Patient Undergoing Peritoneal Dialysis
Dhiruv Bakshi, Deep Phachu. Saint Vincent Hospital, Worcester, MA.

Introduction: Acute genital edema is a well-documented complication of peritoneal dialysis (PD); and is seen in 4-10% of patients. While most incidents occur via obvious defects in the peritoneal membrane, we present a case of acute scrotal wall edema thought to be due to microtears in the peritoneal membrane.

Case Description: A 46 year old male on PD for the past 20 months presented with complaints of acute scrotal swelling. Shortly after his first dwell via continuous cycling peritoneal dialysis (CCPD), he suffered a severe coughing bout while supine. He awoke the following day with diffuse, bilateral, nonreducible and nontender scrotal swelling. CCPD was temporarily held and swelling improved, but immediately re-occurred after resumption of CCPD. CT of the abdomen and pelvis did not show a patent processus vaginalis, inguinal hernia or other obvious peritoneal membrane defect. Scrotal ultrasound did not show a fluid collection but showed diffuse scrotal wall edema. To confirm that this edema was of PD origin, we added 30 mL of gastrograffin into 1 liter of PD fluid and let this dwell for 3 hours after which repeat CT abdomen and pelvis showed a contrast-enhanced scrotum (Figure 1). CCPD was discontinued and patient was transitioned to intermittent hemodialysis with complete resolution of his edema within 7 days.

Discussion: While scrotal edema is not uncommon in patients on PD, the mechanism for development is usually related to an obvious defect, such as an inguinal hernia or patent processus vaginalis. In our patient however, we hypothesize that microtears in his peritoneal membrane caused by the acute coughing episode may have been the culprit. To our knowledge, there is no gold-standard test for diagnosing peritoneal microtears in PD, however our method of instilling 30 mL of gastrograffin in 1 liter of peritoneal dialysis fluid may be beneficial in aiding diagnosis. Moreover, we hypothesize that serial imaging done at one, two and three hour intervals may provide additional information regarding the location of such microtears.
PD patients have not been well tested, we planned for ceftriaxone 1 gram during a long, daily dwell. Patient was discharged on a course of IP ceftriaxone with resolution of her symptoms.

Discussion: In this case, the patient’s history was key to raising a high clinical suspicion for an unusual pathogen. Neisseria zoogedectis is often misidentified as Pasteurella, dismissed as skin contaminant or not recognized at all [3]. We were able to identify this microbe and promptly treat with appropriate antibiotic with resolution of infection. Neisseria zoogedectis is a pathogen that can cause peritonitis, especially in patients with household pets. Patient education regarding maintenance of PD equipment and exercising extreme caution when pets are near should be of utmost importance.

TH-PO352
The Phantom of the Peritoneum
Christopher El Mouhayyag,1,2 Pui Susan W. Cheung,1 Massachusetts General Hospital, Boston, MA; Brigham and Women’s Hospital, Boston, MA

Introduction: Patients in urgent need of dialysis are commonly started on hemodialysis (HD) via a central venous catheter. More recently, acute to urgent start peritoneal dialysis (PD) is becoming an alternative. Studies have shown that the incidence of acute and chronic pancreatitis in PD patients was higher compared to HD patients and the general population. Most studies looked at patients on chronic PD. Here, we present a case of urgent start PD complicated by acute pancreatitis.

Case Description: A 58-year-old woman with a past medical history pertinent for ischemic stroke and CKD stage V with loss to follow up for months, and a one-week-old PD catheter presented to the emergency department with tonic-clonic seizures. She was given lorazepam with no response, so she was transferred to a tertiary care hospital. Labs showed a BUN of 112 mg/dL, similar to the past month (94-112 mg/dL), Cr 15.2 mg/dL, cGFR of 2 mL/min/1.73 m2, potassium of 5.5, lactate 0.6 mmol/L, bicarbonate 15 mg/dL, creatinine kinase 347. CT head was unremarkable. EEG showed no evidence of seizure activity. She was started on PD with low volume runs of 500mL, which she tolerated and gradually increased to 1L. She was eventually extubated successfully. However, while into her fourth run, she started complaining of severe abdominal pain, nausea and vomiting. The PD was stopped. Lipase level came back elevated at 3000. CT abdomen pelvis showed pancreatitis and peripancreatic edema with surrounding fluid consistent with acute pancreatitis. PD was held, and the patient was switched to HD. She improved and was discharged home with an outpatient dialysis unit. Her seizure was thought to be due to her old stroke per neurology. She was transitioned back to PD 8 weeks later and has tolerated it well.

Discussion: The majority of ESKD patients are started on in-center HD via a central venous catheter. The use of PD has been increasing in the last decade. Unplanned hemodialysis via a CVC is associated with higher rates of infection and reduced rates of survival compared to PD. Ideally, all patients with CKD should start dialysis in a planned elective manner rather than urgently. The evidence with regard to pancreatitis while on PD is controversial. Some studies report a higher incidence, while others do not. This case is the first to report acute pancreatitis in an urgent start of PD.

TH-PO353
A Peculiar Case of Pica in Peritoneal Dialysis (PD) Peritonitis
Pushpa Devulapalli, Jared G. Imber, Dia R. Waguespack, Jade M. Teckell.
The University of Texas Health Science Center at Houston John P and Katherine G Mc Govern Medical School, Houston, TX

Introduction: Anemia is found in majority of patients with CKD. It is associated with an increased risk of cardiovascular disease, morbidity and mortality in patients dependent on dialysis. Iron supplementation is usually advised to help improve symptoms and quality of life as well as reduce cardiovascular complications.

Case Description: Our patient is a 30 year old woman with history of ESRD secondary to anti-GBM disease on peritoneal dialysis with history of recurrent PDA peritonitis who presented to the emergency room due to abdominal pain, fevers, chills, nausea, and vomiting. She was hemodynamically stable with no leukocytosis but borderline left shift. CT of abdomen showed small bowel wall thickening. PD effluent samples were collected for gram stain and culture. Analysis showed turbidity and a WBC count of 58k with 80% neutrophils. She was started on broad spectrum antibiotics. Culture eventually grew Acinetobacter pittii. On further investigation, she reported eating dirt and clay for weeks. Bacteria of the genus Acinetobacter are ubiquitously distributed in nature, found in various types of soils. Ion panel showed low iron, low TIBC, and low ferritin. Iron was not given during admission due to active infection. Acinetobacter has a tendency to form biofilms which can cause recurrence of infection. The decision was made to start PD catheter in and she was sent home on a course of PO Cefoxitin later, she presented again with similar symptoms. During this admission, PD catheter was removed and she was transitioned to HD.

Discussion: Our case is a reminder of the surprising prevalence of pica in the ESRD population. Pica can go unrecognized until metabolic abnormalities or complications arise. Physicians do not routinely investigate pica due to underreporting and lack of information as well as guilt and fear of judgement from patients. CKD is a key player for major stress and can trigger pica. A common co-morbid condition associated with pica is anemia. Patients can have metabolic derangements such as alkalosis, hypoalbuminemia, ascorbic acid deficiency and zinc deficiency. Soil pica can affect certain electrolytes (potassium, phosphate and calcium) depending on soil composition and these electrolytes are further exacerbated in ESRD patients. Pica has extreme significance in the nutritional status of patients with kidney disease and should not be neglected in its implications on these patients.

TH-PO354
Alternatives to Daytime In-Center Hemodialysis and Employment in Patients with Kidney Failure
Kevin F. Erickson,1 Kerri L. Cavanaugh,2 Wolfgang C. Winkelmayer,1 Monique R. Pappadis,3 Jose J. Perez,2 Baylor College of Medicine, Houston, TX; 1Vanderbilt University, Nashville, TN; 2The University of Texas Medical Branch at Galveston Development Office, Galveston, TX.

Background: Maintaining employment is a priority for many patients with kidney failure. Yet, many working aged patients face the U.S. stop working with the onset of kidney failure. Access to a dialysis treatment schedule outside of working hours may help patients to remain employed.

Methods: We analyzed data from the US National Dialysis Registry to determine whether access to nearby facilities offering evening dialysis shifts and home dialysis increases the likelihood that patients are able to continue working after they start dialysis. Our cross-sectional analysis included working-aged patients (ages 18-54) receiving dialysis in US facilities in 2016. In a negative binomial regression model, we examined the associations among exposures of interest (the presence of facilities offering home dialysis or evening dialysis shifts in a patient’s locality) and the number of employed working-aged adults at each dialysis facility. The multivariable model adjusted for observed patient, dialysis facility, and geographic characteristics, including information about individual patient employment at the onset of dialysis.

Results: We identified 4,860 US dialysis facilities with information about patient employment in 2016. Median employment among working aged adults at these facilities was 17.9% (interquartile range 8.8% to 28.6%). In fully adjusted regression models, the presence of at least one facility offering evening dialysis shift in a county was associated with a 5% increase in the relative rate of maintaining employment among working-aged patients receiving dialysis in the county (risk ratio (rr) 1.05; 95% Confidence Interval (CI) 1.01 to 1.09; p=0.02). The presence of at least one facility offering home dialysis in a county was associated with a 26% increase in the relative rate of maintaining employment (rr 1.26; 95% CI 1.18 to 1.34; p<0.001). The likelihood of employment did not increase with additional facilities in a county offering home dialysis.

Conclusions: Access to dialysis schedules outside of regular working hours – evening dialysis shifts and home dialysis – is associated with increased employment among patients with kidney failure. Efforts to increase access to these alternative dialysis treatments could help patients to continue working.

TH-PO355
REVOLUTIONIZE III: Consequences of Recurrent Hyperkalemia on Healthcare Resource Utilization and Cost
George L. Bakris,1 Abiy Agirso,2 Alexandra Gotsringers,3 Manasvi Sundari,4 Helen Guo,4 Elaine M. Louden,1 Erin Cook,2 Ellen Colman,3 Fan Mu,3 Pooja N. Desai,4 1Department of Medicine, University of Chicago, Chicago, IL; 2US Evidence, US Medical Affairs, AstraZeneca, Wilmington, DE; 3Analysis Group, New York, NY; 4Analysis Group, Los Angeles, CA; 4Analysis Group, Boston, MA; 2US Renal, US Medical Affairs, AstraZeneca, Wilmington, DE.

Background: Hyperkalemia (HK) is associated with increased healthcare resource utilization (HRU) and costs, but there are limited data on the impact of HK recurrence on these in patients (pts) with chronic kidney disease (CKD). This real-world study describes all-cause medical costs and HRU in pts with recurrent HK (rHK), non-recurrent HK (nrHK) and normokalemia (NK).

Methods: Pts aged ≥18 years with stage 3/4 CKD were identified from Optum’s de-identified Market Clarity data; HK was classified as rHK or nrHK by a claims-based algorithm. Pts with rHK were 1:1 exact and propensity-score matched with separate cohorts of HK diagnosis with either medical costs and HRU (n=675 rHK or nrHK or NK cohort). Continuous insurance was required for 12 months before and after the index date. Study outcomes were all-cause medical costs and HRU over 12 months.

Results: There were 4549 matched pairs in the rHK vs NK analysis and 1599 matched pairs in the NK vs HRU analysis. The HK cohorts had significantly higher mean per-pt all-cause medical costs than the NK cohort ($34,163 vs $15,175) and rHK cohort ($52,290 vs $38,233) over 12 months (Table). HRU rates were also significantly higher in the rHK and nrHK cohorts. The incidence costs were driven by increased inpatient medical costs with rHK vs NK and rHK vs HRU.

Conclusions: Large increases in all-cause medical costs and HRU after HK recurrence illustrate the unmet need for chronic management of HK in pts with stage 3/4 CKD, such as through long-term novel potassium binder therapies.

Funding: Commercial Support - AstraZeneca

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

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Baseline Characteristics of Early Enrollees in TRACK, a Prospective Study of Hyperkalemia Management Decision-Making

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Background: The TRACK study is a prospective, observational, implementation science study designed to address the evidence gap regarding healthcare provider decision-making and management of patients with hyperkalemia (HK).

Methods: The study will enroll 1250 patients with HK in the US and Europe and record management decisions, treatment objectives and outcomes, HK recurrence and attainment of target renin-angiotensin-aldosterone system inhibitor (RAASI) dose during 12 months following an index episode of HK. The planned sample size provides a margin of error <3% to estimate endpoints of interest such as attainment of target doses of RAASI therapies at month 12. Eligible participants are adults with serum K+ > 5.0 mmol/L collected during standard of care within 14 days prior to informed consent. Baseline characteristics of early enrollees are presented descriptively.

Results: Baseline characteristics and initial HK management approach are shown for the first 62 enrollees. Chronic kidney disease (CKD) and/or heart failure was present in 90% of enrollees. A mineralocorticoid receptor antagonist was used by 7% and other RAASI by 5%, by 53%. RAASi discontinuation and discontinuation during the qualifying HK episode was reported for (18%). Median K+ was 5.4 mmol/L (IQR 5.2-5.6), eGFR 26 mL/min/1.73m2 (IQR 15, 35). The most common initial management strategies for the index episode of HK, apart from monitoring serum K+, were prescription of a low K+ diet and use of K+ binders (Table). We anticipate enrolling approximately half of the planned 1250 participants for presentation at Kick Week.

Conclusions: TRACK will characterize contemporary provider decision-making in patients with HK and its impact on HK recurrence across a broad range of patient types in a variety of practice settings in the US and Europe.

Funding: Commercial Support - AstraZeneca

### Table: Baseline characteristics and initial management strategy in patients with hyperkalemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=62</th>
<th>% Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>19 (31)</td>
<td>21 (35)</td>
</tr>
<tr>
<td>Serum K+ (nmol/L)</td>
<td>5.4 (IQR 5.1-5.7)</td>
<td>5.4 (IQR 5.1-5.7)</td>
</tr>
<tr>
<td>Heart failure or diabetes</td>
<td>35 (56)</td>
<td>54 (87)</td>
</tr>
<tr>
<td>Heart failure without CKD</td>
<td>15 (21)</td>
<td>15 (21)</td>
</tr>
<tr>
<td>CKD without HF</td>
<td>9 (15)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>RAASi</td>
<td>37 (60)</td>
<td>60 (97)</td>
</tr>
<tr>
<td>Other RAASI</td>
<td>9 (15)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Other medication</td>
<td>6 (10)</td>
<td>10 (16)</td>
</tr>
<tr>
<td>No initial medication</td>
<td>15 (24)</td>
<td>24 (39)</td>
</tr>
</tbody>
</table>

Note: Data are n (%) or median (IQR). RAASi = renin-angiotensin-aldosterone system inhibitors; CKD = chronic kidney disease; HF = heart failure; IQR = interquartile range.

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

Underline represents presenting author.
TH-P0359
Evaluation of Efficacy, Safety, and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: An Interim Analysis (Actualize)
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Background: Sodium zirconium cyclosilicate (SZC), a novel highly selective polyanion binder, is approved in China for treatment of hyperkalemia (HK), a potential life-threatening electrolyte imbalance condition. This interim analysis from an ongoing multi-center, prospective, non-interventional study evaluated the efficacy, safety and treatment patterns of SZC in Chinese HK patients under real-world settings (NCT05212126).

Methods: This study included patients ≥18 years with documented HK from 40 sites in China, taking/willing to take SZC treatment. The interim analysis included patients who have completed 1 month follow-up. As per Chinese label, SZC treatment was categorized into correction phase (FAS-P1) and maintenance phase (FAS-P2), respectively. With an SZC mean daily dose of 11.5g in FAS-P1, the sK+ levels were reduced significantly from baseline, 5.9 mmol/L to 5.0 mmol/L (A=K –0.9 mmol/L), after correction phase, 51.3% and 77.8% patients showed sK+ levels between 3.5-5.0 mmol/L of at least 1.5 and 0.5 mmol/L in FAS-P1 and FAS-P2, respectively. An SAE was reported in 1.5% and 0.5% patients in FAS-P1 and FAS-P2, respectively reporting AEs with varying severities. A reduction in MACE and MACE+ was observed in FAS-P1, with ≥1.5% of patients reporting MACE and MACE+ in FAS-P2, respectively.

Results: A total of 193 patients and 354 patients were enrolled in FAS-P1 and FAS-P2, respectively. With an SAE level of ≥1.5% and ≥0.5%, patients showed ≥1.5% and ≥0.5% reductions in sK+ levels between 3.5-5.0 mmol/L and 3.5-5.0 mmol/L in FAS-P1 and FAS-P2, respectively. An SAE was reported in 1.5% and 0.5% patients in FAS-P1 and FAS-P2, respectively reporting AEs with varying severities. A reduction in MACE and MACE+ was observed in FAS-P1, with ≥1.5% of patients reporting MACE and MACE+ in FAS-P2, respectively.

Conclusions: From the interim analysis, SZC was effective and safe in treating HK. Hence, SZC can be considered a standard treatment for acute and chronic HK in China.

Funding: Commercial Support - AstraZeneca
Results: Of the 1688 patients admitted in the post-Lokelma period, 271 were suitable for analysis. 265 patients were selected from the pre-Lokelma period. Participants in both periods were well matched (Figure 1). In the post-Lokelma period, patients were 69% less likely to require emergency temporary CVC (OR 0.31; CI 0.21 – 0.47) and 73% less likely to need emergency HD (OR 0.27; CI 0.18 to 0.40). These results were consistent after sequential adjustment for potential explanatory variables (Figure 2).

Conclusions: Lokelma was associated with a signification reduction in emergency temporary CVC and emergency HD in patients presenting to a tertiary renal unit with hyperkalaemia.

TH-PO362
The Beneficial Effect of Sodium Zirconium Cyclosilicate on the Continuity of Renin-Angiotensin-Aldosterone System Inhibitors in the Management of Hyperkalaemia: A Retrospective Observational Study
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Background: Sodium zirconium cyclosilicate (SZC), a non-absorbed non-polymer zirconium silicate, is a new potassium binder for hyperkalaemia. A previous report showed that the administration of SZC in patients with hyperkalaemia allows a higher continuation rate of renin-angiotensin-aldosterone system inhibitors (RAASI). However, few comparative studies have focused on the clinical utility between SZC and existing potassium binders. The purpose of this study was to evaluate the effect of SZC on the continuation of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) in patients with hyperkalaemia compared to that of calcium polystyrene sulfonate (CPS).

Methods: Patients treated with ACEIs/ARBs, who were newly prescribed SZC or CPS for hyperkalaemia at a tertiary referral hospital between August 2020 and April 2022, were enrolled in this single-center, retrospective, observational study. The primary outcome measure was ACEIs/ARBs prescription three months after the initiation of potassium binders.

Results: A total of 174 patients on ACEIs/ARBs who were newly administered SZC (n=62) or CPS (n=112) were enrolled. At 3 months, significantly higher in the SZC group than in the CPS group (89% vs. 72%). Multivariate logistic regression models showed that SZC was independently associated with the primary outcome (odds ratio 2.66, 95% confidence interval 1.05-7.43). The proportion in this comparison also showed a significant association between SZC and the primary outcome.

Conclusions: The current study demonstrated that the administration of SZC in patients with hyperkalaemia allows for a higher continuation rate of ACEIs/ARBs than CPS. These findings suggest that SZC have potential benefits for patients with hyperkalaemia receiving RAASi.

TH-PO363
A Paralyzing Consequence: Succinylcholine-Induced Hyperkalaemia, A Rare but Dangerous Side Effect
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Introduction: Succinylcholine is a depolarizing neuromuscular blockade agent used during general anesthesia. Succinylcholine use can cause hyperkalaemia and cardiovascular instability in certain susceptible patients. Here we describe a case of succinylcholine-induced hyperkalaemia with cardiac arrest.

Case Description: A 27-year-old male with a medical history of alcohol use disorder was admitted to the ICU for rhabdomyolysis and septic shock due to MRSA pneumonia requiring mechanical ventilation. Following successful extubation, the patient had immobility due to profound weakness with an EMG demonstrating subacute sensory motor axonal polyneuropathy. He had also developed post-intubation dysphonia and laryngoscopy was recommended. Prior to laryngoscopy, his serum potassium level was 3.9 mEq/L. Upon administration of succinylcholine for intubation, he had a cardiac arrest. Immediate repeat labs revealed a serum potassium level of 9.2 mEq/L. Nephrology was contacted for emergent dialysis. In the interim, temporizing measures were given, including insulin with dextrose and calcium gluconate. A repeat serum potassium level was then 8.4 mEq/L with another level 30 minutes later being 3.3 mEq/L. The patient recovered without needing dialysis and was eventually discharged to an acute rehabilitation facility.

Discussion: Succinylcholine causes intracellular potassium efflux when binding to acetylcholine receptors. Several pathologic states cause an upregulation of acetylcholine receptors that predispose patients to a higher risk of critical hyperkalaemia. These states include severe infections, rhabdomyolysis, diffuse atrophy, immunization, denervation injury or diseases, and trauma. Identifying these conditions prior to using succinylcholine is vital. If succinylcholine use is required, close monitoring of the potassium level and cardiac function is necessary. The optimal treatment for patients with succinylcholine-induced hyperkalaemia includes those treatments that redistribute potassium back inside cells. Dialysis has a limited role in treatment and poses a greater risk and delayed time to treatment. Succinylcholine-induced hyperkalaemia is a rare, life-threatening condition, and practitioners should be aware of predisposing factors and appropriate treatment.

Impact of Sodium Zirconium Cyclosilicate on Serum Potassium and Bicarbonate in Patients with Hyperkalaemia and Metabolic Acidosis Associated with CKD: NEUTRALIZE Study
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Background: Acidosis and hyperkalaemia are common in CKD. The dual effect of sodium zirconium cyclosilicate (SZC), a selective binder of potassium (K) and ammonium, on serum K+ (sK+) and serum bicarbonate (sHCO3−) was evaluated in CKD patients with hyperkalaemia (HK) and metabolic acidosis.

Methods: In the NEUTRALIZE study (NCT04727528), patients with CKD (Stage 3–5) not on dialysis with HK (sK+ ≥5.1 to ≤5.9 mmol/L) and metabolic acidosis (sHCO3− 16–20 mmol/L) were randomized 1:1 to SZC 10 g TID for ≤48 h. Patients achieving normokalaemia (HK; sK+ ≤3.5 0.5 mmol/L) were randomized 1:1 to TID 10 g SQ or placebo (PBO) for 4 weeks. Primary endpoint was patients (%) maintaining HK at end of treatment (EOT) without rescue. Key secondary endpoints were patients (%) with HK ≥3 mmol/L increase in sHCO3− without rescue, and change in sHCO3− from baseline (BL) to EOT.

Results: Patients (n=229) were screened and 37 were randomized and received treatment. (n=17; PBO n=20; high screen failure rate and slow enrolment led to early study termination). Mean age was 63.3y, 68% male, and 87% White. Mean sK+ (mmol/L) at BL was 5.4 (SZC) and 5.5 (PBO) and for sHCO3− (mmol/L) 16.1 (SZC) and 15.6 (PBO). At EOT, patients maintaining HK was 88.2% for SZC and 20.0% for PBO (OR, SZC vs PBO, 56.2; P<0.001). Due to small patient number, P-values for secondary endpoints are nominal: sHCO3− (mmol/L) at EOT was 18.2 for SZC vs 16.5 for PBO (P=0.050). Patients maintaining HK and ≥3 mmol/L increase in sHCO3− without rescue was 35.3% (SZC) and 5.0% (PBO; P<0.05). For SZC, trends were seen towards a decrease in sK+ and an increase in sHCO3− (Figure). No safety concerns were reported.

Conclusions: SZC effectively lowered sK+ and maintained HK during treatment. Despite low patient number, trends towards significance were seen for the increase in sHCO3− with SZC.

Funding: Commercial Support - AstraZeneca

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Prevalence, Recurrence, and Prognosis of Hyperkalemia in Real-World Patients in China

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Background: Hyperkalemia is a common and life-threatening electrolyte disorder. However, data on hyperkalemia burden in China especially its relationship to clinical outcome in real-world patients remain limited. We conducted a retrospective cohort study to investigate the prevalence, recurrence and prognosis of hyperkalemia in a large tertiary hospital in China.

Methods: Patients aged ≥18 years who had at least one serum potassium measurement from January 2018 to December 2021 in a large tertiary hospital in China were enrolled and followed up until April 2022. The primary endpoint was the proportion of patients who experienced a hyperkalemia event (serum potassium [SK] >5.0 mmol/L). Secondary endpoints included the proportion of patients who experienced hyperkalemia recurrence and all-cause mortality rate in patients with hyperkalemia. Risk factors associated with all-cause death in patients with hyperkalemia were analyzed using logistic regression (exploratory).

Results: A total of 55,288 patients were enrolled (median age: 54.0 years; 44.0% were male). Overall, 1,131 patients (2.1%) experienced hyperkalemia (428 [0.8%] had SK >5.5 mmol/L and 167 [0.3%] had SK >6.0 mmol/L). 73.2% of patients with hyperkalemia were first diagnosed in the emergency department. Besides, hyperkalemia recurrence occurred in 12.4% patients during the 30 days follow-up, among them 6.6% patients recurred in 7 days. The 1-, 2-, 3- and 4-year all-cause mortality rates in patients with hyperkalemia were 18.5%, 19.5%, 19.9% and 20.2%. Risk factors for all-cause death were serum potassium (per 1g/dL) [HR: 1.328, 95%CI: 1.033-1.078, p=0.027] and hemoglobin level (per 1g/dL) [HR: 2.027, 95%CI: 1.460-2.815, p<0.01].

Conclusions: Hyperkalemia was common in real-world patients in China with relatively high recurrence and poor prognosis. In fact, hyperkalemia is not only considered as an occasional one-time critical event, but also affects long-term outcome and required continuous management.

Real-World Experience with Sodium Zirconium Cyclosilicate for Hyperkalemia in the Acute Inpatient Setting

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Background: The potassium binder sodium zirconium cyclosilicate (SZC) is often used for hyperkalemia treatment in the hospital. Its utility in this setting remains unknown, having been studied largely among outpatients and patients on dialysis. We sought to evaluate the real-world efficacy of SZC monotherapy for acute hyperkalemia in a large health system with a diverse patient population.

Methods: We included all adult (≥18) patients admitted to emergency departments or hospitals of Northwell Health in 2021-22; who received SZC due to a serum potassium (K) ≥5 mEq/L; and received no concomitant K-lowering therapy (loop diuretics, bicarbonate, insulin, albuterol, potassium binders, dialysis). Only the first SZC dose per patient was analyzed, and K was evaluated for up to 24 hours. We examined the mean reduction in K overall and by predefined hyperkalemia severity stratifications.

Results: Among 4186 patients, mean (SD) age was 71.3 (15.3) years with 55.3% men. Mean (SD) K was 5.6 (0.35) mEq/L. The proportion of patients with K ≥5.4, 5.5-5.9, 6-6.4, and ≥6.5 mEq/L were 39.8%, 50.7%, 7.0%, and 2.4%, respectively.SZC resulted in mean (SD) K decrease 0.56 (0.71) mEq/L within 3 hours, with greater reductions at higher baseline K levels (Figure). By 24 hours, 58.9% of patients had a decline in K of ≥0.5 mEq/L and 77.4% had K <5.5 mEq/L.

Conclusions: In the largest real-world study of SZC monotherapy in the acute setting, we found SZC to be effective for moderately severe acute hyperkalemia. Treatment efficacy was achieved after administration, and most patients had a clinically meaningful response. Further studies could help define the role of SZC with more severe hyperkalemia and when used with other therapeutic agents.
**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only**

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Hypokalemia is an Enigma

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Introduction: Hypokalemia is common, but severe hypokalemia (K < 2.5 mmol/L) is rare, with a narrower differential. This unique case presents a patient whose interminable hypokalemia was an enigma and whose labs were significantly discordant with presentation.

Case Description: A 47y/o man with diabetic CKD II presented to the ER with global weakness and paresthesias for two days. He denied diarrhea, nausea, or vomiting, but admitted to taking homeopathic OTC supplements from his home country with unknown content. One of these supplements was potassium vitamin plus another vitamin which was benzoate for diminished strength across all muscle groups. Labs showed severe hypokalemia <1.5mEq/L, AKI, hypokalemia, and combined HAGMA and NAGMA. Other electrolytes were normal. EKG revealed sinus rhythm. He was admitted to the ICU and started on oral and parenteral potassium supplementation. HAGMA results were available the next day. KCl 25 grams of potassium were given over 8 hours and the patient remained asymptomatic. After investigation, a history of HAGMA proved negative and its origin remained unclear. Due to resolute NAGMA and hypokalemia, RTA was considered due to a negative diarrhea workup. Urine studies revealed a mixed picture - negative urine anion gap but high pH consistent during hospitalization. His family brought his OTC medications on the day of discharge, which contained phenelzine (PhE), which was discontinued. Despite dramatic corrective measures, potassium levels improved marginally; it took days of hospitalization to normalize.

Discussion: PhE, a stimulant-laxative and OTC weight loss supplement, is banned in most countries due to carcinogenic effects, but still available in developing countries, and studies show harmful impact on kidneys due to toxicity and electrolyte imbalances. Although the patient did not experience diarrhea, PhE, mainly eliminated by his kidneys, led to his lab anomalies. Persistent NAGMA, hypokalemia, and no diarrhea suggested RTA, which was neither proximal nor distal RTA. Studies relay urinary pH is less reliable than anion gap as an indicator of RTA type. Chronic diarrhea mimics proximal RTA with a negative anion gap but variable pH which depends on hydration, and thus the urine sodium delivered to the collecting duct. Several cases of PhE-induced hypokalemia were reported, having similarly mild symptoms relative to the degree of hypokalemia, likely due to the chronicity of use as in this patient. Thus, chronic PhE use may result in milder symptoms for severe hypokalemia than expected.

Hypokalemic Rhabdomyolysis as an Unusual Consequence of Cryptosporidium-Associated Diarrhea in an Immunocompromised Host: A Case Report

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Introduction: Hypokalemic rhabdomyolysis is rare and frequently overlooked. While most case reports associate it with renal potassium wasting, gastrointestinal losses leading to rhabdomyolysis have been sparsely reported. We report a case of an immunocompromised individual with cryptosporidium-associated diarrhea resulting to hypokalemic rhabdomyolysis.

Case Description: A 38-year-old Filipino male with a two-month history of anorexia, weight loss, and diarrhea presented to our institution with bilateral lower extremity weakness. Pertinent findings include hypotonia, decreased muscle strength in both lower extremities, and diminished deep tendon reflexes. Workup revealed a positive HIV test, serum creatinine 1.38 mg/dL (eGFR 64.40 mL/min/1.73m²), blood urea nitrogen 21.07 mg/dL, and potassium 1.44 mmol/L. The complete blood count, electrolycardiogram, thyroid function tests, and other serum electrolytes were unremarkable. The calculated urine potassium-creatinine ratio of 0.9, turbostatic tubular gradient of 3.1, normal anion gap metabolic acidosis, and a negative urine anion gap were all consistent with lower gastrointestinal potassium loss. Rhabdomyolysis was confirmed with positive urine myoglobin and elevated serum creatinine kinase (15,573 U/L). Upon further investigation into the diarrhea, he was diagnosed with cryptosporidiosis. He received potassium supplementation and adequate hydration and eventually started on anti-retroviral drugs for the eventual resolution of symptoms.

Discussion: Potassium release into the intestinal fluid is crucial in regulating muscle blood flow during skeletal muscle contraction. Severe hypokalemia, whether renal or extrarenal in origin, attenuates this physiologic vasodilation resulting in relative ischemia and muscle necrosis. Hypokalemia caused by lower gastrointestinal losses only occurred on day 2, but diarrhea was persistent, as observed in this patient with cryptosporidiosis, or if accompanied by significant volume loss. This case underscores the significance of excluding rhabdomyolysis in patients with profound symptomatic hypokalemia. Thorough evaluation and clinical suspicion can aid in accurate diagnosis and prompt treatment.

An Unusual Electrolyte Disturbance in Iron Man Athlete

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Introduction: Endurance athletes are at risk for developing numerous electrolyte disorders during competition, famously hypotension. The incidence ranges from 0 to 18% in participants of marathons and may be as high as 51% in longer endurance events. Other disturbances with potassium and acid base balance may also be present. The healthcare and performance industries continue to try optimize this balance.

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An Unexpected Cause of Hypokalemia and Metabolic Alkalosis

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Introduction: Ectopic ACTH syndrome (EAS) is a rare cause of Cushing’s syndrome and is often linked with cancer, particularly neuroendocrine tumors, among which bronchial carcinoids are the most common. ACTH-secreting pulmonary carcinoids are often small and pose diagnostic/therapeutic challenges.

Case Description: A 21-year-old man presented to the hospital with psychosis symptoms. His BP was 140/90 mmHg. Laboratory test results are listed in Figure 1A. Further workup revealed low serum levels of renin < 0.1 ng/ml/hour and aldosterone 3.1 ng/dL. AM serum cortisol, 24-hour urine cortisol, and ACTH levels were elevated at 49.5 mcg/dL, 5,994 ug/l, and 238 pg/ml, respectively. Brain MRI showed a 5mm pituitary adenoma (Fig 1B). High-dose dexamethasone suppression test resulted in less than 50% suppression of serum cortisol, indicating a potential source of ectopic ACTH secretion.

Discussion: Inferior petrosal sinus sampling resulted in non-functional pituitary adenoma. A CT scan revealed an adenoma (Fig 1B). High-dose dexamethasone suppression test resulted in less than 50% suppression of serum cortisol, indicating a potential source of ectopic ACTH secretion.

The patient was discharged home hypokalemic but symptom free. A month later, she was readmitted with hypokalemia and hyperaldosteronism. She had severe hypokalemia despite high dose oral potassium, ACE inhibitors and spironolactone. She was switched to hemodialysis and insulin dose decreased. Her potassium levels normalized on a standard bath of 2K (2 mEq/L). She is off potassium and spironolactone. Her symptoms improved dramatically.

Discussion: Hypokalemia is very common in peritoneal dialysis patients and can lead to fatal cardiac arrhythmia. In most cases it is amenable to treatment with potassium supplements or addition of ACE inhibitors or spironolactone. However, in our patient, ACE inhibitors failed to treat her hypokalemia while bilateral leg weakness and pain. She had severe hypokalemia despite high dose oral potassium, ACE inhibitors and spironolactone. She was switched to hemodialysis and insulin dose decreased. Her potassium levels normalized on a standard bath of 2K (2 mEq/L). She is off potassium and spironolactone. Her symptoms improved dramatically.

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on potassium supplementation with external defibrillator. She was taken off potassium supplementation until her potassium stabilized and was started on stable potassium levels and no other cardiac medications.

Discussion: In normal pregnancy, vitamin B12 levels can decline by as much as 30% by the third trimester. Typically, recommendations are to replete if symptomatic or with macrocytic anemia. Dangerously low levels of potassium leading to cardiac arhythmias may be reversible following vitamin B12 replacement therapy. This is monitored by the manufacturer. No cases were described in pregnancy. However, in more recent experience, this was found not to be clinically significant. Potassium levels are not routinely checked during parenteral vitamin B12 administration. This raises the question if we should check potassium levels in certain circumstances. Ordering providers should be aware of hypokalemia after vitamin B12 supplementation with consideration of following potassium level after administration especially in pregnancy.

TH-PO380

Refractory Hypokalemia in a Patient with Ectopic Adrenocorticotropic Hormone (ACTH) Secretion
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Introduction: Due to similarities in structure, aldosterone and cortisol bind to mineralocorticoid receptors with similar affinity. The enzyme 11b-hydroxysteroid dehydrogenase (11b-HSD) limits the effect of cortisol at this receptor by converting cortisol to cortisone which is inactive at this site. Deficiency in 11b-HSD allows for unopposed cortisol stimulation at this receptor which mimics a state of mineralocorticoid excess. This condition manifests clinically with hypertension, hypokalemia, and metabolic alkalosis. We report a case of mineralocorticoid excess from ectopic production of ACTH leading to profound, refractory hypokalemia.

Case Description: A 56-year-old female with a history of COPD and large cell neuroendocrine carcinoma presented with one day of dyspnea, chills, and bilateral lower extremity edema. Lab work was remarkable for creatinine 1.4 mg/dL (baseline creatinine 0.7), iCO2 > 40 mmol/L, potassium 2.2 mEq/L, and WBC 11.3 x 10^9/L with 87% neutrophils. CT angiography chest showed LLL subsegmental PE and multifocal pneumonia. The patient was admitted for management of pneumonia and started on IV fluids, broad-spectrum antibiotics, subcutaneous enoxaparin, and oral IV potassium supplementation. She was noted to have worsening hypokalemia to 1.6 mEq/L despite aggressive repletion. A comprehensive chart review revealed nine months of intermittent episodes of moderate to severe hypokalemia and metabolic alkalosis starting one month after her neuroendocrine lung cancer diagnosis. A VBG showed pH 7.48, CO2 77 mmHg, and HCO3 56 mEq/L, suggestive of a primary metabolic alkalosis. 24-hour urine potassium was 68 mEq which confirmed inappropriately elevated urine potassium loss unopposed by a rise in the serum potassium level. The urine sodium was normal. CT angiography chest showed LLL subsegmental PE and multifocal pneumonia. The patient was admitted for management of pneumonia and started on IV fluids, broad-spectrum antibiotics, subcutaneous enoxaparin, and oral IV potassium supplementation. She was noted to have worsening hypokalemia to 1.6 mEq/L despite aggressive repletion. A comprehensive chart review revealed nine months of intermittent episodes of moderate to severe hypokalemia and metabolic alkalosis starting one month after her neuroendocrine lung cancer diagnosis. A VBG showed pH 7.48, CO2 77 mmHg, and HCO3 56 mEq/L, suggestive of a primary metabolic alkalosis. 24-hour urine potassium was 68 mEq which confirmed inappropriately elevated urine potassium loss unopposed by a rise in the serum potassium level. The urine sodium was normal.

Discussion: This case emphasizes the importance of thoroughly working up persistent hypokalemia. Ectopic ACTH production leading to mineralocorticoid excess in patients with malignancy is a rare occurrence. Without establishing a diagnosis, appropriate management cannot be sought.

TH-PO381

The Dual Diagnosis: Hypokalemic Rhabdomyolysis Unveils an Adrenal Nodule
Abhina Bhan, Mohamed Taher, Kartik Kalra. Geisinger Medical Center; Danville, PA.

Introduction: The occurrence of rhabdomyolysis as the initial manifestation of primary hyperaldosteronism (PHA), accompanied by severe hypokalemia is uncommon. We present a distinctive case where a patient with hypertension experiences myalgia, which was found to be due to a left adrenal nodule, revealing severe hypokalemia causing rhabdomyolysis, ultimately leading to the identification of adrenal nodule.

Case Description: 61 year old female with past medical history of hypertension presented to the hospital evaluation of weakness and myalgias occurring for 2 weeks. She denied drug abuse, diuretics or liquorice use. No significant family history. Blood pressure (BP) 165/102 mm Hg and tenderness to palpation of thighs bilaterally. Lab work was remarkable for creatinine 1.4 mg/dL (baseline creatinine 0.7), iCO2 > 40 mmol/L, potassium 2.2 mEq/L, and WBC 11.3 x 10^9/L with 87% neutrophils. CT angiography chest showed LLL subsegmental PE and multifocal pneumonia. The patient was admitted for management of pneumonia and started on IV fluids, broad-spectrum antibiotics, subcutaneous enoxaparin, and oral IV potassium supplementation. She was noted to have worsening hypokalemia to 1.6 mEq/L despite aggressive repletion. A comprehensive chart review revealed nine months of intermittent episodes of moderate to severe hypokalemia and metabolic alkalosis starting one month after her neuroendocrine lung cancer diagnosis. A VBG showed pH 7.48, CO2 77 mmHg, and HCO3 56 mEq/L, suggestive of a primary metabolic alkalosis. 24-hour urine potassium was 68 mEq which confirmed inappropriately elevated urine potassium loss unopposed by a rise in the serum potassium level. The urine sodium was normal. CT angiography chest showed LLL subsegmental PE and multifocal pneumonia. The patient was admitted for management of pneumonia and started on IV fluids, broad-spectrum antibiotics, subcutaneous enoxaparin, and oral IV potassium supplementation. She was noted to have worsening hypokalemia to 1.6 mEq/L despite aggressive repletion. A comprehensive chart review revealed nine months of intermittent episodes of moderate to severe hypokalemia and metabolic alkalosis starting one month after her neuroendocrine lung cancer diagnosis. A VBG showed pH 7.48, CO2 77 mmHg, and HCO3 56 mEq/L, suggestive of a primary metabolic alkalosis. 24-hour urine potassium was 68 mEq which confirmed inappropriately elevated urine potassium loss unopposed by a rise in the serum potassium level. The urine sodium was normal.

Discussion: This case emphasizes the importance of thoroughly working up persistent hypokalemia. Ectopic ACTH production leading to mineralocorticoid excess in patients with malignancy is a rare occurrence. Without establishing a diagnosis, appropriate management cannot be sought.

TH-PO382

Renal Replacement Therapy in Treatment of Adult-Onset Ornithine Transcarbamylase Deficiency
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Introduction: Hyperammonemia is a relatively common disorder that has a spectrum of presentations ranging from confusion to coma. The less common etiology of hyperammonemia is related to urea cycle disorders such as ornithine transcarbamylase deficiency (OTCD). This X-linked enzymatic disorder results in an accumulation of ornithine, orotic acid and urea with incomplete penetrance. The majority of cases occur as congenital enzyme disorders that may present with severe, development effects and high mortality. However, the enzyme deficiency may also be inherited with incomplete penetrance such that the disorder is triggered by high protein catabolism states at later life stages.

Case Description: Here presented is a case of a 61 year old female without prior medical history who presented with somnolence after initiation of corticosteroids for acute back pain. No evidence of infection, hemodynamically stable and serum ammonia was 233 mcg/dL. The patient had no hepatic dysfunction and was evaluated for urea cycle disorder. Intermittent hemodialysis (IHD) was used for rapid lowering of serum ammonia levels. Following IHD ammonia improved to 118 mcg/dL. However, within 24h ammonia increased to 223 mcg/dL. The patient received a second session of IHD followed by initiation of CVVH to prevent rebound accumulation. CVVH was continued for approximately 24h to allow for administration of nitrogen scavengers (benzoxide and phenylacetate). The patient was initiated on intravenous nitrogen scavengers, low protein/high glucose/high fat diet until mental status improved. Genetic testing identified X-linked heminyngry variant for OTCD.

Discussion: This case report explores the tandem use of large surface area dialyzer via HD and continuous veno-venous hemofiltration (CVVH) for rapid ammonia filtration. Rapid withdrawal of IHD prior to maintenance therapy with nitrogen scavengers has been associated with rapid reaccumulation of ammonia if the urea cycle co-factors are not replaced. This is a method that has been previously studied in the pediatric population with limited application to the adult population due to its rarity (1 in 56000 births). However, we applied these principles to an adult with success and improvement in clinical outcome.

TH-PO383

Urinary Response to Consumption of Plant-Based Meat Alternatives: Secondary Analysis of the SWAP-MEAT Trial
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Background: Consumption of excess animal meat can exacerbate kidney disorders such as urinary stone disease and chronic kidney disease. Plant-based meat alternatives, “plant-meat”, have entered the commercial market. It is not known whether plant-meat confers the same health benefits as whole vegetables because plant-meat is highly processed food. We hypothesized that consumption of plant-meat reduces dietary load of acid, phosphorus, and nitrogen compared with consumption of animal-meat.

Methods: SWAP-MEAT was a randomized crossover trial in which participants consumed a2 servings/day of either plant-meat or animal-meat for 8 weeks each, while keeping all other foods and beverages similar. We analyzed fasting spot urine samples from participants at baseline and after each phase of plant-meat or animal-meat. We used a linear mixed-effects model to investigate if the change in urine indices was different between baseline and at the end of each phase, adjusting for urine creatinine.
TH-P0386
Nonsteroidal Anti-Inflammatory Drug-Induced Type I (Distal) Renal Tubular Acidosis
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Introduction: Acute kidney injury (AKI) is the most recognized kidney toxicity of non-steroidal anti-inflammatory drugs (NSAIDs), but NSAIDs have also been linked to the development of acid-base disorders. Here, we present a patient with a history of frequent ibuprofen consumption resulting in the manifestation of a type 1 renal tubular acidosis (RTA).

Case Description: A 36-year-old man with a history of C6-C7 spinal injury due to a snow-boarding accident causing spastic paraplegia presented to an emergency department with new-onset agitation and confusion. His medications included ibuprofen 800mg every 6-8 hours and oxycodone. Brain imaging and blood and urine cultures were unremarkable. Urine toxicology was positive for his prescribed agent. Laboratory investigations were notable for a serum ammonia of 97 mmol/L (normal range: 16 – 60), albumin of 4.4 g/dL, and a creatinine of 2.5 mg/dL. Urinalysis revealed a pH of 7.26, low urine pCO2 of 25 mmHg, and a urine sodium of 13 mmol/L. There was no evidence of hyperkalemia or metabolic acidosis, and hemoglobin and hematocrit were stable.

Discussion: This case adds to several reports illustrating the association of ibuprofen with type 1 RTA in setting of preserved renal function. Ibuprofen is postulated to inhibit carbonic anhydrase (CA) II yielding impaired urinary acidification and luminal reabsorption of bicarbonate. Hypokalemia is associated with type 1 RTA and are potent stimulators of ammoniagenesis. Although impairment of CA is usually associated with proximal (type 2) RTA, impairment of CAII can cause a distal RTA.

TH-P0387
Unveiling the Enigma: Hypokalemia Paralysis in Sjögren-Associated Renal Tubular Acidosis
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Introduction: Hypokalemic Paralysis (HP) is a rare life-threatening disorder presenting as muscle weakness and low serum potassium levels. This case series focuses on two female patients with Sjögren’s syndrome-associated renal tubular acidosis (SS-RTA) who developed HP. SS-RTA is a form of distal renal tubular acidosis where the kidneys are unable to adequately acidify urine and reabsorb bicarbonate, resulting in an acid-base imbalance. The SS-RTA is thought to occur due to inflammation caused by Sjögren’s syndrome-associated autoantibodies. Although distal renal tubular acidosis causes hypokalemia, HP is rare. The important differential diagnoses include Hypokalemic Periodic Paralysis (HypoPP) and Thyrotoxic Periodic Paralysis (THypoPP). This case highlights the association between SS-RTA and HP.

Case Description: Case 1: A 26-year-old female with intellectual impairment presented with vomiting, weakness, altered sensorium, and hypercapnic respiratory distress. Her psychiatric history included self-harm and mechanical ventilation. Investigations confirmed hypokalemia, normal anion gap metabolic acidosis (NAGMA), and SS-RTA. Treatment included intravenous (IV) potassium and sodium bicarbonate. Follow-up was done on an outpatient basis for correction of hypokalemia and NAGMA.

Case 2: A 47-year-old female with hypertension and chronic kidney disease presented with new-onset agitation and confusion. Her medications included ibuprofen 800mg every 6-8 hours and oxycodone. Brain imaging and blood and urine cultures were unremarkable. Urine toxicology was positive for her prescribed agent. Laboratory investigations were notable for a serum ammonia of 97 mmol/L (normal range: 16 – 60), albumin of 4.4 g/dL, and a creatinine of 2.5 mg/dL. Urinalysis revealed a pH of 7.26, low urine pCO2 of 25 mmHg, and a urine sodium of 13 mmol/L. There was no evidence of hyperkalemia or metabolic acidosis, and hemoglobin and hematocrit were stable.

Discussion: This case adds to several reports illustrating the association of ibuprofen with type 1 RTA in setting of preserved renal function. Ibuprofen is postulated to inhibit carbonic anhydrase (CA) II yielding impaired urinary acidification and luminal reabsorption of bicarbonate. Hypokalemia is associated with type 1 RTA and are potent stimulators of ammoniagenesis. Although impairment of CA is usually associated with proximal (type 2) RTA, impairment of CAII can cause a distal RTA.
Rare Presentation of Primary Sjögren Syndrome, Hypokalemic Paralysis: A Case Report
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Introduction: Sjögren’s Syndrome is a multisystem autoimmune disorder characterized by chronic inflammation of exocrine glands, sicca syndrome. Among extra glandular manifestations renal involvement occurs as tubulointerstitial nephritis (TIN) and glomerular damage. Distal renal tubular acidosis (dRTA) is the most common presentation of TIN. However, dRTA may rarely be severe enough to present as hypokalemic paralysis. Also, Sjögren’s syndrome presenting for the first time with hypokalemic paralysis secondary to dRTA without other glandular manifestations is also very rare. Our patient had severe hypokalemic paralysis secondary to dRTA as the first manifestation of primary Sjögren’s syndrome.

Case Description: Methodology: We report a case of 45 years old lady, recently diagnosed as depressive illness with no other pre-morbid, who presented to us with acute onset of severe weakness in all four limbs for last 4 days. There was no other complaint. Clinical examination revealed hyporeflexia in four limbs with no other positive findings. Laboratory workup revealed severe hypokalemia, normal anion gap metabolic acidosis, alkaline urine and strongly positive serological markers of Sjögren’s syndrome, (anti-RO, anti-LA, ANA). Result: We treated that patient by intravascular replacement of potassium, oral, alkali, replacement and corticosteroids. Patient showed an excellent response to this treatment. She was followed up for the recurrence of tubular dysfunction and other systemic manifestations of Sjögren’s syndrome.

Discussion: This report highlights that Sjögren’s syndrome is a rare but an important cause of hypokalemia and therefore should be considered in diagnosis of hypokalemia.

Is Diabetic Ketoacidosis Synonymous with Death in Patients on Enfortumab Vedotin for Urothelial Carcinoma?
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Introduction: Enfortumab vedotin (EV), is a novel breakthrough therapy which received accelerated FDA approval in 2019 for the treatment of metastatic urothelial carcinoma in patients who have failed other lines of treatment. The characteristics of its adverse effects especially diabetic ketoacidosis (DKA) are not well understood.

Case Description: A 57-year-old male with no history of diabetes, diagnosed with urothelial carcinoma two years prior, failed several lines of treatment including platinum-based chemotherapy and immune checkpoint inhibitors. He developed metastasis and was started on EV. After his second dose of EV, he was admitted to the ICU for diabetic ketoacidosis (DKA) with a high anion gap metabolic acidosis, serum bicarbonate of 12 mEq/L, blood Ph 7.2, hyperglycemia to 450 mg/dL, positive ketones in urine, an elevated C-peptide, with an initial hemoglobin A1C of 7.7%. He was in shock requiring multiple pressors and developed oliguric AKI (serum creatinine 1.5 mg/dL, baseline 0.7 mg/dL). He was intubated for airway protection and started on continuous renal replacement therapy. Despite aggressive treatment, the patient died on hospital day 2.

Discussion: EV is an antibody-drug conjugate which joins an anti-HER2 directed against the cell adhesion molecule,nectin-4, which is highly expressed in urothelial carcinoma, with monomethyl auristatin E, an inducer of cell cycle arrest and apoptosis. Just 2 cases of DKA due to EV have been reported since its approval for use in metastatic urothelial carcinoma (One at the 2020 American Thoracic Society Conference and the other at the 2021 American Society of Nephrology Conference). The precise mechanism for the development of DKA is yet unidentified. An elevated C-peptide, noted in one of the reported cases, suggests insulin resistance, but the very rapid progression of the acidemia and death within three days in both cases suggests some other effects of the drug on glucose metabolism still to be elucidated. There is an FDA warning on its use in patients with glucose over 250 mg/dL, but this was insufficient to prevent DKA in the

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
reported patients. Our patient had an elevated A1C on admission. Therefore, we strongly
suggest screening for diabetes in every patient considered for EV, and to avoid if A1C is
greater than 7%.

TH-PO392
Continuous Renal Replacement Therapy (CRRT) Worsening Acidosis
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Introduction: Euglycemic ketoacidosis (EDKA) is an uncommon cause of high
anion gap metabolic acidosis (HAGMA) and should be suspected in diabetics with
normal blood glucose (BG) who develop HAGMA. EDKA can complicate continuous
renal replacement therapy (CRRT) when poor intake is accompanied by dialysate caloric
losses. We describe a patient with EDKA on CRRT following peritonitis from perforated
diverticulitis.

Case Description: A 52-year-old AA male with a history of HTN, T2DM, obesity
and ESRD on HD presented with diarrhea, left lower quadrant (LLQ) pain and 2 episodes
of emesis. On exam, he had LLQ tenderness and leukocytosis with left shift. Imaging
showed diverticulitis with multiple fistulas and organizing collection suspicious of
abscess. Initially, managed conservatively, but later had signs of peritonitis with free fluid
and pneumoperitoneum on imaging, requiring sigmoidectomy. Post-op he was in septic
shock, requiring vasopressor support and switched to CRRT from HD. He remained NPO,
first awaiting ostomy creation and later due to poor mentation. He continued CVVHDF
using Phrixolim and Primosal solutions (both glucose-free dialysate and replacement
fluid), however had worsening HAGMA without diarrhea or hyperlactatemia. His BG
remained <200 mg/dL. Starvation ketoacidosis was suspected and confirmed with serum
Beta hydroxy butyrate (BHB) levels of 7.6. He was started on TPN and transitioned to
intravenous fluid, however had worsening HAGMA without hyperlactatemia. His BG
levels normalized in parallel with a decrease BHB levels. Within 2 days of feeding his Hco3
levels normalized in parallel with a decrease BHB levels.

Discussion: Euglycemic ketosis is driven by insulin deficiency and insulin resistance,
starvation, and an excess of counter-regulatory hormones. In absence of external
nutrition, glucose content of replacement fluid, especially phosphate-containing fluid can
cause negative caloric balance with glucose loss of ~ 80g in the effluent which is more than
SGLT2, a known cause of EDKA. In our patient, the day of ketonemia detection,
metabolic acidosis had worsened despite appropriately dosed CRRT with minimal
lacitetaemia, while not on insulin and the use of phosphate-containing replacement fluid
providing a perfect storm to develop euglycemic ketoacidosis while being on CRRT. This
case highlights the need to consider EDKA in the differential diagnosis of high anion gap
metabolic acidosis in patients on CRRT.

TH-PO393
Unraveling the Enigma: Deciphering Recurrent Metabolic Acidosis and the
Elusive Kabadi Syndrome
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Introduction: This case report explores the diagnostic challenges posed by rare
metabolic acidosis conditions. It focuses on Kabadi syndrome (KBS), accompanied by
mitochondrial complex II deficiency. Understanding and managing KBS remains difficult due to its rarity
and limited knowledge of the condition. In highlighting the complexity of such cases, we
emphasize the need for thorough investigation into rare etiologies.

Case Description: A 65-year-old female with a 10-year history of chronic pancreatitis with
recurrent life-threatening severe anion gap metabolic acidosis (AGMA) over three years,
requiring frequent admissions to the intensive care unit. She presented with respiratory
distress, altered mental status, and abdominal pain. Laboratory findings consistently showed
severe acidemia, low bicarbonate, and elevated anion gap. Glucose levels were normal,
with positive ketones. Workup revealed consistently elevated lipase levels with normal liver function tests. Genetic testing was inconclusive, except for low carbometic
levels. Imaging indicated chronic pancreatitis. Management involved insulin therapy,
hydrochlorothiazide to control acidosis, pancreatic enzymes, and carnitine supplementation,
leading to resolution; eventually, medication non-compliance led to readmissions.

Discussion: KBS, or pancreatic ketoacidosis, is a rare condition characterized by
euglycemic ketoacidosis. It is triggered by elevated pancreatic lipase levels, resulting in
fat necrosis and ketone production. The pathophysiology involves the release of
free fatty acids, converting them into ketone bodies and causing metabolic acidosis.
Carnitine deficiency further impairs ketone clearance and contributes to acidemia. In this
patient, the combination of KBS and carnitine deficiency adds complexity. Carnitine
supplementation may protect against recurrence; especially as cognitive impairments
associated with carnitine deficiency may explain medication non-compliance. This
case underscores the importance of comprehensive investigations, genetic testing,
and innovative thinking in unraveling rare etiologies. The multidimensional treatment
approach includes fluid management, acidosis correction, pain management, pancreatic
enzymes replacement therapy, nutritional support, and carnitine supplementation. This
report highlights the complexity of rare AGMA etiologies, emphasizing perseverance,
innovative investigations, and personalized approaches.

TH-PO394
An Unusual Case of Metabolic Acidosis
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Introduction: Metabolic acidosis is common in hospitalized patients, and more than
half the patients admitted to intensive care units have metabolic acidosis. The cause of
acidosis is usually apparent from the clinical setting, but in rare instances, a methodical
workup is needed to decipher the underlying cause. We present an unusual case of
metabolic acidosis.

Case Description: A 40 yr. woman with Mitochondrial Encephalopathy with
Lactic Acidosis and Stroke-like episodes (MELAS), presented with sudden worsening of
electro-muscular weakness. An initial work up ruled out acute stroke, and patient
was started on intravenous L-arginine for MELAS. On day five, she developed acute
ecephalopathy and severe acidosis (Figure-1). The severe non-gap metabolic acidosis was
thought to be from L-arginine. Following discontinuation of IV L-arginine and initiation
of bicarbonate supplementation, the patient’s acidosis improved rapidly.

Discussion: Metabolic acidosis has been reported with prolonged use of L-arginine,
particularly in high doses. The mechanisms by which L-arginine causes metabolic acidosis
remains unclear. While arginine is administered as arginine hydrochloride, the number of
protons added is not significant enough to cause severe acidosis. Although the urine anion
gap was negative in our patient, possibly due to exogenous bicarbonate, the urine osmolar
gap indicated a renal tubular acidosis. This was confirmed by generalized aminoaciduria
and low levels of directly measured ammonia. There was no evidence of phosphaturia or
hypophosphatemia. Interestingly, in the isolated perfused tubule exposure to L-arginine
causes inhibition of bicarbonate reabsorption in the proximal tubules. Metabolic acidosis
could augment L-arginine absorption in the intestine worsening acidosis. Our case
highlights that L-arginine can be an unusual cause of severe metabolic acidosis. The
physiology underlying this clinical observation requires further studies.
TH-PO396

Patent Foramen Ovale Causing Lactic Acidosis
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Introduction: Lactic acidosis is secondary to the accumulation of protons and lactate in body fluids and is associated with poor clinical outcomes and increased mortality. Hypoxemia leads to increased anaerobic glycolysis causing excess generation of lactate. Congenital cyanotic heart defects are associated with an increased risk for lactic acidosis, which is also rarely seen in acyanotic heart disease. Here we present a case of a patient with patent foramen ovale (PFO) causing lactic acidosis, which resolved after its closure.

Case Description: A 70-year-old white male with a history of hypertension, and remote smoking presented with worsening shortness of breath for a few hours. He had hypoxemia with oxygen saturation between 83% to 88%; his heart rate ranged from 100 to 110 beats per minute, and his respiratory rate ranged from 22 to 30 breaths per minute. Initial blood gas showed a pH of 7.53, pCO2 of 24.8 mm Hg, and PO2 of 48.7 mm Hg on room air. His initial chemistry showed a sodium level of 139 mmol/l, potassium of 4.0 mmol/l, bicarbonate level of 12 mmol/l, chloride level of 101 mmol/l, anion gap of 26 mmol/l. BUN of 34 mg/dl, creatinine of 0.98 mg/dl, serum albumin level was 4.1 g/dl. He had normal pro-BNP and lactic acid of 4.8 mmol/l. Chest X-ray was negative for any signs of volume overload or infiltrate. Common etiologies of lactic acidosis were considered and ruled out. The patient never had hypotension, and pan cultures were negative. The lactic acid level remained elevated even after tachypnea had improved. Pulmonary / Cardiac shunting was suspected, and the patient underwent an echocardiogram with an agitated saline contrast study, which showed a right-to-left shunt. The patient underwent transesophageal echocardiography, which was suggestive of mild-to-moderate pulmonary hypertension, right ventricular systolic pressure was 40 mmHg, and 6 mm PFO with a right-to-left shunt. The patient underwent percutaneous closure of the PFO, leading to the resolution of hypoxemia and normalization of the lactate and anion gap. Significant right to left shunting through the PFO contributed to his hypoxemia, which likely worsened recently, contributing to Type A lactic acidosis.

Discussion: After excluding common etiologies, nephrologists should consider cardiac and pulmonary shunts in the differential diagnosis when evaluating patients with elevated anion gap metabolic acidosis with lactic acidosis.

TH-PO397

Mind the Gap: Pyroglutamic Acidosis as a Not-so-Rare Cause of High Anion Gap Metabolic Acidosis (HAGMA)
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Introduction: In addition to the common causes of high-anion gap metabolic acidosis (such as lactic acidosis, ketoacidosis, and toxic alcohol ingestion), pyroglutamic acidosis can also result in HAGMA. This case report illustrates a patient in which otherwise unexplained metabolic acidosis was attributed to 5-oxoproline accumulation in the setting of chronic acetaminophen exposure and malnutrition.

Case Description: A 39-year-old man with a history of paraplegia, malnutrition, and remote smoking presented with worsening shortness of breath for a few hours. He had hypoxemia with oxygen saturation between 83% to 88%; his heart rate ranged from 100 to 110 beats per minute, and his respiratory rate ranged from 22 to 30 breaths per minute. Initial blood gas showed a pH of 7.53, pCO2 of 24.8 mm Hg, and PO2 of 48.7 mm Hg on room air. His initial chemistry showed a sodium level of 139 mmol/l, potassium of 4.0 mmol/l, bicarbonate level of 12 mmol/l, chloride level of 101 mmol/l, anion gap of 26 mmol/l. BUN of 34 mg/dl, creatinine of 0.98 mg/dl, serum albumin level was 4.1 g/dl. He had normal pro-BNP and lactic acid of 4.8 mmol/l. Chest X-ray was negative for any signs of volume overload or infiltrate. Common etiologies of lactic acidosis were considered and ruled out. The patient never had hypotension, and pan cultures were negative. The lactic acid level remained elevated even after tachypnea had improved. Pulmonary / Cardiac shunting was suspected, and the patient underwent an echocardiogram with an agitated saline contrast study, which showed a right-to-left shunt. The patient underwent transesophageal echocardiography, which was suggestive of mild-to-moderate pulmonary hypertension, right ventricular systolic pressure was 40 mmHg, and 6 mm PFO with a right-to-left shunt. The patient underwent percutaneous closure of the PFO, leading to the resolution of hypoxemia and normalization of the lactate and anion gap. Significant right to left shunting through the PFO contributed to his hypoxemia, which likely worsened recently, contributing to Type A lactic acidosis.

Discussion: After excluding common etiologies, nephrologists should consider cardiac and pulmonary shunts in the differential diagnosis when evaluating patients with elevated anion gap metabolic acidosis with lactic acidosis.

TH-PO398

Severe ICU-Acquired Metabolic Acidosis due to Pyroglutamic Acidosis (5-Oxoprolineinuria)
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Introduction: Anion gap metabolic acidosis (AGMA) is an acid-base disturbance frequently encountered in the intensive care unit (ICU). However, pyroglutamic acidosis (PGA) is a rare cause of ICU-acquired metabolic acidosis.

Case Description: A 56-year-old woman with a recent large stroke requiring craniectomy with abdominal bone flap was readmitted for septic shock from an abdominal abscess. Her course was complicated by new intracranial hemorrhage, persistent encephalopathy requiring prolonged mechanical ventilation via tracheostomy, malnutrition requiring tube feeds, and multiple episodes of acute kidney injury (AKI). A month after readmission, she developed AGMA of unclear etiology, with arterial pH 7.31, arterial PCO2, 16 mmHg, bicarbonate 9 mmol/l (down from 21-31), anion gap 17 mmol/l (up from 5-6), albumin 1.2 g/dl, creatinine 1.5 mg/dl, lactic acid 2.5 mmol/l, and beta-hydroxybuterate 0.1 mmol/l. Notably, since she had received several N-acetylcarnitine 500-650 mg four times daily, which was stopped upon nephrology consult. She received N-acetylcysteine 600 mg twice daily for 5 days. She required continuous renal replacement therapy (CRRT) for one day for transient oliguria and worsening AKI (peak SCR 1.9 mg/dl) from recurrent septic shock, with sustained resolution of her acid-base disturbance. However, a urine sample sent for organic acids prior to CRRT initiation ultimately revealed elevated pyroglutamic acid.

Discussion: Acetaminophen normally undergoes cytochrome metabolism to N-acetyl-p-hexoxoamine imine (NAPQI), a highly reactive oxidation product that is detoxified by glutathione. In glutathione deficiency, a buildup of the organic anion pyroglutamic acid (5-oxoproline) can occur. In predisposed patients – classically older malnourished women – chronic therapeutic acetaminophen use can induce acquired glutathione deficiency and PGA, which likely explains the severe AGMA out of proportion to renal dysfunction in our case. As most labs do not measure 5-oxoproline locally, PGA is likely underrecognized and underreported, though it features in the modern GOLDMARK mnemonic for AGMA (glycoals, 5-oxoproline, L- and D-lactate, malnutrition, acute kidney injury, renal failure, ketosis). Moreover, though this is one of only a few prior published cases of ICU-acquired PGA, this case illustrates that PGA must be considered on the differential diagnosis of unexplained ICU-acquired AGMA.

TH-PO399

Amiloride or Furosemide for the Treatment of Edema in Nephrotic Syndrome (AMILOR): A Pilot Study
Ferruh Artunc, Elisabeth Vogel, Bernhard N. Bohnert, Daniel Essigke, Anja Schork. Eberhard Karls-Universitat Tubingen Medizinische Fakultat, Tubingen, Germany.

Background: According to findings from nephrotic mouse models, edema formation in nephrotic syndrome (NS) is caused by sodium retention through activation of the epithelial sodium channel ENaC. In these models, edema formation could be prevented by ENaC blockade with amiloride. The monocentric randomized controlled AMILOR study investigated the anti-edematous effect of the ENaC blocker amiloride in nephrotic patients in comparison to standard therapy with the loop diuretic furosemide.

Methods: Patients with acute NS (n=10 per arm, etiology MCD n=6, MN n=8, FSGS n=2, amyloidosis n=1, IgAN n=1, other n=2; age 53 [interquartile range 38-61], male/ female 13/7) and eGFR (CKD-EPI)-30 ml/min/1.73m2 were randomized to treatment with amiloride (start 5mg/d, max.15mg/d) or furosemide (40mg/d, max.120mg/d) over 16 days. Overhydration (OH) was measured by bioimpedance spectroscopy (Body Composition Monitor, Fresenius). Depending on the course of OH, the dose was adjusted on days 2.5, 5.5 and 14 and if necessary, HCT was added on d8 (start 12.5mg/d, max. 25mg/d). The primary endpoint was the decrease in OH on d8. The study was terminated prematurely due to insufficient recruitment and low statistical power due to a low actual effect size.

Results: Median baseline OH was 5.3 L/1.73m2 (26 [18-34]% of extracellular water [ECW]) in the amiloride arm and 6.2 L/1.73m2 (28 [24-29]% ECW) in the furosemide arm. On d8, OH decreased to 3.7 L/1.73m2 (19 [16-27]% ECW) in the amiloride arm and to 5.1 L/1.73m2 (21 [13-28]% ECW) in the furosemide arm. Till d16, OH decreased significantly to 60 [29-93]% or 2.2 L/1.73m2 (12 [9-24]% ECW) in the amiloride arm and to 69 [57-85]% or 3.4 L/1.73m2 (17 [14-27]% ECW) in the furosemide arm. The decrease in OH on d8 and d16 was not significantly different between both arms. Hydration losses >5.3 ml (max. 5.7 ml) occurred in n=3 patients taking amiloride (all GFR according to CKD-EPI-Cys >40ml/min/1.73m2).

Conclusions: The AMILOR study is the first randomized controlled pilot study on the use of diuretics in NS demonstrating an antiedematous effect of the ENaC blocker amiloride with a significant difference to furosemide. This, amiloride emerges, as an alternative to the standard therapy with furosemide. The knowledge gained lays the foundation for the design of a larger multi-centre study with greater statistical power.
TH-PO400
Correlation Between Conventional Ultrasound and Microchip Technology Ultrasound in Evaluating Pulmonary and Inferior Vena Cava in AKI Patients Undergoing Renal Replacement Therapy
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Background: Point of care ultrasonography is an essential tool in nephrologists physical examination. Ultrasound examination using microchip technology-BrayeCell RNA a recent technological advance and should be compared with the traditional piezoelectric. So the study aims to compare both technologies, in the analysis of two extra-cavitary volume parameters: B-lines and Inferior venous collapsibility index (IVC). Seeking to verify the correlation between the piezo electrics and microchip technologies for evaluating pulmonary B-lines was strongly positive, with a mean of 0.8 ± 0.3 L. The correlation between the piezoelectric and microchip technologies for evaluating pulmonary B-lines was strongly positive, by correlation coefficients of 0.96 and 0.93 at the beginning and 1 hour, respectively (P < 0.001). Similarly, the correlation coefficients for IVC showed 0.70 and 0.87 at the beginning and 1 hour respectively (P <0.001), indicating a moderate correlation.

Conclusions: On AKI patients under RRT USG by Butterfly IQ microchip has an excellent correlation with traditional piezoelectric technology and combines advantages related to portability, easy handling and low cost with reliability in obtaining parameters for volume assessment obtained at the bedside.

Results: A total of 200 exams were done with a mean age of 73.5 ± 13, including 20 male patients (39%). Conventional HD was performed in 25.7% of cases, with a mean prescribed ultrafiltration of 1.6 ± 0.9 L. The correlation between the piezoelectric and microchip technologies for evaluating pulmonary B-lines was strongly positive, with a mean of 0.8 ± 0.3 L. The correlation between the piezoelectric and microchip technologies for evaluating pulmonary B-lines was strongly positive, by correlation coefficients of 0.96 and 0.93 at the beginning and 1 hour, respectively (P < 0.001). Similarly, the correlation coefficients for IVC showed 0.70 and 0.87 at the beginning and 1 hour respectively (P <0.001), indicating a moderate correlation.

Conclusions: On AKI patients under RRT USG by Butterfly IQ microchip has an excellent correlation with traditional piezoelectric technology and combines advantages related to portability, easy handling and low cost with reliability in obtaining parameters for volume assessment obtained at the bedside.

TH-PO401
Chronology of Cyst Epithelium Transformation to Renal Cell Carcinoma Through scRNA-seq
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Background: We have described a mouse model suitable for studying the progression of renal cell carcinoma (RCC). Upon deletion of a single gene (Tsc1) by a kidney-specific Cre (KspCre) in specific segments of the nephron, the mTORC1-dependent downregulation of polycystin-1 initially triggers the establishment of an overt cystic phenotype. Mutated epithelial cells then transform into cancerous lesions. The slow progression over the phenotype allows to dissect between mechanisms driving cyst formation, and the ones supporting epithelial malignant transformation. However, mutant cells lose epithelial markers, making it difficult to follow the next steps of transformation.

Methods: Our RCC model (Tsc1−/−KKO) was crossed with mTmG strain, ubiquitously expressing membrane Tomato (mT) marker that recombines to mGFP (mG) upon KspCre expression, allowing to discriminate mutated cells over time. Mutant kidneys were characterized by histological and immunofluorescence analysis. Kidney single cell suspension was characterized by flow cytometry. Chromium 10x single cell RNA sequencing (scRNA-seq) was performed on 20,000 cells from P80 mutant and ctrl kidneys.

Results: mTmG;Tsc1−/−KKO mutants were comparable to our previous RCC model, with the epithelium lining the cysts progressively transforming to papillae (P20), cystadenomas (P50), and carcinoma (P80). All the structures identified were mG, allowing following the mutated cell transformation. Indeed, flow cytometric analysis confirmed the expansion of the mG population at P80, consistent with the reported prominent proliferation of Tsc1 KO cells. scRNA-seq identified clusters of cells from all the segments of the nephron, both in mutant and ctrl kidneys. Cells deriving from the distal tubule and collecting duct were identified by Egfl9 transcript. This uniquely defined the Tsc1 KO cells and their expansion in the mutated kidney. Interestingly, we identified sub-clusters of mG cells with a proliferative and de-differentiated profile, and we observed the expansion of different immune populations in mutated kidneys, potentially supporting the RCC progression.

Conclusions: We generated a model of RCC through which we can dissect between driving events of cytogensis and mechanisms supporting epithelial transformation to cancerous lesions. scRNA-seq represents a valuable approach to deciphering key mechanisms and new populations in RCC.

TH-PO402
Selective V2 Vasopressin Receptor Blockade Increases Urinary Exosome Pendrin Expression in Patients with Autosomal Dominant Polycystic Kidney Disease
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Background: Tolvaptan, a selective V2 vasopressin receptor (V2R) antagonist, has shown to improve kidney function and acid retention biomarkers in ADPKD-treated patients. However, the underlying mechanisms of this association remain unclear. Here we investigate the effect of Tolvaptan on renal acid-base handling in ADPKD by analyzing the urinary abundance of Pendrin and the B1 subunit of V-ATPase, which regulate HCO3− and H+ transport in the collecting ducts.

Methods: In this prospective study, 24 ADPKD patients were enrolled from the Bern University Nephrology Department. Patients were allocated with a 1:1 ratio in the Tolvaptan and no-Tolvaptan groups. All patients performed baseline and 2-year follow-up visits. Net acid excretion (NAE) and net gastrointestinal alkali absorption (NGIA), markers of acid and alkaline intake, were calculated from 24h urine. Second morning spot urine samples with freshly added protease inhibitors and immediately frozen at −80 °C were used to isolate urinary exosome proteins with an already established differential centrifugation method. Primary polyclonal anti-rabbit antibodies for Pendrin and the B1 subunit of V-ATPase were used for immunoblotting. Changes in urinary exosome abundance were normalized by Alix (exosome housekeeping protein).

Results: 19 patients (9 with and 10 without Tolvaptan) were included in the final analysis. 5 patients were excluded because Alix was not detectable. Compared to baseline, urinary exosome Pendrin abundance increased by 134.4% only in Tolvaptan-treated patients (p = 0.01) after two years. Pendrin abundance strongly and directly correlated with NAE (rho 0.75, p < 0.01) at baseline, and inversely with NVEA (rho = -0.51, p < 0.03) during follow-up. Urinary HCO3− excretion was associated with Pendrin expression over time (rho 0.73, p < 0.01). Ultimately, changes in urinary exosomal Pendrin were inversely associated with plasma potassium (rho -0.71, p = 0.03) only in the Tolvaptan group.

Conclusions: Urinary exosome Pendrin expression is sensitive to subtle changes in the acid-base status of ADPKD patients. Tolvaptan increases the expression of Pendrin in urinary exosomes, supporting the hypothesis that selective V2R blockade exerts an effect on systemic acid-base status of ADPKD patients.

TH-PO403
Automated Detection and Quantification of Individual Collagen Fibers Indicates Collagen Dynamics Underlying Increased Fibrotic Index in ADPKD
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of kidney failure. While cysts are the most obvious phenotype, accumulating evidence indicates the involvement of the extracellular matrix in the kidney and other organs. The most abundant protein in this matrix is collagen, which is encoded by 44 genes comprising supramolecular assemblies making up 28 collagen types. As such, histological methods to assess overall collagen are valuable and routinely used in ADPKD research, yet they are limited by variability and insensitivity. We used CT-FIRE software that automatically detects individual collagen fibers to determine fiber density in glomeruli and tubules in an ADPKD mouse model.

Methods: Four-month-old Pkd1−/− mice were compared to WT. All mice were F1 progeny from a 129/SVc57BL6J cross. Kidneys were fixed, cryosectioned, and stained with Sirius red. Tissue area and fibrotic index were determined using ImageJ and collagen fibers software that automatically detects individual collagen fibers to determine fiber density in glomeruli and tubules in an ADPKD mouse model.

Results: The acid-base status of ADPKD patients. Tolvaptan increases the expression of Pendrin in urinary exosomes, supporting the hypothesis that selective V2R blockade exerts an effect on systemic acid-base status of ADPKD patients.

TH-PO404
Automated Detection and Quantification of Individual Collagen Fibers Indicates Collagen Dynamics Underlying Increased Fibrotic Index in ADPKD

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

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Correction of PKD by Gene Transfer into Pkd1-Null Mouse Model

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Background: Autosomal dominant polycystic kidney disease (ADPKD) causes renal cysts and insufficiency due mainly to Pkd1 mutations. Since microscopic cysts in ADPKD kidneys are likely formed in utero, we re-expressed wild-type Pkd1/Pc1 protein in Pkd1-/- mice via germ line by series of complementary gene transfer to assess for long-term cure of severe cystogenesis and neonatal death.

Methods: Pcl1 re-expression in the most severe mouse model Pkd1-/- was assessed by 3 strategies using genomic Pkd1 under its own regulatory elements (Pkd1wt), driven by kidney specific regulatory elements (0008t SB, Pkd1wt) or Pkd1-/- (RBt). Renal molecular (qPCR, IB), tubular (staining, IF, RNAscope) and functional (BUN, hct) analyses were performed.

Results: Pkd1wt mice targeted with 2 distinct Pkd1wt gene transfers, of ~8-fold overexpression and intense RNAscope signal over all tubular segments and glomeruli similarly to endogenous cell profile, fully rescued Pkd1 phenotype. Pkd1wt one- and high-copy gene transfers conveyed 0.6- or 7-fold Pkd1 endogenous levels respectively. One copy Pkd1 transfer initiates cysts after birth ~P3 and confer sufficient Pkd1 expression during maturation to correct proximal tubules and glomeruli to minimize distal cyst and to postpone but not prevent cyst in collecting ducts. This transfer extended Pkd1 life survival by ~4-fold. High-copy Pkd1 transfer provide proper targeting and expression levels for complete rescue during renal maturation, and significantly retard cyst in proximal and collecting tubules at post-maturation but is insufficient to prevent distal cysts. This transfer increased lifespan by ~25-fold. Pkd1 transfers show that collecting tubules require higher Pkd1 expression during maturation and that SB regulatory elements appreciably overlap with those of the endogenous promoter. High-copy renal Pkd1wt transfer resulted in similar expression to endogenous Pkd1 with widespread and homogeneous weak Pkd1 cellular signal, partially rescuing glomeruli and all cystic tubular segments during maturation and attained therapeutic levels with increased lifespan by ~4-fold.

Conclusions: Our study determined that Pkd1 intragenic sequences not only control levels of expression but also the upstream sequences, also regulate spatio-temporal expression pattern. One-copy Pkd1 is sufficient to substantially delay cystogenesis. Pcl1 re-expression can considerably extend lifespan or eliminate PKD.

Funding: Government Support - Non-U.S.

Delivering Nucleic Acids to ADPKD Cystic Cells via a Nucleic Acid Binding and Cell-Penetrating Antibody

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Background: Mutations in Pkd1, which encodes polycystin-1 (PC1), cause ~78% of autosomal dominant polycystic kidney disease (ADPKD) cases. We have shown that transgenic expression of the Pkd1 200 aa C terminal tail (CCT) in the Pkd1 200 aa PC1 C terminal tail (CTT) and in the Pkd1wt 200 aa PC1 C terminal tail (Pc1wt) mouse model of ADPKD suppresses cyst phenotype and preserves renal function. To overcome the challenge of delivering CTT-encoding cDNA or mRNA to cystic epithelia we used the lupus-derived antibody 3E10-D31N and its humanized version, V66. These cell-penetrating antibodies non-covalently bind and deliver nucleic acids to tumors by targeting the nucleoside transporter ENT2. Specific targeting of tumors occurs due to increased ENT2 expression in proliferative tissues.

Methods: Trial #1: one 200µg dose of 3E10-D31N labeled with fluorochrome IR700, administered to 11-week Pkd1-/-KO mice. Trial #2: 3 doses of V66 (100µg/dose) combined with mRNA encoding GFP (20µg/dose), administered 24 hours apart to 13-week Pkd1-/-KO mice. In vivo imaging system (IVIS) and immunofluorescence microscopy (IF) were used to assess treatment results.

Results: IVIS imaging of Trial #1 kidneys revealed absence of fluorescently labeled 3E10-D31N in untreated controls, suggesting specificity of the total radiance efficiency (TRE) observed in treated WT and pre-cystic mice. Interestingly, treated pre-cystic mice showed an ~50% increase in TRE relative to treated WT, suggesting that this approach can successfully target highly proliferative ADPKD tissue. IVIS imaging of kidneys from Trial #2 revealed GFP fluorescence only in cystic kidneys from mice that were treated with V66/GFP mRNA, and not in cystic tissue from mice that received GFP mRNA alone or untreated mice. Interestingly, a positive correlation was observed between kidney size and TRE levels. Finally, IF analyses revealed GFP present in a punctate cytoplasmic pattern in cystic epithelial cells of animals that received V66/GFP mRNA and not in controls.

Conclusions: 3E10-D31N/V66 targets cystic epithelia and delivers GFP mRNA that drives transgene expression next day. We will next deliver PC1wt and determine PC1wt expression and potential impacts of this intervention on the development of cystic phenotype. This strategy could support the delivery of other potentially therapeutic mRNAs or cDNAs in the context of other renal diseases.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

Poster: Thursday

Title: Correction of PKD by Gene Transfer into Pkd1-Null Mouse Model

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

Underline represents presenting author.

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Genetic Diseases: Cystic - Therapeutic Investigations and Prognosis

PAN1021 has an OCT profile anticipated to reduce the risk of lactic acidosis in ADPKD. Murine studies suggest that immune cell function and metabolic defects influence disease progression; both of which are altered in obesity. Caloric restriction (CR), in turn, slows PKD progression in mice.

Methods: Using the C57Bl/6 J Pkd1 P2R277C (Ppk1/PC1) mouse, we established a diet-induced obesity model of ADPKD by ad libitum feeding a high fat diet (HFD, 42% calories from fat) for 4 weeks to 7 months of age; control diet (CD, 13% calories from fat, matched composition). PKD severity, fat mass (quantitative magnetic resonance), and kidney immune (flow cytometry) and metabolic (LC-MS/MS) state were assessed at study end.

Results: Compared to consumption of CD, HFD caused a 1.2-fold (p<0.01) increase in body weight in males (M)/females (F) and a 2.4-fold in M (p<0.05) and F (p<0.05) increase in fat mass. Interestingly, PKD severity only significantly worsened in females on HFD vs CD not males: increased kidney weight/femur length (1.4-fold, p<0.01), cyst- (1.98-fold, p<0.01) and fibrotic- volume (2-fold, p<0.05). Kidney metabolism revealed significant dysregulation of the kynurenine pathway, which we recently identified as key modifier of PKD progression and immunosuppression, e.g., kynurenine was increased in KA) increased by 3.1-fold (p<0.001) and 1.26-fold (M) in mice on HFD vs CD. Of note, CR resulted in a 3-fold reduction in KA (p<0.05) in a separate age/sex matched study of Ppk1/PC1 mice. Correlatively, the kidney immune landscape of Ppk1/PC1 mice on HFD significantly shifted towards immunosuppression with increased regulatory T cells, M2-like infiltrating macrophages (1.4-fold, p<0.001), and CR decreased immune landscape (1.8-fold, p<0.01).

Conclusions: We established a model of ADPKD that mimics clinical findings of patients with ADPKD and high adiposity, although the sex dimorphism needs further investigation. We also outline potential avenues for redifferentiation of mice on HFD to a mouse model that more closely mimics human disease. We will next investigate the role of the kynurenine pathway in diet-induced obesity as a potential mechanistic link. The model will allow evaluation of novel therapeutic/nutritional avenues to reduce adiposity and slow PKD progression as well as adiposity-linked mechanisms driving cyst kidney growth.

A Novel Kidney-Selective AMPK Activator Shows Renal Cystic Disease and Fibrosis in PKD Mice

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Background: ADPKD is characterized by progressive enlargement of fluid-filled cysts, leading to inflammation and fibrosis, and a decline in kidney function. Metformin, the only FDA-approved AMPK activator and most commonly used drug for the treatment of type 2 diabetes, reduced mTOR-mediated cell proliferation and CFTR-mediated ion transport in Pkd1 mutant cells and inhibited cyst growth of rapid PKD models. However, metformin-associated lactic acidosis, a potentially lethal side effect, raises concerns about its application for long-term treatment of ADPKD. Metformin is a biguanide that requires an organic cation transporter (OCT) to be taken up by cells and is transported into the kidneys via OCT2; however, it is not a substrate for OCTN1/2 and is eliminated in urine. In collaboration with Panco Therapeutics, we tested biguanides with improved potency for AMPK, OCT2, and OCTN1/2. PAN1021 was 38x more potent for OCT2 and >100x more potent of OCTN1/2 than metformin, thus reducing renal elimination. Previously, PAN1021 decreased mTOR signaling, proliferation, anion secretion, and in vitro cyst formation of human ADPKD cells. Here, we compared effects of PAN1021 and metformin in kidney disease, inflammation, and fibrosis in an orthologous PKD mouse model.

Methods: PAN1021 (100mg/kg) or metformin (300mg/kg) was delivered to Pkd1-/-/Pkd2-/- mice, an early onset PKD model, by daily gavage from 5 to 20 wk. Mice were killed 3 h after the last treatment, and blood and kidneys were collected for analysis.

Results: PAN1021 had no effect on body weight, appearance, or behavior of the PKD mice, indicating that the drug was safe, and it caused a significant decrease in kidney weight/body weight (%body weight). The body weight of the PKD mice increased ~1.4-fold vs CD. Both drugs reduced renal fibrosis and BUN. PAN1021 reduced P65/S6, a component of mTOR signaling, and PCNA, a proliferation marker. It potently reduced TNF-α and F480, inflammation markers, and e-SMA and collagen 1A1, fibrosis markers, and restored the levels of PPARγ, a regulator of fatty acid oxidation.

Conclusions: A novel kidney-selective AMPK activator PAN1021 inhibits renal mTOR, cell proliferation, cyst growth, tissue inflammation, and fibrosis in PKD mice. PAN1021 has an OCT profile anticipated to reduce the risk of lactic acidosis in ADPKD patients.

Funding: NIDDK Support
**TH-PO408**

The Effect of Lowering Uric Acid with a Xanthine Oxidase Inhibitor on PKD in Mice

*Anjana Chaudhary, Zhibin He, Daniel Atwood, Allen Davidson, Charles L. Edelstein. Univ of Colorado, Aurora, CO.*

**Background:** In rodents uricase converts uric acid (UA) to allantoin to uric acid inhibition with oxonic acid (OXO) raises serum UA. The aim of the study was to determine the effects of lowering UA with the xanthine oxidase inhibitor, oxypurinol (OXY), in a mouse model of PKD.

**Methods:** Pkd1<sup>W81X</sup>/RC (RC) mice, a hypomorphic Pkd1 gene model. OXO (300 mg/kg) or Oxy (24 mg/kg) + L-arginine (increases solubility of Oxy) treatment from day 35 to 120 of age. UA measured by LC/MS-MS. Male/female analyzed together. Cyst size (% of kidney mass) and cyst number and cyst area determined on cross sections by a computerized algorithm.

**Results:** See Table. Pharmacokinetic studies in normal rodents showed a 5-fold increase in serum UA 2 hrs after OXO dosing. Oxy did not affect PKD in mice likely because baseline UA levels were low in rodents (0.35 mg/dL) due to uricase. So, the effect of OXY that increases UA in mice was determined. In RC mice, OXO resulted in a significant increase in serum UA, 2 kidney/body weight ratio (2K/BW) (%) and cyst indices. Mechanisms of increased PKD caused by OXY were investigated: OXY resulted in a 50% increase in serum UA and an increase in pro-inflammatory cytokines/cytokines in the kidney: IL-5, IL-6, CXCL1. On polarized light UA crystals were not seen and caspase-1, a marker of the inflammasome, was not increased in OXY-treated kidneys. Oxy resulted in a 300% decrease in serum UA and significantly decreased the increase in 2K/BW and cyst index by increasing UA and OXY concentrations.

**Conclusions:** Increasing serum UA by inhibiting uricase with OXO results in an increase in kidney weight and cyst indices. The combination of OXY + OXY decreased the increase in kidney weight and cyst indices induced by OXO. A potential mechanisms of how OXY causes increased cyst growth in RC mice is induction of a pro-inflammatory cytokine storm in the PKD kidney in the absence of UA crystals or infiammatoris activation.

**Funding:** Commercial Support - XORTX Pharmaceuticals

*\( \text{UA (mg/dL)} \)

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*P<0.05. RDI=relative densitometry units, N=8-16 per group

**TH-PO409**

Therapeutic Blocking of IL-17A Binding to IL-17RA Diminishes PD-L1 Expression Is A Novel Therapeutic Approach for ADPKD

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**Background:** ALDH1A1 is responsible for oxidation of acetaldehyde in mammals, which is upregulated in various cancers to drive cancer growth. ALDH1A1 is associated with tumor immunity by regulating the ratio of effector T cells to Treg cells within tumor tissues. However, the role of ALDH1A1 and its relationship with PD-L1 as well as the PD-L1-mediated immune response in ADPKD remains elusive.

**Methods:** To investigate the role of ALDH1A1 and its relationship with PD-L1 in ADPKD, we treated Pkd1 mutant mouse models with the ALDH1A1 inhibitor Difelikefalin (D) or tolvaptan (T) alone or together with nanoparticles carrying PD-L1 antibody and evaluated their effect on cyst growth, immune response and fibrosis as well as on specific PKD associated signaling pathways by immunostaining. Western blot, qRTPCR and flow cytometry analysis. To increase kidney specificity, nanoparticles were conjugated with PD-L1 and kidney specific cadherin-16 (CDH16) antibodies.

**Results:** ALDH1A1 was upregulated in cyst lining epithelial cells in Pkd1 mutant kidneys. Targeting ALDH1A1 with its specific inhibitor Difelikefalin decreased cyst growth as seen by the decrease of cystic index, KW/BW ratio and BUN levels in Pkd1<sup>W81X</sup>/RC kidneys as well as cyst lining epithelial cell proliferation by the decrease of the activation of AKRA, AKT, STAT3 and STAT5. In addition, treatment with Difelikefalin decreased the expression of CD8+ T cells and PD-L1 expression was characterized by the increase of CD8+ T cells as examined by flow cytometry analysis, and decrease the recruitment of macrophages. Our CHIP assay indicated that ALDH1A1 bound with the promoter of PD-L1 to regulate its transcription. Treatment with Difelikefalin decreased cyst epithelial cell death which mediated by the downregulation of PD-L1 and the activation of CD8+ T cells in Pkd1<sup>W81X</sup>/RC kidneys. ALDH1A1 can also bind with the promoter of CCL2 to regulate its transcription, which is responsible for the recruitment of macrophages. Treatment with Difelikefalin and mesoporous silica nanoparticles (MSN) conjugated with PD-L1 and CDH16 antibodies showed a synergistic effect on cyst growth.

**Conclusions:** ALDH1A1 is a novel transcription factor which binds the promoters of specific genes, such as PD-L1, CCL2 and fibrotic genes. Targeting ALDH1A1 with its inhibitor either alone or in combination with nanoparticle-mediated PD-L1 antibody is a novel therapeutic strategy for ADPKD.

**Funding:** Other U.S. Government Support

**TH-PO410**

Targeting ALDH1A1 with Nanoparticle-Based Immunotherapy on Kidney PD-L1 Synergistically Delays Cyst Growth

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**Background:** ALDH1A1 is responsible for oxidation of acetaldehyde in mammals, which is upregulated in various cancers to drive cancer growth. ALDH1A1 is associated with tumor immunity by regulating the ratio of effector T cells to Treg cells within tumor tissues. However, the role of ALDH1A1 and its relationship with PD-L1 as well as the PD-L1-mediated immune response in ADPKD remains elusive.

**Methods:** To investigate the role of ALDH1A1 and its relationship with PD-L1 in ADPKD, we treated Pkd1 mutant mouse models with the ALDH1A1 inhibitor Difelikefalin (D) or tolvaptan (T) alone or together with nanoparticles carrying PD-L1 antibody and evaluated their effect on cyst growth, immune response and fibrosis as well as on specific PKD associated signaling pathways by immunostaining. Western blot, qRTPCR and flow cytometry analysis. To increase kidney specificity, nanoparticles were conjugated with PD-L1 and kidney specific cadherin-16 (CDH16) antibodies.

**Conclusions:** ALDH1A1 was upregulated in cyst lining epithelial cells in Pkd1 mutant kidneys. Targeting ALDH1A1 with its specific inhibitor Difelikefalin decreased cyst growth as seen by the decrease of cystic index, KW/BW ratio and BUN levels in Pkd1<sup>W81X</sup>/RC kidneys as well as cyst lining epithelial cell proliferation by the decrease of the activation of AKRA, AKT, STAT3 and STAT5. In addition, treatment with Difelikefalin decreased the expression of CD8+ T cells and PD-L1 expression was characterized by the increase of CD8+ T cells as examined by flow cytometry analysis, and decrease the recruitment of macrophages. Our CHIP assay indicated that ALDH1A1 bound with the promoter of PD-L1 to regulate its transcription. Treatment with Difelikefalin decreased cyst epithelial cell death which mediated by the downregulation of PD-L1 and the activation of CD8+ T cells in Pkd1<sup>W81X</sup>/RC kidneys. ALDH1A1 can also bind with the promoter of CCL2 to regulate its transcription, which is responsible for the recruitment of macrophages. Treatment with Difelikefalin and mesoporous silica nanoparticles (MSN) conjugated with PD-L1 and CDH16 antibodies showed a synergistic effect on cyst growth.

**Conclusions:** ALDH1A1 is a novel transcription factor which binds the promoters of specific genes, such as PD-L1, CCL2 and fibrotic genes. Targeting ALDH1A1 with its inhibitor either alone or in combination with nanoparticle-mediated PD-L1 antibody is a novel therapeutic strategy for ADPKD.

**Funding:** Other U.S. Government Support

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
First-in-Human Study of an mTORC1-Selective Inhibitor for the Treatment of ADPKD

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Janssen Research and Development LLC, Raritan, NJ.

Background: There are no disease modifying therapies currently available for patients with autosomal dominant polycystic kidney disease (ADPKD). The mechanistic target of rapamycin complex 1 (mTORC1) is a protein kinase complex and key regulator of cellular metabolism and proliferation that promotes cyst formation and growth. We are developing a mTORC1-selective inhibitor to slow kidney disease progression in patients with ADPKD, while reducing the incidence of mTORC2-associated toxicities that have limited other rapalogs in ADPKD clinical trials. In addition to demonstrating selectivity for mTORC1 inhibition over mTORC2 inhibition, our compound has previously been demonstrated to reduce disease burden in ADPKD animal models. The objective of this first-in-human study was to assess the safety, tolerability and pharmacokinetics of single ascending doses of our compound in healthy adult volunteers.

Methods: In this double-blind, single ascending dose (SAD) study, we enrolled healthy adult volunteers into 4 sequential ascending dose cohorts. Subjects were randomized to receive our compound or placebo. Safety, tolerability and pharmacokinetics were assessed at baseline and at multiple timepoints after dosing.

Results: In this SAD study, our compound was safe and well tolerated at all dose levels examined. All adverse events related to our compound were mild. Concentrations of our compound increased with increasing doses. Our compound was safe and well tolerated after a single dose in healthy volunteers. A planned phase 1b, multiple ascending dose study in patients with ADPKD will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics with repeated doses of our compound.

Funding: Commercial Support - Janssen R&D

Hypoxia-Inducible Factor-Prolyl Hydroxylase (HIF-PH) Inhibitor Accelerates Liver Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: It has been reported that hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitor promotes renal cyst formation due to activation of HIF. However, the effect on liver cysts is unclear. In this study, we will analyze the effects of HIF-PH inhibitor on liver cysts and their mechanisms.

Methods: We used Pkd1 conditional knockout mice (Pkd1flox/flox Mv-I-Cre mice). Mice were injected with polyinosinic-polycytidylic acid for 6 consecutive days at 5 days of age to inactivate Pkd1. Both cystic and non-cystic mice were randomly assigned to vehicle-only and enarodustat-treated groups (non-Cystic (CT), non-Cystic (Ena), Cystic (CT) and Cystic (Ena) group). Enarodustat was mixed in feed. Mice were sacrificed at 8 weeks of age. We analyzed the phenotype of cystic livers by liver/body weight ratio (LV/BW), and cystic index (CI) which was defined as the percentage of areas occupied by cysts. For evaluation of cell proliferation, immunohistochemical staining for proliferating cell nuclear antigen (PCNA) was performed. We also performed western blotting of signaling pathway of cyst growth by using whole liver.

Results: There was no significant difference in body weight among 4 groups. Mice treated with enarodustat exhibited a significant high level of hematocrit in both non-cystic and Cystic (CT) and Cystic (Ena) groups (p<0.001). There was no significant difference in LV/BW, but the Cystic Index (CI) of liver was significantly elevated in Cystic (Ena) group (30.8±8.5%) than in Cystic (CT) group (18.0±5.9%; p<0.05). Masson-Trichrome staining showed accelerated liver fibrosis in the Cystic (Ena) group. PCNA positive cells in the epicardial cells was higher in the Cystic (Ena) groups than in the Cystic (CT) group (p<0.02). In immunohistochemical staining of glucose transporter 1, the positive area rate was significantly higher in the Cystic group than in the non-Cystic group and was significantly expressed in the Cystic (Ena) group. Western blotting showed that phosphorylated Erk and phosphorylated p70S6K tended to be upregulated in the Cystic (Ena) group.

Conclusions: HIF-PH inhibitor accelerated liver cyst formation via proliferation of cyst lining cells by activating the MAPK pathway and mTOR pathway.

Time-Restricted Feeding and Autosomal Dominant Polycystic Kidney Disease: A Pilot, Randomized Clinical Trial

Courtney Steele, Erin R. Coleman, Diana George, Heather Farmer-Bailey, Sumana Ramanathan, Adriana Gregory, Wei Wang, Berenice Y. Gittomer, Michelle Chonchol, Elizabeth Thomas, Timothy L. Kline, Kristen L. Nowak.

University of Colorado Anschutz Medical Campus, Aurora, CO; Mayo Clinic Minnesota, Rochester, MN.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited progressive kidney disease leading to cyst growth. Time-restricted feeding (TRF) is a novel fasting regimen that restricts eating to a particular window (typically 8 hrs/day) which could slow cyst growth based on preclinical models.

Methods: A 12-month, randomized controlled, single-blind, behavioral dietary intervention trial was utilized to compare TRF vs. a healthy eating advice without TRF control group (HE). Participants underwent baseline and 12-month measurements, including adherence via meal logging (primary outcome), anthropometric measures, blood/urine sampling, and magnetic resonance imaging (MRI) to determine height adjusted total kidney volume (htTKV) and abdominal adiposity (exploratory outcomes). The behavioral intervention sessions were taught by a registered dietician via zoom with classes held weekly for the 1st month and then monthly. Independent t-tests and Pearson’s bivariate correlations were performed.

Results: Twenty-nine participants were randomized (TRF n=14, HE n=15) including (23 females) (F) 48±9 yrs of age (mean±s.d.), body mass index (BMI) 32.0±5 kg/m², estimated glomerular filtration rate 75±24 mL/min/1.73m² and htTKV 710 (334,1018) mL/m (median [IQR]). 71% (n=19) of TRF and 87% (n=13) of HE participants completed the intervention. The eating window was 9.5±2.0 hours for TRF (60% achieving the 8-hour window) and 12.±6.1(mean±s.d.) for HE groups (p=0.07). Likelihood to adhere to TRF at 12 months was 8±2 points (10-point likert scale). Both groups lost weight: -3.7 [-8.1,2.6] % and -3.6 [-8.1,0.4] % (median[IQR]) in the TRF and HE group, respectively. Annual percent change in htTKV was 2.8 [0.8,4.3] % and 4.0 [2.4,11.5] % in the TRF and HE groups, respectively. Both change in weight (r=-0.674, p=0.0002) and change in visceral adipose volume (r=-0.54, p=0.009) were positively correlated with change in htTKV.

Conclusions: Both TRF and HE groups lost modest weight after the 12-month intervention. The 8-hour eating window appeared to be difficult to adhere to in the TRF group, although satisfaction of adherence was high. Weight and adiposity loss may be more important drivers of kidney growth than timing of eating.

Funding: NIDDK Support, Private Foundation Support

Development of a Clinical Trial Enrichment (CTE) Tool for Autosomal Dominant Polycystic Kidney Disease

Varun Aagarwal, Susana Zaph, Randolph J. Leisey, Lauren E. Quinlan, Zhanhuo, Juan F. Morales, Christine E. Miller, Pronobesh Dasmahapatra, Wendy Vanasco, Klaus Romero, Sorin V. Fedele, Critical Path Institute, Tucson, AZ; 2Polycystic Kidney Disease Outcomes Consortium, Tucson, AZ; 3Tifts Medical Center, Boston, MA; 4Sanofi, Boston, MA.

Background: Despite the regulatory advances in ADPKD including the qualification of total kidney volume (TKV) as a prognostic enrichment biomarker and its designation by the FDA as a reasonably likely surrogate endpoint, the clinical development paradigms for ADPKD remain challenging.

Methods: Registry (Mayo, Emory, Colorado), longitudinal (CRISP), and RCT data (HALT) were curated and mapped to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) standards. Model-Informed Drug Development (MIDD) approaches to predict time to end-stage renal disease (ESRD) were employed with estimated glomerular filtration rate (eGFR) decline and total kidney volume (TKV) as longitudinal markers. The data was divided with 80% for training and 20% for validation. To build the joint model, we identified the appropriate longitudinal progression model, the appropriate time to event ESRD model, and incorporated the impact of longitudinal markers on event hazard.

Results: Two base models that captured the overall trend of TKV and eGFR were examined and the one with a lower Akaike Information Criteria (AIC) score was chosen. Covariates were: Age of diagnosis, baseline age, baseline eGFR, and baseline logTKV as continuous covariates Race, sex, and presence of hypertension at baseline as categorical covariates Age of diagnosis, baseline age, baseline TKV and sex as covariates for the TKV longitudinal model Baseline age, baseline eGFR, race and baseline TKV as covariates for the eGFR longitudinal model. Longitudinal event models (MIDD) were computed and the most successful model was selected based on the lowest AIC (best fit) before incorporating longitudinal markers. A graphical user interface (GUI) for the CTE tool was constructed for the creation of virtual simulations of disease progression. The tool models different trial durations, population sizes, and hypothetical magnitude of drug effects on TKV/eGFR progression and predict their impact on ESRD.

Conclusions: A quantitative tool can be utilized to model disease progression trajectories in defined ADPKD subpopulations and potentially simulate impact on ESRD based on theoretical drug effects on TKV/eGFR progression. The tool may be beneficial in clinical trial design to ultimately benefit ADPKD patients.

Funding: Other U.S. Government Support, Commercial Support - Sanofi, Private Foundation Support

Kynurenines and Change in Body Mass Index in Autosomal Dominant Polycystic Kidney Disease

Kristen L. Nowak, Zhiying You, Courtney Steele, Berenice Y. Gittomer, Michel Chonchol, Jelena Klawitter. University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: We have previously described that overweight and obesity are associated with kidney disease progression in individuals with early-stage autosomal dominant polycystic kidney disease (ADPKD). We have also reported dysregulated kynurenine metabolism, which associated with kidney disease severity, in early-stage patients with ADPKD. As the tryptophan-kynurenine pathway has been reported to be dysregulated in obesity, and kynurenines can induce and potentiate oxidative stress and...
inflammation, we hypothesized that baseline kynurenine circulating concentrations would associate with changes in renal function in patients with ADPKD.

Methods: 357 participants with ADPKD and estimated glomerular filtration rate (eGFR) >60 ml/min/1.73m² who participated in HALT Study A and had repeated measurements of kynurenines, BMI, and covariates were included. Twelve key tryptophan metabolites were previously measured in plasma using a validated liquid chromatography-mass spectrometry assay. The time-associating variables between kynurenines (individual mean and mean change over time) and change in BMI over 48-months were assessed using linear mixed effects regression models.

Results: 388 years, eGFR was 90±17 ml/min/1.73m², and height-adjusted total kidney volume was 724±413 ml/m². Greater individual log-transformed mean concentrations of kynurenic acid (β-estimate 1.37 [0.41], 3.01)], and quinolinic acid (β-estimate 2.34 [0.02, 4.23]) and a lower concentration of kynurenine (β-estimate -0.52 [0.3, -0.95]) were associated with greater increase in BMI after adjustment for demographics, study randomization, eGFR, baseline height-adjusted kidney volume, and genotype.

Conclusions: Some kynurenines were associated with change in BMI in ADPKD patients. Further research should evaluate whether kynurenines could serve as a biomarker of associated kidney growth in patients with ADPKD.

Funding: NIDDK Support

TH-PO417
Assessing Formoterol Treatment in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease
Brennan Winkler, Mykhailo Fedoruk, Xiaofeng Zuo, Peifeng Deng, Wayne R. Fitzgibbon, Oleg Palyn, Joshua H. Lipschutz. Medical University of South Carolina, Charleston, SC

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a disease caused by mutations in the genes PKD1 and PKD2 that results in cyst growth within the kidney, eventually leading to kidney failure. Tolvaptan is currently the only drug approved for treating ADPKD, but it is only modestly effective and has significant side effects. ADPKD is associated with metabolic dysfunction. Treating the metabolic dysfunction in ADPKD may be therapeutic. A metabolic modulator, formoterol, is a beta-2 adrenergic receptor agonist commonly prescribed for chronic obstructive pulmonary disease. Our previous research has demonstrated the effectiveness of formoterol in treating some forms of chronic kidney disease (CKD). Metabolic dysfunction is thought to be corrected by formoterol’s ability to stimulate mitochondrial biogenesis. We hypothesize that formoterol treatment in a mouse model of ADPKD will be therapeutic in reversing, stopping, or slowing disease progression.

Methods: RC/RC mice, a model of ADPKD generated using mutagenesis in PKD1 from a human family, will be treated using osmotic mini pumps filled with formoterol for six months at 1mg/kg body weight/day after they reach the age of three months. Pumps from a human family, will be treated using osmotic mini pumps filled with formoterol for six months at 1mg/kg body weight/day after they reach the age of three months.

Results: Male mice To date, a trend toward lower kidney/body weight (p=0.28) and liver/body weight (p=0.07) ratios is observed in the formoterol-treated compared to the vehicle-treated group, which may indicate decreased cystogenesis. Females: In progress.

Rats in progress.

Conclusions: Preliminary data suggest that formoterol may have an effect on cyst growth, though additional cohorts of treated and untreated mice need to be studied.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO418
Validation of the Mayo Imaging Classification System for Predicting Renal Outcome in ADPKD

Background: The Mayo Imaging Classification is used to predict the rate of disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD). The goal of this study was to validate its ability to predict renal prognosis in a large cohort of patients with ADPKD.

Methods: Included were ADPKD patients with ‘typical’ disease, at least one height-adjusted total kidney volume (HTKV) measurement, ≥2 eGFR estimates and ≥3 years follow-up. The stability of the classification, kidney growth rate and eGFR decline rate were calculated for each Mayo HTKV class at various timepoints. The observed eGFR decline rate at these timepoints were compared to the values predicted by the Mayo Clinic formula for future eGFR. Kaplan-Meier survival analysis was performed to predict end stage kidney disease (ESKD) using Mayo HTKV class as a predictor variable.

Results: We included 619 patients with a mean age of 47 ± 11 years and an eGFR of 63 ± 25 ml/min/1.73m² at baseline. The majority of patients (70.0 - 88.9%) remained in their baseline Mayo HTKV class after 6 years of follow-up. The mean eGFR decline and TKV growth rate during the follow-up period were -3.26 ± 2.49 ml/min/1.73m²/year and 5.29 ± 3.97%/year, respectively. There was considerable variation in kidney growth and eGFR decline rates within each Mayo HTKV class. The observed eGFR decline at follow-up was not significantly different from the predicted values for Mayo HTKV classes 1A, 1B, 1C and 1D. However, the observed eGFR decline of Mayo HTKV class 1D was significantly less than observed at baseline in patients with PKD2 mutations. The classification was a strong predictor for ESKD.

Conclusions: The Mayo Imaging Classification demonstrates acceptable stability over time and is predictive of the rate of eGFR decline albeit with wide inter-individual variations. The ability to predict future eGFR decline for individual patients might be improved by developing equations that include additional prognostic covariates.

TH-PO419
Applicability of Mayo’s Autosomal Dominant Polycystic Kidney Disease Prognostic Tool in the Southeast Asian ADPKD Population
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Background: Mayo autosomal dominant polycystic kidney disease (ADPKD) prognostic tool revolved around the height-adjusted total kidney volume (HTKV) measurement using MRI at a single point of time adjusted with age, and it was recognized as a strong predictor for kidney disease progression in patients with ADPKD. This study reports 24-month prospective longitudinal studies examining the applicability of the Mayo ADPKD prognostic tool in the Southeast Asian cohort in a tertiary center in Malaysia.

Methods: Convenience sampling was completed on March 2021. Patients were subjected to a single non-contrasted T2W-MRI scan examination utilizing the ellipsoid method with subsequent yearly blood samples collected for analysis. Total kidney volume (TKV) was measured by 2 radiologists and the average of 2 results was recorded. Correlation of glomerular filtration rate generated from the Mayo ADPKD prognostic tool and serum osmotic mannitol glomerular filtration rate of patients according to 2009 CKD-EPI equations were tested with Spearman correlation coefficient and Bland-Altman analysis.

Results: A total of 30 patients were enrolled with a median age of 39.5 years (33.5, 52.0) and predominantly female (54%), and of Chinese (60%) ethnicity. Median TKV (mm³) was 412.3 (297.2, 659.2) and in patients dropped out at month 24, eGFR(ADPKD) correlated very strongly with eGFRMayo during the 24 months study with R²=0.100 (bias of -0.196, precision=0.395), R²=0.972 (bias of -0.204, precision=0.390), R²=0.952 (bias of 4.670, precision=10.930) respectively, p<0.001. eGFR_Mayo demonstrated an accuracy of 42.6 - 98% within 10mls/m1.73m² of serum eGFR_Mayo

Conclusions: Mayo’s ADPKD prognostic tool demonstrated its applicability to the Southeast Asian ADPKD population with a very strong correlation to eGFR_Mayo, low bias, and high precision. Long-term data with a larger sample size needs to be evaluated in future studies.

Funding: Government Support - Non-U.S.

Spearman correlation coefficient & Bland-Altman analysis

TH-PO420
Tolvaptan Use and Prescribing Patterns in Patients with Autosomal Dominant Polycystic Kidney Disease: A Multicenter Real-World Experience
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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common genetic disease leading to End Stage Kidney Disease. Tolvaptan was approved and is being used to treat patients with rapidly progressing disease. In this study we describe the real-world experience of Tolvaptan use among patients with ADPKD.

Methods: We retrospectively identified adult patients with ADPKD enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program and treated with Tolvaptan through the University of Kansas Medical Center (KUMC) and University of Iowa Hospitals and Clinics (UIHC) from 2018 to 2023. The investigators abstracted data and treating physicians reviewed and confirmed the data. We performed descriptive analysis of the patients’ demographics, baseline labs, Tolvaptan prescribing trends, reasons for stopping treatment, and frequency of imaging surveillance.

Results: The study includes 134 patients, 115 from KUMC and 19 from UIHC. The average age of start of Tolvaptan treatment was 42.67 and 36.17 years respectively for KUMC and UIHC. Male to female ratio was approximately 1:1 for KUMC and 1.2 for UIHC. Amongst the 134 ADPKD cohort, 87% were Caucasian, and the remaining 13% comprised of African American and Hispanic ethnic groups. In the UIHC cohort, 95% were Caucasian. By March 2023, 63% and 58% remained on Tolvaptan and of the KUMC and UIHC

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Underline represents presenting author.
cohorts respectively. The two major reasons for discontinuing Tolvaptan included intolerance of polyuria and polydipsia (26% in KUMC and 50% in UIHC) and renal transplantation (17% in KUMC and 13% in UIHC). The average fluid intake was 5.23 and 3.36 Liters respectively in the KUMC and UIHC cohorts. The starting dose combination of 45 mg (AM)/15 mg (PM) was prescribed to most patients at both KUMC (90%) and UIHC (80%). For many patients, prescribing physicians had to considerably titrate Tolvaptan doses to moderate side effects.

Conclusions: The findings of this descriptive study provide valuable insights into the real-world use of Tolvaptan in treating patients with ADPKD. A higher percentage of patients with ADPKD are discontinuing Tolvaptan compared to trials findings due to polyuria and polydipsia. The study also highlights the need for considerable titration of Tolvaptan dose to manage symptoms.

TH-PO421
Kidney Function Decline in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients: Assessment of Real-World Effectiveness of Tolvaptan
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Background: In clinical trials, tolvaptan led to a slower decline in kidney function (vs. placebo) in ADPKD patients at risk of rapid kidney decline. The objective of the current study is to evaluate real-world effectiveness of tolvaptan by comparing annual rate of change in kidney function, as measured by eGFR, in adult ADPKD patients treated with and without tolvaptan.

Methods: From May 2019 to September 2022, 57 US nephrologists completed a web-based survey using medical records of ADPKD patients treated with tolvaptan for 2 years (as cases). A cohort of ADPKD patients in Mayo class 1C to 1E not treated with tolvaptan was obtained from CRISP, HALT-PKD (data provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases) and OVERTURE studies (controls). Cases and controls were matched 1:1 on baseline age, gender and chronic kidney disease (CKD) stage. Kidney function decline was compared between cases and controls using mixed models, which included treatment, time, and a treatment-by-time interaction as fixed effects and patient-specific intercepts and slopes (for time) as random effects.

Results: Of the 149 cases treated with tolvaptan, controls matched for age, sex and CKD stage were identified for 110 cases. Among these 110 matched pairs, the majority were female (78%), aged 43 (SD: 10.1) years on average, and 76% were in CKD stage 3a or earlier. Mean eGFR at baseline was 60 mL/min/1.73m² among cases and 63 mL/min/1.73m² among controls. The annual change in eGFR was -2.23 mL/min/1.73m² among cases vs -3.62 mL/min/1.73m² among controls with a statistically significant difference of 1.40 mL/min/1.73m² per year (95% CI: 0.05, 2.74, p = 0.042). A second analysis, whereby cases and controls were matched on baseline age, gender and eGFR resulted in 98 matched pairs. In comparison of the 98 matched pairs tolvaptan was associated with a trend in reduction of decline rate by 1.18 mL/min/1.73m² per year (95% CI -0.22, 2.58, p=0.097).

Conclusions: In the current analysis, tolvaptan showed real world effectiveness in slowing decline in eGFR when compared to matched historical controls, consistent with its efficacy in clinical trials.


TH-PO422
Liberation of Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Interim Data from a European Union Post- Authorization Safety Study (EUPASS)
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Background: After risk of drug-induced liver injury was detected during tolvaptan clinical development for the treatment of ADPKD, a real-world pharmacovigilance study was required as a condition of EU regulatory approval. We provide an interim-analysis of 6-years of liver safety data from EUPASS.

Methods: This is an interim analysis from a prospective, observational study enrolling patients prescribed tolvaptan for ADPKD in everyday clinical practice. Data are obtained through physician records collected as part of regular standard of care. Per the prescribing label, liver enzymes are monitored monthly for the first 18 months of treatment and once every 3 months thereafter, and patients and providers are required to report adverse events suggestive of liver injury. The data collection period was Oct 2016–Apr 2022. An independent hepatic adjudication committee (HAC) evaluates all reported cases of drug-induced liver injury. No Hy’s law cases/deaths have been reported.

Results: Of 45,339 ADPKD patients treated with maximally tolerated dose of a V2RA were included. While on a low salt (<6 g/24h) and low protein (<0.8 g/24h) diet, patients were given additional salt and protein during a baseline study period to mimic regular intake, which was replaced by placebo during four 2-week periods: low salt/low protein, low salt/regular protein, low protein/regular salt and regular protein/regular salt intake in random order. Primary independent end-point was change in 24h urine volume (Δ 24hUV). Second endpoints were change in quality of life, measured glomerular filtration rate (mGFR), blood pressure and copeptin level.

Results: Twelve patients (49±7 years, 25.0±5% male, mGFR 59±23 mL/min/1.73m²) were included. Baseline salt- and protein intake was 10.8±1.3 g/24h and 2.1±0.2 g/kg/24h.

During the low salt and low protein treatment periods, intake significantly decreased to 5.8±1.6 g/24h and 0.8±0.1 g/kg/24h respectively. Baseline 24h urine volume (5.9±1.2 L) diminished to 5.2±1.1 L (-11%, p=0.004) on the low salt & low protein and to 5.4±0.9 L (-8%, p=0.04) on the low salt intake. Reduction in 24h urine volume tended to be greater in patients with lower urine osmolality (-16 vs -7%, p=0.1). Polyuria QoL scores improved with changes in urine volume. mGFR decreased on the low salt & low protein intake, while mean arterial pressure did not change during the study periods. Plasma copeptin decreased significantly during low salt and low protein periods.

Conclusions: Changes in intake of salt and protein have only a minor effect on urine volume in V2RA-treated ADPKD patients. In subjects with most severe vasopressin resistance, i.e. those with the lowest baseline urine osmolality, this antipolyuric effect tended to be most pronounced. Reduction of osmotic intake decreased plasma copeptin and might therefore improve the antipolyuric effect of a V2RA.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO425

Eight Years of Canadian Real-World Assessment of Tolvaptan in ADPKD: C-MAJOR Study and Safety Monitoring and Distribution Program

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Background: Tolvaptan is approved in Canada for slowing renal function decline and kidney enlargement in patient with ADPKD. As required by Health Canada, a patient registry study evaluating long-term clinical outcomes (C-MAJOR) and a hepatic safety monitoring and distribution program (HSMDP) to mitigate risk of liver injury were implemented. The aim of this interim analysis is to describe patient characteristics at tolvaptan initiation from the C-MAJOR study and to report on liver transaminase elevations rates and treatment persistence through the HSMDP.

Methods: C-MAJOR is a non-interventional, observational, multi-centre study of ADPKD patients treated with tolvaptan. HSMDP ensures tolvaptan is dispensed under controlled liver function monitoring.

Results: As of February 2023, 469 patients were enrolled in C-MAJOR. At baseline, 51% were female, with a mean (SD) age of 45 (12) years, BP 129 (13)/83 (10) mmHg and eGFR 64 (28) mL/min/1.73 m2. Overall, 68% were in early CKD stages 1, 2 and 3a. Total kidney volume was 1963 (1538) mL, 80% had a family history of ADPKD. 38% had a family history of early-stage cystic kidney disease, and 91% were at high risk of disease progression (Mayo Imaging Class 1C-D-E). The most common clinical manifestations were hypertension (84%), hepatic cysts (71%) and kidney pain (24%). From the HSMDP, 2418 patients who initiated tolvaptan reported an elevation of transaminases (>3x ULN), with 11 (0.45%) meeting guidelines for permanent discontinuation. No cases of drug-induced liver injury were reported. Occurrence of ALT levels greater than 3x ULN were seen up to 81 months post tolvaptan initiation and of these, 32% of the episodes occurred following the first 18 months of treatment. Treatment persistence rates at 12, 24 and 36 months were 84%, 77% and 72%, respectively.

Conclusions: This analysis provides Canadian real-world evidence that most ADPKD patients treated with tolvaptan are at high-risk of disease progression and three-year treatment persistence is similar to phase III study data. The HSMDP in Canada has been effective at avoiding the incidence of drug-induced liver injury associated with tolvaptan.

Funding: Commercial Support - Otsuka Canada

TH-PO426

Development Program of 2-deoxy-D-glucose (2DG) for the Treatment of ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the growth of fluid-filled kidney cysts due to abnormal epithelial proliferation. We have demonstrated that ADPKD cyst epithelial cells undergo metabolic reprogramming with increased aerobic glycolysis (Warburg effect) and so are exclusively dependent on glucose for energy production. This can be exploited to treat ADPKD using an analog of glucose, 2-deoxy-D-glucose (2-DG), that inhibits glycolysis. We have shown that 2DG is effective at slowing cyst growth in both rapid and slowly progressive mouse PKD models. 2DG has previously been tested in over 200 normal human volunteers and showed no evidence of toxicity. We have demonstrated that 2DG is effective at slowing cyst growth in both rapid and slowly progressive mouse PKD models. 2DG has previously been tested in over 200 normal human volunteers and showed no evidence of toxicity. We have demonstrated that 2DG is effective at slowing cyst growth in both rapid and slowly progressive mouse PKD models. 2DG has previously been tested in over 200 normal human volunteers and showed no evidence of toxicity.

Methods: Our first-in-human study is proposed to be a multicenter Phase 1B uncontrolled, multiple ascending dose clinical trial. ADPKD patients aged 18–60 yr were included in the study. Subjects were recruited nationally and signed an informed consent. ADPKD patients were randomized to receive either study drug, 40 mg of pravastatin or matching placebo each day for a 2-year period. Baseline visits were ongoing between 2017 and 2022. All participants were randomized to receive either study drug, 40 mg of pravastatin or matching placebo each day for a 2-year period. Baseline assessments included demographics, medical history, total kidney volume (TKV) and renal blood flow (RBF) by magnetic resonance imaging, Glomerulitis

Table. Multivariable model showing hazard ratios for the outcome of kidney failure or eGFR <15 mL/min/1.73 m2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>1.11</td>
<td>(1.075, 1.15)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>1</td>
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<tr>
<td></td>
<td>Female</td>
<td>0.94</td>
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<tr>
<td>Serum creatinine (mg/dL)</td>
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<td>(5.87, 58.03)</td>
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<tr>
<td>Mayo Imaging Classes</td>
<td>0.34</td>
<td>(0.06, 2.56)</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.34</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>1.74</td>
</tr>
<tr>
<td>Genotype - PKD2</td>
<td>5.05</td>
<td>(2.72, 9.38)</td>
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<tr>
<td></td>
<td>- PKD1</td>
<td>6.55</td>
</tr>
<tr>
<td>Serum carbon dioxide - mmol/L</td>
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<td>(0.76, 0.93)</td>
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<tr>
<td>Hemoglobin - g/dL</td>
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<td>(0.63, 0.92)</td>
</tr>
<tr>
<td>Diastolic BP - mm Hg</td>
<td>1.02</td>
<td>(1.00, 1.04)</td>
</tr>
<tr>
<td>Body mass index - kg/m2</td>
<td>1.04</td>
<td>(1.01, 1.07)</td>
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TH-PO427

Prognostic Model for Progression of Autosomal Dominant Polycystic Kidney Disease to Kidney Failure

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disease that leads to kidney failure (ESKD), typically in the fifth decade of life. Given the variability between individuals in the rate of progression to ESKD there is significant unmet need for an accurate prognostic model that can predict the course of disease failure in early individual patients. CRISP IV is the longest extant ADPKD cohort (21 years), providing a unique opportunity to determine the association between clinical observations early in the disease and hard clinical outcomes.

Methods: Data collected from participants in the CRISP and HALT-A studies between 2001 and 2022 were modeled using multivariable Cox proportional hazards. The outcome was a composite of kidney failure (dialysis or kidney transplant) and eGFR <15 mL/min/1.73 m2. Candidate dependent variables were picked on the basis of face validity, and selected for inclusion in the model by iterative forward selection.

Results: Of 759 included participants with a median follow-up of 8.2 years, 123 (16.2%) reached the composite endpoint. A prognostic model was built using 5 essential variables. Four clinical variables (serum CO2, hemoglobin, BMI, diastolic BP) were found to add independently to this model.

Conclusions: We have developed a prognostic model that can predict kidney failure in an ADPKD patient over a time horizon of 15 years. The next step is to validate this in an external ADPKD registry cohort and create a risk calculator.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
How Well Do Risk Assessment Guidelines Perform for ADPKD? 

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Background: The approval of Tolvaptan for treatment of ADPKD heralds a new era when mechanism-based therapy is now possible. However, Tolvaptan is an expensive drug associated with potentially serious side-effects and is currently reserved for patients at high-risk for progression to ESKD. Two sets of risk assessment guidelines for ADPKD are now available based on the consensus of two panels of nephrologists from Canada and Europe. How well do these guidelines perform in risk assessment has not been formally assessed.

Methods: We conducted a prospective study in 474 patients with typical imaging pattern of ADPKD by MRI who also had detailed clinical and laboratory data. We used age- and height-adjusted total kidney volume to derive the Mayo Clinic Imaging Class as a “gold-standard” for risk assessment (i.e. low-risk: IA-1B; high-risk: IC-1E). We then applied the revised Canadian guidelines (Can J Kidney Health Dis. 2018) and the updated European guidelines (NDT 2022) to our patient cohort to assess their performance.

Results: The study cohort consisted of 286/474 (60%) high-risk patients with MCIC 1C-1E. Applying the updated Canadian risk assessment algorithm resulted in exclusion of 245/474 (52%) patients including 86/286 (30%) of the high-risk patients. The resultant cohort (229/474) was enriched with 88% high-risk patients but also included 12% of low-risk patients. The updated European guidelines provide a 3-step hierarchal algorithm, which applied when excluded in total number of 55 (157/286) of high-risk patients. During the last step, neither patients could be classified due to a lack of eGFR slope information. The resultant cohort (180/474) was enriched with 72% high-risk patients but also included 28% (51/180) of low-risk patients.

Conclusions: Risk assessment in ADPKD is evolving process that needs to be redefined by new clinical data and test technologies. Clinical guidelines should be evaluated using real-life data and those that enrich high-risk patients while minimize low-risk patients have most clinical utility.

Funding: Government Support - Non-U.S.

Identification and Characterization of Biomarkers from Cell-Free DNA Methylation in ADPKD Patients

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Background: ADPKD is caused by mutations of PKD1/PKD2. However, there is no proper biomarker for this disease. Recently, circulating cell-free (cf) DNA has attracted considerable interest as a potential biomarker. In this study, we aimed to identify cfDNA methylation signatures and the differential methylation regions (DMRs) with 5% methylation difference between the pediatric ADPKD patients and age-matched healthy individuals. The DMRs associated signaling pathways were analyzed with gene set enrichment analysis (GSEA).

Results: We isolated cfDNA from plasma and urine and performed EM-Sequencing to identify cfDNA methylation signatures and the differential methylation regions (DMRs) with 5% methylation difference between the pediatric ADPKD patients and age-matched healthy individuals. The DMRs associated signaling pathways were analyzed with gene set enrichment analysis (GSEA).

Conclusions: This study identifies cfDNA methylation signatures and the differential methylation regions in ADPKD patients, and the 10 candidate DMRs and the associated genes and pathways are potential biomarkers and novel mechanisms for ADPKD progression.

Funding: NIDDK Support
ADPKD, while 376 (99.7%) didn’t have ADPKD. The overall sensitivity of the ICD-9 codes for ADPKD was 92.3% and the specificity was 99.7%. In the nephrology clinic, the sensitivity was 94.6% and the specificity was 100%. In the non-nephrology clinic, the sensitivity was 88.4% and the specificity was 99.7% (Figure 1).

Conclusions: Utilizing ICD-9 to identify patients with ADPKD is of excellent overall sensitivity, specificity, PPV, and NPV. The sensitivity tends to be higher in the nephrology clinic vs non-nephrology clinic.

Figure 1: Diagnostic Accuracy Test Results For ADPKD

TH-PO433
Omnics Profiling of Tolvaptan-Treated Autosomal Dominant Polycystic Kidney Disease Patients
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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening genetic kidney disease and the fourth leading cause of kidney failure. Dialysis or transplant are current treatments for end-stage ADPKD patients, and no other ideal efficient therapeutic strategy exists. The selective vasopressin V2-receptor antagonist, Tolvaptan, was used to treat hyponatremia in heart failure but was approved by FDA for ADPKD treatment in 2018; however, there are limitations for ADPKD patients to receive Tolvaptan treatment and its significant side effects severely affect patient’s life quality. In this study, we use omics tools to discover potential therapeutic targets with fewer side effects for ADPKD patients.

Methods: Tolvaptan was started with the 45-0-15 dose, then titrated to 60-0-30 after two months. Blood and urine were collected before Tolvaptan treatment and 2, 3, 6, 9, and 12 months after treatment. Omics profiling was performed using SureSelect XT HS2 mRNA Library Preparation kit (Agilent, USA) and sequenced on Nextseq. Differential expression analysis was performed using StringTie and DEseq with Welchgene Bioch’s in-house pipeline. Genes with p-value < 0.05 and > 2.0-fold changes were considered significantly differentially expressed. Functional enrichment assay was performed using cluster Profiler v3.6.

Results: Our data indicate that cytoskeleton-regulating proteins and junctional proteins: NBP10, RGD2A, MYH1, NPPB9, SLC9B1F1, and TUBB7P were involved in the regulation of cytoskeleton in Tolvaptan-treated ADPKD patients. In addition, the downstream junctional and cytoskeleton regulating genes of the above proteins (Log2 ratio: CRIB3, 11.01; CLDN10, 10.09; MAPK10, 7.34; FGFB7, 9.47; MYH14, 7.04) were significantly (p<0.05) preserved after Tolvaptan treatment that may be involved in the regulation of calcium, Rho GTPases, and PAK Pathway signaling. Furthermore, Hypoxanthine, Creatine, L-a-aminobutyric acid, and Trimethylamine N-oxide were significantly decreased in our metabolomics data analysis, showing paracellular transportation in kidney cells was inhibited.

Conclusions: Our data shows Tolvaptan treatment regulates the integrity of tight junctions and paracellular transportation of kidney cells. It elucidates the possible targets in inhibiting side effects and provides novel therapeutic targets that may be served in ADPKD treatments with fewer side effects.

Funding: Private Foundation Support

TH-PO434
Association Between PKD1 Truncating Mutations and Accelerated eGFR Decline in ADPKD Patients: Implications for Early Identification and Intervention
Hamad Ali,1,2 Barrak Alahmad,2 Yousif Bababehani,2 Sarah R. Senum,2 Mohamed Abu-Farha,2 Jahad Abubaker,2 Fahd Al-Mulla,2 Peter C. Harris.3
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Background: ADPKD severity varies due to allelic and genic heterogeneity. Identifying patients at risk of rapid disease progression may improve outcomes. This study aims to explore the association between PKD1 types (truncating vs. non-truncating) mutations & rate of eGFR decline in ADPKD patients.

Methods: This study followed up 42 PKD1-ADPKD patients with clinically & genetically confirmed diagnoses for an average of 6.6±3.8 years. Renal function tests were performed annually, and eGFR was calculated using the CKD-EPI Creatinine Equation (2012).

Results: Patients with PKD1 truncating mutations had a more rapid rate of eGFR decline per year (-4.7 ± 0.7 ml/min/1.73 m2 per year) compared to patients with PKD1 non-truncating mutations (-3.5 ± 0.7 ml/min/1.73 m2 per year) (P<0.001).

Conclusions: This study highlights the association between PKD1 truncating mutations & a more rapid rate of eGFR decline in ADPKD patients. Identifying patients with potential rapid disease progression may aid in early intervention & better disease management to improve outcomes.

Funding: Government Support - Non-U.S.

Analysis of ADPKD progression per PKD1 mutation type

<table>
<thead>
<tr>
<th>PKD1 Mutation</th>
<th>Estimated eGFR Decline per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Truncating</td>
<td>-4.7 ± 0.7 ml/min/1.73 m2</td>
</tr>
<tr>
<td>Non-truncating</td>
<td>-3.5 ± 0.7 ml/min/1.73 m2</td>
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</tbody>
</table>

a estimated from mixed effects model adjusted for sex, age at visit, and birth year
b estimated from stratified mixed effects models adjusted for sex and birth year.

P-value of interaction was obtained from an interaction term.

TH-PO435
Comparison of the Total Kidney Volumes Using the Ellipsoid Equation and Manual Segmentation in ADPKD
Hyun Bae Jang,1 Caroline Reinhold,2 Ahsan Alam,2 ‘McGill University, Montreal, QC, Canada; 1McGill University Health Centre, Montreal, QC, Canada.

Background: Total kidney volume (TKV) is an important prognostic biomarker of disease progression in autosomal dominant polycystic kidney disease (ADPKD). The gold standard of manual segmentation TKV (mTKV) is time and labor-intensive. The ellipsoid equation TKV (eTKV) is commonly used in clinical practice, but assumes uniform growth of the kidneys. Our study examined the correlation between the eTKV and mTKV and we examined cases individually where there was misclassification.

Methods: We analyzed coronal T2-weighted MRI slices for 143 patients with ADPKD from a single centre. eTKV was determined using standard orthogonal measurements. The ground truth mTKV was performed by a single trained individual. Pearson’s correlation coefficient was calculated and a Bland-Altman analysis was performed. A confusion matrix was generated to illustrate the misclassification in the Mayo Imaging Classification (MIC) between the two approaches. We explored cyst imaging features where the difference in TKV methods was ≥20%.

Results: The mean age of the cohort was 45 (SD 15), 46% were male, hypertension prevalence was 71%, the median eTKV was 76.0 ± 29.7 cm3 (IQR 46-107), height-adjusted TKV was 86.5 ± 20.7 cm3 (IQR 49-130), and tolvaptan use was 45%. The correlation coefficient between both TKV measures was 0.96. The Bland-Altman analysis showed wide limits of agreement [-49.45%, 25.15%], and 24 patients were reclassified by one MIC risk category. Of the 25 patients (17%) who exhibited ≥20% difference between the two measures, 23 patients were characterized as having large exophytic cysts.

Conclusions: The eTKV is efficient and generally reliable for calculating TKV, but it may lose accuracy in patients with large exophytic cysts. Further study should explore the association of exophytic cysts with kidney disease progression. Understanding whether exophytic cysts should be included in the TKV estimation may aid in risk stratification.

TH-PO442
Comparison of Diagnostic Accuracy of ICD-9 vs. ICD-10 for ADPKD Patients
Kuwait University Health Sciences Centre, Safat, Kuwait; 2Dasman Diabetes Institute, Kuwait City, Kuwait; 3Harvard Medical School, Boston, MA; 3Kaohsiung Municipal Siaogang Hospital, Kaohsiung, Taiwan.

Background: Genetic Diseases: Cystic - Therapeutic Investigations and Prognosis

Conclusions: Utilizing ICD-9 to identify patients with ADPKD is of excellent overall sensitivity, specificity, PPV, and NPV. The sensitivity tends to be higher in the nephrology clinic vs non-nephrology clinic.

Figure 1: Diagnostic Accuracy Test Results For ADPKD

TH-PO435
Comparison of the Total Kidney Volumes Using the Ellipsoid Equation and Manual Segmentation in ADPKD
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Conclusions: The eTKV is efficient and generally reliable for calculating TKV, but it may lose accuracy in patients with large exophytic cysts. Further study should explore the association of exophytic cysts with kidney disease progression. Understanding whether exophytic cysts should be included in the TKV estimation may aid in risk stratification.
Confusion Matrix of Mayo Imaging Class Determined By Total Kidney Volume Using Ellipsoid Equation (eTKV) and Manual Segmentation (mTKV)

<table>
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<th>eTKV</th>
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<td>0</td>
<td>0</td>
<td>23</td>
<td>1</td>
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</tr>
<tr>
<td>4</td>
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TH-PO436

Prognosis of Polycystic Kidney Disease: FinnGen Study
Tomas J. Visser,1 Tapio Hellman,2 Anni Kauko,3 Matias Simons,4 Timo Jahnukanen,1 Jaakko Helve,1 Patrik Finne,1 Daniel Gordin,1 Teemu Niiranen,1 Helsingin yliopisto, Helsinki, Finland; 2TYKS Turku, Turku, Finland; 3Turun yliopisto, Turku, Finland; 4University Hospital of Heidelberg, Heidelberg, Germany; 5HUS-yhtyma, Helsinki, Finland; 6Finnish Registry of Kidney Diseases, Helsinki, Finland.

Background: The extra-renal complication risk and progression rate of autosomal dominant polycystic kidney disease (PKD) are incompletely understood. We assessed the clinical outcomes of PKD in the FinnGen study, which covers nearly 10% of the Finnish population (N=473681).

Methods: PKD patients and clinical outcomes were identified using ICD diagnosis codes. The outcomes of interest were death, start of dialysis or transplantation (RRT), major adverse cardiovascular events (MACE), subarachnoid hemorrhage (SAH) or cerebral aneurysm, and diverticular disease. In a smaller sample with data available for estimated glomerular filtration rate (eGFR), we compared the risk of adverse outcomes and kidney function decline in PKD patients and controls (diabetes mellitus [DM] patients) using multivariable-adjusted Cox regression and repeated linear mixed models. The cases and controls were matched with a ratio of 1:4 by age, sex and eGFR.

Results: The study sample included 674 PKD patients. The incidence of clinical outcomes in these patients is reported in Figure 1. The risk of adverse outcomes in PKD patients (N=173) compared to DM patients (N=692) is reported in Figure 2. The risk of death, RRT, SAH or cerebral aneurysms, and diverticular disease was greater in PKD patients compared to DM patients (p<0.02 for all). The eGFR decreased more rapidly in PKD patients compared to DM patients (-2.31 [95% CI, -2.41 to -2.22] vs -1.62 [95% CI, -1.76 to -1.48]; p<1x10^-10).

Conclusions: Our study identified several potential diagnostic biomarkers in ADPKD. The TNFR-I, TNFR-II, TNFSF21, IGFBP-6, and TGF-βRII, fibrosis biomarkers (MMP-7, MMP-3, Eotaxin, WIFDC2), and other biomarkers (Resistin, EPHB4, FENB2, and CAD17). Specifically, the level of MMP-7 was increased 1.8-, 3.2-, 6-, and 8.2-fold in ADPKD patients with CKD3-4, respectively. Among the 155 upregulated and 49 downregulated proteins, the mRNA levels of 55 and 11 genes were similarly increased or decreased in mouse PKD kidneys. These results suggest that these specific upregulated and downregulated proteins are altered in the kidney and can also be tested as urinary biomarkers.

Conclusions: Our study identified several potential diagnostic biomarkers in ADPKD. The TNFR-I, TNFR-II, MMP-7, and WIFDC2 have been shown to be diagnostic biomarkers in CKD, but the other inflammatory and fibrotic biomarkers are novel for ADPKD.

Funding: NIDDK Support

TH-PO437

A Serum Proteome Study Identifies Novel Biomarkers for Autosomal Dominant Polycystic Kidney Disease
Xia Zhou, Xiaoyan Li, Xiaogang Li, Peter C. Harris. Mayo Clinic Minnesota, Rochester, MN.

Background: ADPKD is a genetic disorder characterized by cyst growth and expansion, and inflammation and renal fibrosis leading to kidney failure. The disease course of ADPKD is highly variable depending on the gene, mutation, and other factors. Better methods to measure disease progression, such as serum biomarkers, are urgently needed in ADPKD to complement total kidney volume data.

Methods: The level of 1500 circulating proteins in serum samples from 45 ADPKD patients with an eGFR 15 ml/min/1.73m² (4 subgroups based on eGFR, CKD1-4) and 12 healthy individuals were measured using the SOMAmer proteomics platform. Differentially expressed proteins (DEPs) were analyzed by Go and KEGG enrichment analyses. Differentially expressed genes in kidneys of Pkd1+/+;Pkd1-Cre mice were identified by RNA-seq.

Results: A total of 155 proteins were upregulated and 49 proteins downregulated in patients with ADPKD and CKD3 compared to healthy individuals (p<0.05). DEPs were associated with several signaling pathways, including cytokine-cytokine receptor interactions, TGF-β signaling, complement and coagulation cascades, TNF signaling, cancer, lipid regulation, and atherosclerosis. Potential individual serum biomarkers were identified by the following criteria: 1) more than >20% increase in CKD2 versus healthy control; 2) more than two-fold increase in CKD4 versus healthy control; and 3) the change of protein level was associated with a decline of eGFR. A total of 31 proteins were identified, including the inflammatory biomarkers (MKC-I, TNFR-I, TNFR-II, TNFSF21, IGFBP-6, and TGF-βRII), fibrosis biomarkers (MMP-7, MMP-3, Eotaxin, WIFDC2), and other biomarkers (Resistin, EPHB4, FENB2, and CAD17). Specifically, the level of MMP-7 was increased 1.8-, 3.2-, 6-, and 8.2-fold in ADPKD patients with CKD3-4, respectively. Among the 155 upregulated and 49 downregulated proteins, the mRNA levels of 55 and 11 genes were similarly increased or decreased in mouse PKD kidneys. These results suggest that these specific upregulated and downregulated proteins are altered in the kidney and can also be tested as urinary biomarkers.

Conclusions: In this cohort of patients with ADPKD, tubular biomarkers did not change with dietary-induced weight loss or metformin, nor did they associate with kidney function decline in ADPKD patients and controls (diabetes mellitus [DM] patients) using multivariable-adjusted Cox regression and repeated linear mixed models. The cases and controls were matched with a ratio of 1:4 by age, sex and eGFR.

Results: The study sample included 674 PKD patients. The incidence of clinical outcomes in these patients is reported in Figure 1. The risk of adverse outcomes in PKD patients (N=173) compared to DM patients (N=692) is reported in Figure 2. The risk of death, RRT, SAH or cerebral aneurysm, and diverticular disease was greater in PKD patients compared to DM patients (p<0.02 for all). The eGFR decreased more rapidly in PKD patients compared to DM patients (-2.31 [95% CI, -2.41 to -2.22] vs -1.62 [95% CI, -1.76 to -1.48]; p<1x10^-10).

Conclusions: Tubular biomarkers, which reflect tubular dysfunction or injury, are associated with incident chronic kidney disease and kidney function decline. Several tubular biomarkers have also been implicated in progression of ADPKD. We evaluated changes in tubular biomarkers in four groups of patients with ADPKD who participated in one of two clinical trials (metformin therapy and diet-induced weight loss), based on evidence suggesting that such interventions could reduce tubule injury.

Methods: 66 participants (26M:40F) with ADPKD and estimated glomerular filtration rate (eGFR)<30 ml/min/1.73m² who participated in either a 12-month metformin clinical trial (n=22 metformin [max dose 2,000 mg/d]; n=23 placebo) or 12-month dietary weight loss study (n=10 daily caloric restriction [DCR], 30% restriction); n=11 intermittent fasting (IFM; 3x/wk) were included in assessments of urinary tubular biomarkers (kidney injury molecule-1 [KIM-1], fatty-acid binding protein [FABP], interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1], neutrophil gelatinase-associated lipocalin [NGAL], clusterin, and human cartilage glycoprotein-40 [YKL-40]; normalized to urine creatinine), at baseline and 12 months. The association of baseline levels with change in eGFR or htTKV over one year, after adjustments for demographics, group assignment, and clinical characteristics (Table).

Results: Mean±s.d. age was 48±8 years, eGFR was 71±16 ml/min/1.73m², and baseline BMI was 30.5±5 kg/m². None of the tubular biomarkers changed with any intervention as compared to placebo. Tubular biomarkers were not associated with change in eGFR or htTKV over one year, after adjustments for demographics, group assignment, and clinical characteristics (Table).

Conclusions: In this cohort of patients with ADPKD, tubular biomarkers did not change with dietary-induced weight loss or metformin, nor did they associate with kidney disease progression.

Funding: NIDDK Support
**TH-PO439**  
Evaluation of the Predictive Ability and Concordance of Prognostic Scores for Rapid Progression in ADPKD: A Multicenter Cohort  
Irene Cristalli, 1,2 Elhussein A. Elhassan, 1,3 Katherine A. Benson, 1 Carlotta P. Cristalli, 1 Anna Vella, 1 Francesca Ciurl, 1 Francesca Montanari, 1 Gaetano La Manza, 1,3 Jan Halbritter, 1,3 Peter J. Conlon, 4,5 IRCCS Università degli Studi di Bologna, Bologna, Italy; 6 Università degli Studi di Bologna, Bologna, Italy; 7 Beaumont Hospital, Department of Nephrology and Transplantation, Dublin, Ireland; 8 Royal College of Surgeons in Ireland Faculty of Medicine and Health Sciences, Dublin, Ireland; 9 Charite Universitätsmedizin Berlin, Berlin, Germany.  

**Background:** ADPKD is characterized by the progressive development of bilateral renal cysts, resulting in enlargement of the kidney volume and ESKD. ERK-NET assessed Tolovanapt indications according to 3 algorithmic criteria: total kidney volume (BTVK) and Mayo Clinic Imaging Class (MCIC), rate of decline in eGFR, and the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score. These scores are alternatively used to define rapid progressor (RP) patients. The aim of this study is to evaluate and improve the concordance of sensitivity and specificity of MCIC and PROPKD predictive abilities for rapid disease progression.  

**Methods:** Data from 3 centers (Bologna, Dublin, Berlin/Leipzig) were assessed. We defined RP with: eGFR slope ≥3 mL/min/1.73 m²/year over 4 years, or MCIC classes 1C-D, or, PROPKD score (≥9). Descriptive statistics were used to summarize clinical parameters. The concordance between MCIC or PROPKD score was assessed using Kappa statistics. In PKD1 missense variants, the REVEL score was obtained and treated as a continuous variable; score greater than 0.65 were considered ‘pathogenic’ and regarded as a predictive score for PROPKD score calculation.  

**Results:** We evaluated 298 ADPKD patients, demographic and clinical data are summarized in Table 1. After 4 yr of follow-up, MCIC (p = 0.041), HBP (p = 0.031), and urological events (p=0.001) result were statistically significant on multivariate analysis (Table 1). Assessment of RP using PROPKD and MCIC scores yielded Kappa Cohen of 0.49; 47.9% (n=143) were concordant, 49.3% (n=47) were discordant. MCIC was assigned using Kappa statistics. In PKD1 missense variants, the REVEL score was obtained and treated as a continuous variable; score greater than 0.65 were considered ‘pathogenic’ and regarded as a predictive score for PROPKD score calculation.  

**Results:** We evaluated 298 ADPKD patients, demographic and clinical data are summarized in Table 1. After 4 yr of follow-up, MCIC (p = 0.041), HBP (p = 0.031), and urological events (p=0.001) result were statistically significant on multivariate analysis (Table 1). Assessment of RP using PROPKD and MCIC scores yielded Kappa Cohen of 0.49; 47.9% (n=143) were concordant, 49.3% (n=47) were discordant. MCIC was assigned using Kappa statistics. In PKD1 missense variants, the REVEL score was obtained and treated as a continuous variable; score greater than 0.65 were considered ‘pathogenic’ and regarded as a predictive score for PROPKD score calculation.  

**Conclusions:** Concordance between scores results low (K of Cohen 0.149). PROPKD is more selective compared to the Mayo. Nevertheless, PROPKD allows the identification of some RP patients excluded from MCIC. The combined use of scoring may increase the ability to identify progressive patients. REVEL score could improve the agreement.

**TH-PO440**  
Impact of the 2021 Glomerular Filtration Rate Estimation Equation in a Cohort of White Polycystic Kidney Disease Patients  
Yarun Caliskan, 1 Abdullah Alpay Kantcez, 1 Ozgur A. Oto, 1 Safak Miroyglu, 1 Serra Artan, 1 Ahmet B. Dirim, 1 John C. Edwards, 1 Halil Yazici, 1 Kristin L. Lentine, 1 Saint Louis University School of Medicine, Saint Louis, MO; 2 Istanbul Universitesi, Fatih, Turkey; 3 Yeditepe Universitesi, Istanbul, Turkey; 4 Koc Universitesi, Istanbul, Turkey.  

**Background:** New estimated glomerular filtration rate (eGFR) equations removed race adjustment, but the impact of this removal on prediction of chronic kidney disease (CKD) staging for autosomal dominant Polycystic Kidney Disease (ADPKD) patients is unclear. We aimed to investigate the impact of new eGFR equations on CKD staging and their associations with clinical characteristics in ADPKD patients.  

**Methods:** We examined data for 288 consecutive White patients with ADPKD [mean age 53±16; 158 (54.9%) women, 130 (45.1%) man] through chart review between 2000-2013 with a median 9-year follow-up (IQ, 6-12 yrs). We computed changes in eGFR resulting from substituting the CKD-EPI 2009 equation for the 2021 equation and the consequent reclassification into different CKD Stages according to KDIGO 2012 classification. Correlates of eGFR changes during follow up are also studied.  

**Results:** Compared to the 2009 equation, CKD-EPI 2021 yielded a higher baseline eGFR, with a median of 2.67 mL/min/1.73 m² (IQR 1.43-3.43) and higher last visit eGFR with a median 2.64 mL/min/1.73 m² (IQR 1.24-3.65). Among the cohort of ADPKD patients, 9% (n=26) were reclassified into a higher category of eGFR, as were the following proportions by baseline (2009) equation: from stage 2, 9.1% (n=6) from stage 3, 9.4% (n=3) from stage 4 and 12.8% (n=6) from stage 5. No patient was re-classified into a more severe CKD stage. Based on last visit eGFR, CKD stage was also reclassified into a higher category in 13.3% (n=26) from CKD stage 2, 12.5% (n=6) from stage 3, 10% (n=2) from stage 4 and 7.9% (n=3) from stage 5. The median changes in eGFR over median 9 years (follow-up - baseline value) calculated by CKD-EPI 2009 and CKD-EPI 2021 was -8.5 mL/min/1.73 m² (IQR 0.5-22.1) and -7.9 mL/min/1.73 m² (IQR 0.5-22.7), respectively. Among the baseline clinical characteristics, smoking was significantly correlated with eGFR decline during follow up (CKD-EPI 2009, p=0.016; CKD-EPI 2021, p=0.186, p<0.018).  

**Conclusions:** Implementing the CKD-EPI 2021 equation in a Caucasian ADPKD population, would increase eGFR by a modest amount. A significant proportion of the patients would be re-classified into a higher eGFR category, with a consequent decrease in the prevalence of stage 5 CKD.
A Diagnosis of Depression/Anxiety Is Associated with More Rapid eGFR Decline in Autosomal Dominant Polycystic Kidney Disease

Kathryn E. Simmons,1 Lawrence S. Ullman,1 Neera K. Dahl,2 1Yale School of Medicine, New Haven, CT; 2Mayo Clinic Department of Internal Medicine, Rochester, MN.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the leading genetic cause of kidney failure. 22-60% of patients with ADPKD are diagnosed with depression, which is associated with worse physical health and decreased dietary compliance with ADPKD guidelines. Depression in chronic kidney disease patients is associated with increased all-cause mortality, but the impact of mental health on ADPKD progression has not been assessed.

Methods: We identified ADPKD patients seen at Yale Nephrology from 2016 to 2021 and retrospectively collected demographic, medical history, and clinical data through automated query and manual chart review. Patients were separated into two groups, those diagnosed with depression and/or anxiety (DA), and those without a diagnosis of depression and/or anxiety (NA). Estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD EPI Creatinine equation. Differences between groups were assessed through chi-squared and Student’s T-test, and the impact of DA on kidney function decline, represented by average change in eGFR, was assessed through simple and multiple linear regression.

Results: There were 49 (26%) patients with DA, and 140 (74%) patients without. DA patients were more likely to be female (p=0.0044), younger (p=0.04), have higher body mass index (BMI) (p=0.021), and be diagnosed with obstructive sleep apnea (p=0.048). There were no differences between Mayo Imaging Classification (MIC) or genotype between the groups, though tolvaptan use was more common in the NDA group (p=0.021). DA diagnosis was not linked to more rapid eGFR decline (p=0.672) with simple linear regression. However, DA was a significant predictor for rapid eGFR decline (p=0.019) on multivariable regression when controlling for factors linked to disease progression, including ADPKD genotype, MIC, kidney stones, hypertension, and diabetes, as well as age, sex, and BMI.

Conclusions: DA is significantly correlated with rapid eGFR decline in ADPKD patients in addition to traditional risk factors such as genotype, age, and MIC. Future investigations may help determine if the impact of DA on eGFR decline is through a clinical, psychological, and/or behavioral mechanism.

Funding: Clinical Revenue Support

Pregnancy and Its Association with Total Kidney Volume in Nulliparous Women with Autosomal Dominant Polycystic Kidney Disease

Bao Zheng, Berenice Y. Gitomer, Kristen L. Nowak, Zhiying You, Michel Chonchol. University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: There is mounting evidence of metabolic dysregulation contributing to polycystic kidney disease (PKD) progression. The maternal metabolic changes during pregnancies are well described, but the relationship between pregnancy and changes in total kidney volume in women with PKD is unclear. In this study, we tested the hypothesis that a pregnancy carried to live delivery in nulliparous PKD women is associated with a total kidney volume in women with PKD.

Methods: This cohort study of 29 women with PKD and 29 control women recruited from the University of Colorado Denver Nephrology Clinic investigated the impact of pregnancy on total kidney volume. Total kidney volume (TKV) was measured using CT imaging. A two-sample T-test was performed for the PKD women with pregnancies (controls). These women were matched 1:1 by age, race, and eGFR (calculated by the MDRD equation). A two-sample T-test was performed for the PKD women with pregnancies (controls). These women were matched 1:1 by age, race, and eGFR (calculated by the MDRD equation). A two-sample T-test was performed for the PKD women with pregnancies (controls). These women were matched 1:1 by age, race, and eGFR (calculated by the MDRD equation).

Results: There were 49 (26%) patients with DA, and 140 (74%) patients without. DA patients were more likely to be female (p=0.0044), younger (p=0.04), have higher body mass index (BMI) (p=0.021), and be diagnosed with obstructive sleep apnea (p=0.048). However, DA was a significant predictor for rapid eGFR decline (p=0.019) on multivariable regression when controlling for factors linked to disease progression, including ADPKD genotype, MIC, kidney stones, hypertension, and diabetes, as well as age, sex, and BMI.

Conclusions: DA is significantly correlated with rapid eGFR decline in ADPKD patients in addition to traditional risk factors such as genotype, age, and MIC. Future investigations may help determine if the impact of DA on eGFR decline is through a clinical, psychological, and/or behavioral mechanism.

Funding: Clinical Revenue Support

Deciphering the Chronology of Cystogenesis and Metabolic Reprogramming

Daniel Spies,1,2 Sara Clerici,1 Laura Cassina,2 Marco ChiaraRalli,2 Alessandra Boletta.1 Unit of Cystic Kidneys Disorders - Alessandra Boletta Lab.1 Universita Vita Salute San Raffaele, Milano, Italy; 2IRCCS Ospedale San Raffaele, Milano, Italy.

Background: ADPKD is among the most prevalent monogenic diseases. Multiple reports et demonstrated that gestational age is associated with increased cyst volume in ADPKD. However, the relationship between gestational age and cyst volume in ADPKD has not been evaluated. In this study, we tested the hypothesis that gestational age and cyst volume in ADPKD are related.

Results: A total of 214 ADPKD patients were included in this study. The mean gestational age was 38.5 weeks (SD 2.4). The median (IQR) TKV for cases and controls was 288 [248-366] and 350 [240-515] ml/m². A two-sample T-test was performed for the PKD women with pregnancies (controls). These women were matched 1:1 by age, sex, and BMI.

Conclusions: DA diagnosis was not linked to more rapid eGFR decline (p=0.672) with simple linear regression. However, DA was a significant predictor for rapid eGFR decline (p=0.019) on multivariable regression when controlling for factors linked to disease progression, including ADPKD genotype, MIC, kidney stones, hypertension, and diabetes, as well as age, sex, and BMI.

Conclusions: DA is significantly correlated with rapid eGFR decline in ADPKD patients in addition to traditional risk factors such as genotype, age, and MIC. Future investigations may help determine if the impact of DA on eGFR decline is through a clinical, psychological, and/or behavioral mechanism.

Funding: Clinical Revenue Support

Financial Implications of Genetic Testing in Nephrology: A Real-Life Evaluation of the Costs Related to Podocytopathy and Collagenopathy Diagnoses

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Background: Collagenopathies and podocytopathies significantly contribute to CKD. Despite concerted efforts to enhance genetic testing guidelines, a data vacuum persists concerning the economic burden for diagnosis these diseases impose on healthcare systems. This study aims to shed light on healthcare resources utilization and healthcare costs associated with collagenopathies and podocytopathies in real-life settings.

Methods: In this multicentric, retrospective study we enrolled all patients with a conclusive genetic diagnosis of podocytopathy and collagenopathy, from our tertiary hospital from Jun 2014 to Dec 2022, as previously described. Direct medical costs from clinical onset to conclusive genetic diagnosis, including medication use, in-hospital visits, invasive procedures, blood sampling, imaging studies, hospital admissions, and genetic tests, were recorded from patient clinical records. These costs were subsequently adjusted for hospitalization days.

Results: The included 43 patients (23 female), with 22 diagnoses of podocytopathies and 21 of collagenopathies. Over a median follow-up period of 3.5 years, patients required a wide range of resources consumption. Overall, the direct medical costs averaged 98,252 euros for medications, 4,125 euros for in-hospital visits, 68,138 euros for biopsies, 68,926 euros for blood tests, 2,560 euros for urinalysis, 9,023 euros for imaging, and 146,000 euros for genetic testing. Remarkably, the annual cost per patient averaged 3,897 euros, aligning closely with the cost of adopting the “exome first” approach.

Conclusions: Our study underscores the significant unnecessary treatments and costs associated with the existing diagnostic approach for collagenopathies and podocytopathies. By adopting an early genetic testing strategy, we can mitigate this burden and reallocate resources more efficiently, providing valuable insights for healthcare policymakers.

Funding: Other NIH Support - Bando Ricerca Salute 2018 (NlKE) by Tuscany Region, Italy
TH-PO447
Large-Scale Case-Control Exome-Wide Association Study Identifies Known and Novel Susceptibility Genes for Idiopathic Nephrotic Syndrome
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Background: The genetic causes of idiopathic nephrotic syndrome (INS) have traditionally been studied using family-based approaches and comprehensive association studies across the age of onset, response to therapy, and ancestry are lacking.

Methods: We conducted an exome sequencing (ES) study on 5,262 children and adult cases with INS caused by focal segmental glomerulosclerosis or minimal change disease, including 1,998 steroid sensitive cases (SSNS) and 3,264 cases that were not known to be responsive to steroids (either steroid resistant or untreated/unknown). Per- gene burden of rare coding variants was assessed by exome-wide collapsing analysis comparing the above 5,262 cases and 28,637 population controls with ES data under dominant and recessive models. Analyses were conducted on the entire dataset and then again after removal of cases harboring diagnostic/pathogenic Mendelian mutations in known FSGS genes and APOL1 high-risk genotypes.

Results: In the analysis on the entire cohort, we identified and retrieved association for many of the known FSGS genes, including WT1 (P = 1.09 × 10^−12; OR = 15.64), COL4A5 (P = 2.37 × 10^−11; OR = 9.83), IN2 (P = 1.87 × 10^−10; OR = 12.22), and several others, under dominant models, and NPHS1 (P = 1.56 × 10^−23; OR = 25.18), NPHS2 (best P = 3.93 × 10^−10; OR = 30.58), SMARCAL1 (best P = 9.91 × 10^−9; OR = 31.97) and several others, under a recessive model. This analysis re-classified CD2AP as an autosomal recessive cause of INS, and points to mutations in CNL5 and OCR1 as common causes of FSGS phenocopies. Removal of solved cases and re-analysis prioritized five novel genes that exceeded the 5% false discovery rate (FDR), one gene that represented a phenotypic expansion of a known Mendelian neurodevelopmental disease, and three genes for which mouse models of the orthologues display glomerulopathy. Three of them are novel candidates for steroid resistant NS and two for SSNS.

Conclusions: These findings expand our understanding of the genetic underpinning of INS, identify novel candidate genes, and highlight the high genetic heterogeneity of disease. Genetic and functional validation studies of these results are ongoing.

TH-PO448
Genotype-First Analysis in an Unselected Health System-Based Population Reveals Variable Penetrance of COL4A5 Variants

Background: Current literature suggests that nearly all hemizygous males with COL4A5 mutations (i.e. X-linked Alport Syndrome [AS]) progress to end-stage kidney disease (ESKD) though most data come from selected cohorts.

Methods: We used exome sequencing data from the Geisinger MyCode DiscovEHR study, an unselected health system-based cohort with exome sequencing and electronic health record data to identify patients with COL4A5 variants reported as pathogenic (P) or likely pathogenic (LP) in ClinVar. Phenotypic data sources included the United States Renal Data System (USRDS), ICD codes, blood and urinalysis data. Patients were categorized into Kidney Disease Improving Global Outcomes (KDIGO) risk categories using estimated glomerular filtration rate (eGFR) and albuminuria (preferentially) or urine dipstick protein data.

Results: Out of 174,418 participants, there were 24 hemizygous males (mean age 53.8 [SD 19.5] years) and 55 heterozygous females (mean age 59.8 [SD 17.6]) with a P/ LP COL4A5 variant, including Glyn62AASp2 (n=48) and 9 missense and 4 protein truncating variants. Overall, 41% of males had KDIGO severely increased risk category and 4% of females had severely increased risk category with lower severity for Glyn62AASp than other variants (Figure). In logistic regression analyses adjusted for age, sex, and race, hemizygous males and heterozygous females were at increased risk of ESKD (females: OR 5.2, 95% CI: 1.2, 21.3; males: OR 36.1, 95% CI: 14.5, 89.7). Few had been diagnosed with Alport Syndrome (21% of males, 9% of females). Only 45% of individuals had completed albuminuria screening, and 1/3 were taking renin angiotensin aldosterone system (RAAS) inhibitors.

Conclusions: In an unselected cohort, we demonstrate a wider spectrum of kidney severity in men and women than has been described previously with variability by genotype. Future studies are needed to determine whether early genetic diagnosis can improve outcomes in Alport Syndrome.

Funding: NIDDK Support

TH-PO449
Small but Clinically Relevant Contribution of Copy Number Variations (CNVs) to Idiopathic Nephrotic Syndrome
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Background: Idiopathic Nephrotic Syndrome (INS) is a frequent cause of kidney failure. The utility of genetic diagnostics within the context of rare variants affecting Mendelian NS-associated genes have been demonstrated on patients with various kidney disease. Nevertheless, genetic studies have overwhelmingly assessed the contribution of single nucleotide variants while the contribution of rare Copy Number Variations (CNV) to INS remains poorly understood.

Methods: We conducted chromosomal DNA microarray (CMA) genotyping on a large cross-sectional cohort of 3,600 INS patients across ages of onset and response to immunosuppressive therapy. An interim analysis of 2,230 INS cases was conducted. To extract CNVs, we used PennCNV with default parameters. Predicted CNVs were annotated against the CNV start and stop boundaries of 221 known Genomic Disorders (GD) and a curated list of 126 genes that, when mutated, are known to cause INS/CNSG or at least contribute to it. A subgroup analysis will be conducted after the removal of solved cases via exome sequencing, partitioning by age of onset, response to therapy, and genetic ancestry.

Results: 18 of 2,230 INS individuals (0.8%) carried a GD-CNV without significant enrichment for a particular subcategory. Notably, we identified 6 (0.3%) individuals with smaller deletions that encompassed INS-associated genes for which a loss-of-function mechanism of disease determination is known: NPHS1 (N=2), FRAS1, HNF1B, LMX1B, and WDR75.

Conclusions: This interim analysis showed that the overall CNV diagnostic rate for INS is relatively low, (~2%), but should not be overlooked since these variants add to the overall genetic diagnostic workup and have direct implications in clinical management for NS (ex steroid avoidance) and risk stratification for extra-urinary complications associated to these variants.

Funding: NIDDK Support

TH-PO450
The Polygenic Burden of Rare Variants Predicts Onset of CKD in the UK Biobank
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Background: Genetic contributors to chronic kidney disease (CKD) have been explored through monogenic mechanisms by rare mutations and polygenic mechanisms through the aggregate impact of many small-effect common variants. In this work, we test whether a polygenic burden of rare variants across numerous genes contributes to CKD by constructing a rare variant polygenic risk score (rvPRS).

Methods: We first conducted a discovery exome-wide association study (exWAS) of rare protein-truncating variants with a calculated severe CKD phenotype based on eGFR below 30 ml/min/1.73m2 using a discovery set of 834 cases and 147,855 British European controls in the UK Biobank (UKB). After excluding known Mendelian CKD genes, an rvPRS was constructed of 124 nominally significant (P<0.05) risk genes associated with severe CKD. As such, the effect of signals filtered through rvPRS124 would not be driven through underlying monogenic mechanisms. We then tested the predictive power of rvPRS124 using a validation set consisting of 688 independent CKD events in the UKB.

Results: In the validation set, rvPRS124 conferred a 21% increase in hazard for incident CKD onset with one rare protein-truncating allele (HR=1.21; 95%CI, 1.01-1.46; P=0.045) after adjusting for age, sex, the first 5 principal components of ancestry, and pertinent clinical risk factors including obesity, myocardial infarction, and smoking. Individuals with 2 or more rvPRS124 alleles (N=1,352) had a 10-fold increase in hazard
for CKD onset compared to individuals with no rPRS124 variants (HR=10.0, 95% CI, 2.5 to 41.8). No single gene in rPRS124 replicated an association with CKD after adjusting for multiple hypothesis testing (P=4x10^-4; 0.05/124), which emphasizes the importance of rare variant polygenic mechanisms underlying CKD. Lastly, through 1000 permutations of random gene sets, we show that the association of rPRS124 with CKD is specific to the selected genes used to construct the score and not solely due to the gene count (P=0.05). 

Conclusions: Using the UKB, we demonstrate a cumulative impact of rare protein-truncating variants in genes not known to have monogenic effects on CKD. An omni-mutational score incorporating each of these clinical risk factors and both Monogenic and common variant polygenic effects, should also include the polygenic burden of rare variants in non-Mendelian CKD-related genes.

TH-PO451 Unraveling the Unknown: A Few Illustrative Examples of the Utility of Genetic Testing for CKD

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Introduction: Genetic testing can offer critical insight into diagnosing disease states that were previously challenging to identify. In the context of CKD, genetic testing using commercially available panels can provide valuable information to guide personalized treatment decisions. We highlight three cases seen in our clinic over the past six months that illustrate the value of genetic testing for CKD.

Case Description: Case 1: 75-year-old self-identified Black male presented to the clinic with elevated creatinine and significant history of treatment-resistant hypertension and hyperlipidemia. Subsequent workup was consistent with Primary Hyperaldosteronism (plasma aldosterone-renin ratio, 58). Genetic testing, pursued initially to identify glucocorticoid remodelable hyperaldosteronism, revealed a CACNA1H mutation, consistent with Type 4 Familial Hyperaldosteronism. Case 2: 56-year-old self-identified Black male with a history of ischemic cardiomyopathy and orthotopic heart transplant seven years ago was evaluated for worsening creatinine. A renal biopsy showed secondary focal segmental glomerulosclerosis and hypertensive arteriolar sclerosis attributed to calcineurin inhibitors. Genetic testing revealed APOL1 homozygosity with G1/G1 alleles. Case 3: 41-year-old self-identified Black female was evaluated for persistent albuminuria and intermittent hematuria over several years with stable serum creatinine. She had no significant medical co-morbidities or family history. Genetic testing revealed COL4A3 mutation, seen with Alport’s syndrome without sensorineural hearing loss.

Discussion: In summary, these cases highlight the tremendous clinical utility of genetic testing in CKD. As genetic testing technologies continue to advance and emerge for specific renal diseases, such as APOL1-mediated CKD, routine genetic testing for patients with CKD is worth considering.

TH-PO452 Reclassification of Genetic Diagnoses: Need for Structure in Re-Evaluation of Genetic Findings

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Introduction: Constant advances and emerging data in genomic medicine cause classifications to evolve. With the advent of foreign clinical findings, the number of single gene disorders is increasing, with over 600 genes described thus far. Genetic variant pathogenicity is classified according to the American College of Medical Genetics (ACMG) guidelines. Although the ACMG guidelines provide a classification with >95% certainty, variants of unknown significance (VUS) do not have enough information to classify, may be reclassified when more information becomes available. The ACMG guidelines suggest that all new data should be incorporated into the genetic evaluation as it becomes available. This includes, but is not limited to, any new patient specific clinical information, family data, and population and case data in the literature. Currently, there are no protocols guiding when and how often to reevaluate genomic data. We present a case which highlights the importance of periodic genetic re-evaluation in a living donor post kidney donation.

Case Description: A 45-year-old female donated her left kidney as a non-directed altruistic donor. At the time of donor assessment, her creatinine was normal (60-70mmol/L), however, she had persistent microscopic hematuria. Given a positive family history of KD in a maternal uncle, genetic testing was performed. This revealed a variant of unknown significance (VUS) in COL4A4 c.3307G>A, p.Glu1103R. Since a VUS is not considered a clinically actionable finding, she elected to proceed with donation. Unfortunately, 5-years post-donation, she had progressive rise in creatinine (125 umol/L). An updated pedigree analysis now revealed that two of her children had developed KD after a minor trauma, two years prior to current evaluation. The initial work-up was negative for autoimmune disorders, hepatitis serology, malignancy screening, mononuclear granulomas. The kidney biopsy revealed severe amyloid deposition along glomerular enlargement and almost complete obliteration of the normal architecture, without vascular or interstitial involvement. The reevaluation of renal tissue did also reveal extensive amloid deposition. The bone marrow biopsy was negative and the patient did not have any other disease predominantly expressed in the skin diaphragm A protein was slightly increased, 19 mg/L. Typing of amyloid by immunohistochemistry (IHC) could not reliably differentiate between AA amyloidosis and AFib. Because the initial genetic testing for hereditary amyloidosis (including testing for SAA1 promoter gene) was negative, a WES was further performed. The patient was identified to be heterozygous for two variants of uncertain significance (VUS) of FGA gene, c.1676A>T, p. (Glu559Val) and c.967C>G, p. (Pro323Ala).

Discussion: This case report illustrates the limitations of amyloid typing by IHC and the role of WES in identifying mutations in hereditary complications. Their presence was heterozygous for two VUS of FGA gene, of which c.1676A>T, p. (Glu559Val) has been previously reported in two German sisters with AFib, while the c. 967C>G, p. (Pro323Ala) has not been reported in the medical literature. Despite that both variants were reported in the VUS, the correlations with the patient’s family history and the severity of renal and specific involvement further outlines that these variants are clinically significant.

TH-PO453 The Role of Whole-Exome Sequencing in Diagnosis of Genetic Disorders: A Case Report of a Novel Mutation in the Fibrinogen A-Alpha Chain Gene

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Introduction: Hereditary fibrinogen amyloidosis (AFib) was first characterized in 1993 in a Persian kindred. Patients with AFib present with renal disease and typically progress to ESRD. We describe a case of AFib with a novel mutation in the FGA gene identified by whole-exome sequencing (WES).

Case Description: A 51-year-old male patient presented to the nephrology clinic for the evaluation of a nephrotic range-proteinuria (5.4 g/day) and decreased eGFR (55 ml/ min/1.73 m2). His family history was notable for stage V CKD of unknown cause (patient’s mother). His past medical history is remarkable for a ruptured spleen and splenectomy following a minor trauma, two years prior to current evaluation. The initial work-up was negative for autoimmune disorders, hepatitis serology, malignancy screening, mononuclear granulomas. The kidney biopsy revealed severe amyloid deposition along glomerular enlargement and almost complete obliteration of the normal architecture, without vascular or interstitial involvement. The reevaluation of renal tissue did also reveal extensive amloid deposition. The bone marrow biopsy was negative and the patient did not have any other disease predominantly expressed in the skin diaphragm A protein was slightly increased, 19 mg/L. Typing of amyloid by immunohistochemistry (IHC) could not reliably differentiate between AA amyloidosis and AFib. Because the initial genetic testing for hereditary amyloidosis (including testing for SAA1 promoter gene) was negative, a WES was further performed. The patient was identified to be heterozygous for two variants of uncertain significance (VUS) of FGA gene, c.1676A>T, p. (Glu559Val) and c.967C>G, p. (Pro323Ala).

Discussion: This case report illustrates the limitations of amyloid typing by IHC and the role of WES in identifying mutations in hereditary complications. Their presence was heterozygous for two VUS of FGA gene, of which c.1676A>T, p. (Glu559Val) has been previously reported in two German sisters with AFib, while the c. 967C>G, p. (Pro323Ala) has not been reported in the medical literature. Despite that both variants were reported in the VUS, the correlations with the patient’s family history and the severity of renal and specific involvement further outlines that these variants are clinically significant.

TH-PO454 An Unusual Genetic Etiology for Adult-Onset FSGS

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Introduction: Focal segmental glomerulosclerosis (FSGS) is a histological pattern that is commonly associated with nephrotic syndrome and characterized by damage to the podocyte cytoskeleton. Genetic FSGS results from mutations in genes encoding podocyte proteins, particularly those predominantly expressed in the slit diaphragm. Here we discuss a case of genetic FSGS associated with mutation of a gene predominantly expressed in the proximal tubules.

Case Description: A 31-year-old African American male was referred to the nephrology clinic for evaluation of stage IV chronic kidney disease (CKD) and nephrotic range proteinuria. He had a history of well-controlled hypertension (not on any antihypertensives) and non-obstructive nephrolithiasis. Given proteinuria of more than 3 grams, suggesting glomerular disease and uncertain etiology of his CKD, a renal biopsy was performed. Biopsy revealed focal segmental glomerulosclerosis and severe interstitial fibrosis with tubular atrophy. Given the patient’s age and the unclear etiology of his FSGS, genetic testing was conducted, which revealed a homozygous mutation in the CLCN5 gene, consistent with Dent Disease type 1.

Discussion: Dent Disease is an X-linked recessive disease due to mutations in the CLCN5 gene that encodes for the electrogenic Cl-H+ exchanger. It usually manifests with proximal tubular dysfunction including low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, and progressive CKD. A novel mutation (L521F) in the CLCN5 gene has been reported to cause defects in podocyte transport and FSGS. However, the L521F mutation is usually not associated with hypercalciuria or nephrolithiasis. Our patient had evidence of both glomerular and tubular involvement. Our case demonstrates the value of genetic testing in patients with CKD of uncertain etiology, particularly in young patients or those with unusual presentations. Understanding the genetic basis of kidney disease can lead to novel discoveries in renal physiology.

TH-PO455 Monogenic Causes Identified in 30.70% of Children with Steroid-Resistant Nephrotic Syndrome: A Single-Centre Study

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second most common cause of end-stage kidney disease in children, mostly associated with focal segmental glomerulosclerosis (FSGS). Advances in genomic science have enabled the identification of causative variants in 20–30% of SRNS patients.

Methods: We used whole exome sequencing (WES) to explore the genetic causes of SRNS in children. Totally 101 patients with SRNS, and 13 patients with sub nephrotic proteinuria and FSGS were retrospectively enrolled in our hospital between 2018 and 2022. For the known monogenic causes analysis, we use the known SRNS gene list of 71 genes through reviewing the OMIM database and literature.
Results: Causative variants were identified in 30.70% of our cohort, and the most frequency of genetic causes in our cohort were WT1 (7/33), NPHS1 (3/33), ADCK4(3/33), TRPC6(3/33) and ANLN (3/33). Five patients carried variants in phenocopy genes, including MYH9, MABF, TTC21B, AGRN, and FAT4. The variant detection rate was the highest in the two subtype groups with congenital nephrotic syndrome and syndromic SRNS. In total, 68.75% of variants we identified were novel, and have not been previously reported in literature.

Conclusions: Comprehensive genetic analysis is key to realizing the clinical benefits of a genetic diagnosis. We suggest that all children with SRNS undergo genetic testing, especially those with early onset and extrarenal phenotypes.

TH-PO456
Genetic Causes of Focal Segmental Glomerulosclerosis in Koreans
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Background: Focal segmental glomerulosclerosis (FSGS) is a relatively common pathologic findings of nephrotic syndrome or chronic kidney disease (CKD) presenting proteinuria. Genetic FSGS, usually not responding to immunosuppressive medications, is more common in younger patients and those who have a family history of kidney disease. Common genetic causes of FSGS include mutations reported COL4A mutations in families, but those of Korean population have not been well investigated.

Methods: The Korean Kidney Disease Disproportion Study is enrolling patients with kidney diseases of presumably genetic origin since 2021. Clinical characteristics of the cases were collected by the referring physicians and the genomic DNA of the enrolled cases were sequenced by multiple parallel sequencing of whole exome sequencing. The variant detection rate was obtained. Pathogenicity of variants were interpreted according to the American College of Medical Genetics (ACMG) guideline referring the resources of gnomAD (genomic Aggregation Database), ClinVar (National Center for Biotechnology Information ClinVar Database), VarSome and other in silico prediction tools.

Results: Of 2,035 prospectively cases of the our cohort, 124 cases (27.4%) Male:Female64.60, mean age of diagnosis 20.8 year (range 0-78 years) had pathologic diagnosis of FSGS. Among them, 20.9% had a positive family history. Genetic diagnosis was obtained in 40.3% (n=50), among which COL4A3-5 (n=8) were the most commonly found causative gene, followed by NPHS1 (n=6), PAX2 (n=5), WT1 (n=4), COQ6/8B (n=4), NUP107p (n=3), TRPC6 (n=3), LAMAS (n=2), MYH9 (n=2), MABF (n=1), Gene testing changed the diagnosis in 8 FSGS to Alport syndrome (AS), leads to extrarenal manifestation screening in 8 (AS, PAX2, MYH9, and MABF), and provided information on potential treatment (coenzyme Q10) in 4 with COQ6/8B mutations.

Conclusions: We found that proportions of causative genes in Korean FSGS are different from previous results of Western countries. Similar to the literature, gene testing was useful in obtaining more precise diagnosis and guiding management.

TH-PO457
Getting the Full Picture: Identifying Cases with Multiple Genetic Diagnoses Using Comprehensive Renal Gene Testing
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Background: Comprehensive genetic testing can provide genetic diagnoses for kidney disease of unknown etiology and those with unexpected phenotypes due to multiple genetic causes.

Methods: Analysis of 42,221 samples tested with the Renasight™ test was performed to identify cases with diagnostic findings in ≥ 2 genes. The cases were categorized based on: 1) disease penetrance: high (variants are expected to cause the condition) or susceptible (variants provide risk for disease development) and/or 2) disease penetrance phenotype: a) distinct phenotypes (2 conditions with dissimilar symptoms), b) same phenotype (2 distinct conditions with the same symptoms), c) combined phenotype (2 distinct genes that interact to cause the same disease (Digenic)).

Results: A total of 818 cases with multiple positive results spanning 130 genes (787 dual and 31 triple) were found, accounting for 7.7% of all tests with a positive result. Of the 369 different gene combinations identified, 274 occurred only once. The most common positive gene result was APOL1 (344, 42.1%), among which, additional positive findings included: high penetrance genes with expected distinct phenotypes (28.9%), TTR (associated with cardiac amyloidosis; 9.5%) and other susceptibility genes (1.2%). Multiple positive findings among the non-APOL1 genes (56.4%) included those with 2 high penetrance genes that cause distinct phenotypes (35.3%), cases with both a high penetrance gene and a susceptibility gene (8.91%), and cases with a TTR finding and a second high penetrance gene (7.2%). Digenic findings comprised 3.8% of all multiple positive cases and those with two separate gene findings that independently cause the same phenotype comprised 1.2% (Table).

Conclusions: We found that 7.7% of patients with genetic kidney disease had multiple etiologies that were responsible for these conditions. Identifying the range of genetic causes determining that comprehensive genetic testing is crucial for identifying the full range of genetic causes of kidney diseases that may be missed by traditional testing methods.

TH-PO458
Genome-Wide DNA Methylation Association Study Identifies DNA Methylation Associated with ESRD
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Background: Kidney disease is a progressive condition affecting >10% of the general population worldwide, of which progression to end-stage renal disease (ESRD) caused poor quality of life and significant premature mortality. Defining DNA methylation biomarkers and understanding their roles in ESRD may help develop preventive and therapeutic strategies for kidney disease progression.

Methods: We conduct a blood-based genome-wide DNA methylation association study of ESRD in 2 independent cohorts (consisting of 1924 samples) from China and Singapore. Two-sample summary-level Mendelian randomization analysis was performed to evaluate the causality of the associations between methylation at DMP and kidney function (eGFR/eGFR decline). We also attempted to identify the candidates of ESRD-related genes underlying the significant associations by integrating the regulatory information from multiple public and published datasets. Using publicly available tools, we analyzed drug candidates for prevention or treatment of CKD progression based on ESRD-related genes.

Results: We identified a total of 922 differentially methylated positions (DMPs) at genome-wide significance (P < 9e-8). Regulatory function analysis of these DMPs have implicated 1255 candidate ESRD-related genes, which are enriched for biological processes related to immunity, GTPase activator activity, and signal complex assembly. All the candidate genes were enriched in key regulatory elements for gene function, including accessible chromatin elements. Of these candidate ESRD-related genes, some are the targets of investigational or approved drugs. Mendelian randomization revealed some causal association between DMPs and kidney function (eGFR/eGFR decline).

Conclusions: Our study demonstrated that DNA methylation play a significant role in the progression of kidney disease. Our study has not only identified DMPs as potential biomarkers for predicting renal progression and further implicated genes as potential therapeutic targets for ESRD treatment.

Funding: Government Support - Non-U.S.
Monogenic Disease Variants in the Swiss Kidney Stone Cohort and Stone-Free Controls

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Background: A with lifetime prevalence of 10%, kidney stones (KS) are among the most common diseases. KS disease (KSD) has a complex pathogenesis influenced by a variety of factors, including dietary intake, fluid consumption, metabolic abnormalities, and a genetic predisposition. A thorough understanding of both the genetic and biochemical factors is crucial for a better diagnosis, therapy, and prevention. However, data from larger cohorts with KSD with detailed profiling are scarce.

Methods: The Swiss Kidney Stone Cohort (SKSC) is a multicenter longitudinal observational study consisting of two distinct groups: Kidney stone formers (KSF) and matched non-KSF (NKSF). Status was confirmed by low-dose CT scan. Blood and urine samples were collected at baseline (KSF, NKSF) and periodically over a 3-year period (KSF). Exome sequencing was performed in all participants, and variants in established KSD genes were assessed according to the ACMG/AMP criteria with subsequent genotype-phenotype analysis. Pathogenicity was defined as a variant that occurred in KSF and not NKSF.

Results: 731 KSF and 201 NKSF were included. A diagnosis of monogenic KSD was established in 10.1% of KSF. Likely pathogenic variants were predominantly located in genes encoding proteins involved in phosphate/calcium metabolism (SLC34A1, SLC34A3, SLC34A1, ALPL, CTP2A1) or cystinuria (SLC3A1, SLC7A9). Of note, 4.5% of KNSFs also carried (likely) pathogenic variants in KSD genes and displayed matching biochemical parameters (e.g., NKSF with cystinuria). The comparison with NKSFs, patients with monogenic KSD showed a significantly deeper decrease in eGFR over a 36-month period (ΔeGFR -4.9 vs. -2.0 mL/min/1.73 m²).

Conclusions: The SKSC is the hitherto largest genetically analyzed KS cohort, accompanied by a control group of confirmed NKSF. The comparison with NKSFs, who also carried (likely) pathogenic variants in KSD genes, suggests that KS occurrence may depend on additional factors that may be either genetic (additional rare or common variants) or environmental. Additionally, the results from genetic analysis in KS genes can help identify patients at higher risk for a faster decline in kidney function.

Funding: Government Support - Non-U.S.

Mayo Clinic Experience with TRPC6 Mutations Using Clinical Whole Exome Sequencing

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Background: Integration of genomic and research testing and multidisciplinary evaluation in a nephrology cohort with CKD of unknown etiology or suspected monogenic disease provides a diagnosis in approximately a third of families. The TRPC6 gene, a member of the transient receptor potential (TRP) superfamily of cation-selective ion channels, encodes the slt diaphragm-associated canonical TRPC cation (Ca2+) channel protein expressed in podocytes. Around 20 missense mutations have been reported, including nine gain-of-function and five loss-of-function mutations that affect TRPC6 channel activity. We present our experience at the Mayo Nephrology Clinic with cases of proteinuric chronic kidney disease found to have TRPC6 variants.

Methods: Testing utilized kidney/nephrotic disease panels, single gene analysis, or targeted Sanger sequencing. Affected regions of the TRPC6 protein were identified using an exome variant calling method of the most patients. Variant classification followed the 2015 guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

Results: Eight probands, all adults, were identified with TRPC6 variants and proteinuric CKD. All variants clustered in Exons 1, 2, and 3. We provided a definitive genetic diagnosis for three probands with pathogenic or likely pathogenic variants, one of which has not been reported previously. In addition, five cases had variants of interest, and among them, three had other first-degree family members with CKD as well. One of the cases with a positive family history had a sibling who was accepted for kidney donation after the donor tested negative for TRPC6 variants.

Conclusions: In summary, TRPC6-related CKD diagnoses have diagnostic and prognostic implications, enabling a more precise diagnosis and changes in management, including the evaluation of safety for living kidney donation. Furthermore, further studies on the functional analysis of TRPC6 variants may provide new insights into diagnostic precision and the mechanisms of the disease.
Conclusions: TRPC6-associated podocyteopathy is a rare cause of genetic FSGS. We have described here 5 patients, demonstrating high intra- and inter-familial variability in age at presentation and outcomes, and that the resulting kidney disease is progressive and frequently results in ESRD. Granular clinical genetic and kidney pathology correlations are ongoing.

Funding: NIDDK Support, Commercial Support - Actio Biosciences

TH-PO466
Clinical and Genetic Characteristics of INF2-Related Monogenic FSGS
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Background: Focal segmental glomerulosclerosis (FSGS) is a histological lesion with diverse aetiologies. Although monogenic forms of FSGS are characterized by a grim clinical course, resulting in early end-stage renal disease (ESRD), they often remain underdiagnosed. Disease-causing variants in INF2 (inverted formin 2), which encodes an essential actin regulatory protein, have been identified as the most common cause of dominantly inherited FSGS; however, the disease has a highly heterogeneous clinical presentation and progression.

Methods: To describe the natural history of INF2-related FSGS, we established an INF2 research group and produced an e-survey describing the clinical outcomes (age at presentation, disease trajectory, histological diagnosis) and genetic data (exon location, and functional domains).

Results: We have received responses from 9 European centers and collected data from 53 patients (21 families), 22 (41.5%) of these cases have not been previously published. The age of initial presentation was 26.3 ± 12.8 years, with the majority of patients presenting with proteinuria and/or edema. Among the 25 patients (47.2%) who underwent kidney biopsy, FSGS accounted for 64% of the histopathologic diagnoses. Of the available data, 18 had reached end-stage kidney disease with a mean time to ESKD of 7.8 years from the presentation. Ten patients have undergone transplantation, and 8 patients had associated Charcot-Marie Tooth neurophyopathy. Most families [19/22; 86.4%] had missense variants spanning exons 2 to 4 that localize to a diaphanous inhibitory domain.

Conclusions: INF2 is an increasingly recognized cause of monogenic kidney disease that can lead to ESKD and has an important impact on responses to treatments. Continued efforts are required to determine phenotype variability and disease severity of INF2-related FSGS globally.

TH-PO445
RAS Inhibition Delays Onset of Nephrotic Syndrome due to TRPC6-Mediated FSGS: A Case Report of a Sibling Pair
Ashley W. Carver, Dorey A. Glenn, Katherine D. Westreich. The University of North Carolina at Chapel Hill, Chapel Hill, NC.

Introduction: Transient receptor potential channel (TRPC6) is a slit diaphragm protein located on the podocyte, and a known genetic cause of focal segmental glomerulosclerosis (FSGS). Upregulation of TRPC6 channel activity is proposed to disturb podocyte structure, leading to proteinuria. ACE inhibitors (ACEi) demonstrate renoprotective benefits, reduction in proteinuria, and are commonly used to reduce proteinuria in FSGS. Here we describe progression to symptomatic nephrotic syndrome in a sibling pair with TRPC6 mediated steroid resistant FSGS as a function of early vs. late initiation of ACEi.

Case Description: Sibling A, the older of the two affected siblings, presented to care at 3 years of age with generalized edema, hypoalbuminemia (1.6g/dL), and nephrotic range proteinuria (UPCR 35mg/mg). Family history revealed that the child’s father had proteinuria since 12 years old, but his renal function was still normal at the age of 19. Genetic analysis revealed a novel heterozygous missense variant at c. 755 C > G, p. (Ala 252 Gly) which was a de novo variant and C-terminal side.

Discussion: Case 1 was the youngest case of developing ESKD and the first case manifesting CNS. In case 5, who was isolated-FSGS case, a variant near the DRS domain. In case 5, who was isolated-FSGS case, a variant near the DRS domain.
TH-PO468
Therapeutic Strategies for Podr138Q Nephrotic Syndrome
Pei-Chen Lu,1,2 Gavin I. Welsh,1 Moin Saleem.1 University of Bristol, Bristol, United Kingdom; 2Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

Background: The most common missense mutation in podocin, Podr138Q, results in steroid-resistant nephrotic syndrome. Podr138Q causes the podocin to be trafficked incorrectly resulting in it being trapped in ER and degraded leading to aberrant function of the slit diaphragm. Understanding the mechanism of this mis-trafficking and degradation may lead to new therapeutic strategies for treating this disease.

Methods: Both Podr138Q and Podr138Q were overexpressed in immortalized human podocytes. These cells were treated with MG132 (lysosome inhibitor), bafilomycin A1 (lysosome inhibitor), and kif-nanosine (Kif1 ER mannose 1 inhibitor). Podocin localization/trafficking was analyzed by western blotting and immuno-fluorescence.

Results: Podr138Q had higher co-localization coefficients with ER than Podr138Q (Fig 1). Podr138Q was mainly degraded by the lysosome, and Podr138Q degraded only by the proteosome (Fig 2A, 2B). Blocking podocin proteosomal degradation with MG132 resulted in Podr138Q being localized to plasma membrane lipid rafts (Fig 2C). Kif1 leads to the accumulation of high mannose N-glycan podocin (Fig 2B). High mannose N-glycan Podr138Q had affinity to calnexin (Fig 2D), and this implies that Podr138Q is degraded via the accumulation of high mannose N-glycan podocin (Fig 2B). High mannose N-glycan Podr138Q may lead to new therapeutic strategies for treating this disease.

Conclusions: Podr138Q is mainly degraded by the lysosome whereas Podr138Q undergoes ERAD. By using a proteasome inhibitor, Podr138Q can be rescued correctly trafficked to lipid rafts. This finding could suggest a new therapeutic target for medical intervention for Podr138Q nephrotic syndrome.

Funding: Private Foundation Support

TH-PO469
Efficacy and Mechanism of Dapagliflozin in Alport Syndrome
Qinmin Zheng, Shuwen Yu, Tong Jun, Yuanying Jin, Zhengying Fang, Qinjie Weng, Wen Du, Junru Li, Pan Xiaoxia, Xiangchen Gu, Jingyuan Xie. Shanghai Jiao Tong University Medical School Affiliated Ruijin Hospital, Shanghai, China.

Background: Alport syndrome (AS) is a hereditary kidney disease caused by COL4A3/A4/A5 mutations. Currently, the standard therapy is RASAI, thus new treatment for AS is urgently needed. SGLT2 inhibitor has been approved for the treatment of diabetic nephropathy and chronic kidney disease, while its therapeutic effect on AS is unknown.

Methods: We conducted an observational, single-arm, prospective study based on patients with AS. One variant caused FSGS phenotype. In vitro study, nonsense mutations produces truncated proteins and damaging the protein stability. Different AS gene variant proteins all significantly reduced the expression level of P53-34. The wild type might inhibit podocyte VEGF leading to shrinkage & immature glomeruli (H.Euda, JASN 2023).

Results: Nine AS patients with heterozygous mutations of COL4A3/A4/A5 were included in this study. One patient died during the study. The eGFR at last time was 58% decrease from baseline. The eGFR at time was 72.5 (61.7-80.1) ml/min/1.73m2. No adverse events were observed in these patients. Consistent with the observational study, the study animal also showed that Dapagliflozin significantly alleviated podocyturia (urinary albumin creatinine ratio). We also observed that mutant mice treated with dapagliflozin exhibited significantly reduced renal proinflammatory cytokines and fibrotic markers, including Ccl2, Ccl5, Cxc10, Vimentin, and Coll1a1 as compared to vehicle-treated mutant mice. These data were also supported by H&E and F4/80 IHC staining showing decreased immune cell infiltration in kidney tissue of dapagliflozin-treated mutant mice.

Conclusions: Alport syndrome is a promising treatment for AS patients, and further studies are required to elucidate the precise mechanism of SGLTI2 inhibitors on retarding AS progression.

Funding: NIDDK Support

TH-PO470
Phenotypic Spectrum Analysis and Molecular Mechanism Study of PAX2 Variants in the Chinese Population
Qian Shen, Hong Xu, Man Q. Sun. Children’s Hospital of Fudan University, Shanghai, China.

Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) is the leading cause of renal developmental failure in children. Dysfunction of transcription factors in PAX2 gene can cause human and mouse CAKUT. Variants in PAX2 gene are also reported to cause Caudal Segmental Glomerulocarcinosis (FSGS). However, the mechanism is not well studied.

Methods: Variants in PAX2 gene and phenotypic spectrum from 16 individuals were summarized. Functional effects of different PAX2 variants were confirmed by constructing wild-type and mutant PAX2 overexpression plasmids. Minigene splicing assay was performed to test function of splicing variants. The plasmid of mutant PAX2 gene associated with FSGS was also transfected into human podocytes. Meanwhile, we further performed RNA-seq to analyze the different signaling between different phenotype.

Results: A total of 16 individuals with 12 different variants PAX2 variants were included in this study. Among them, nonsense mutations (5/16, 31%) were the main type of PAX2 variants. One variant caused FSGS phenotype. In vitro study, nonsense mutations produces truncated proteins and damaging the protein stability. Different PAX2 gene variant proteins all significantly reduced the expression level of P53-34. The wild type might inhibit podocyte VEGF leading to shrinkage & immature glomeruli (H.Euda, JASN 2023).

Conclusions: Our study showed different PAX2 gene variants cause different phenotype. Functional study showed PAX2 gene mutations associated with CAKUT phenotype were mainly involved in PI3K-Akt signaling pathway, neural development, extracellular matrix and other factors, while FSGS phenotype-associated PAX2 gene variants, mainly involved in cell adhesion, actin cytoskeleton related to podocyte development.

TH-PO471
A New BMP-4 Gene Mutation Associated with Adult Focal Segmental Glomerulosclerosis (FSGS)

Introduction: FSGS has been associated with numerous gene defects in children, adolescents & adults. A new BMP-4 gene mutation associated with adult onset FSGS has been successfully used with combined superantithrombotic ACE inhibitors with an ARB.

Conclusions: In 1994 a 40 year(yr) old non-smoking obese man developed nephrotic syndrome & hypertension. His daily protein excretion was 3.6 gms, sothalamate 81 mg/ml, s creatinine 1.2 mg/dl, s albumin 3.0 g/dl & cholesterol 400 mg/dl. He had no signs of systemic diseases, C3 & C4 complement levels, ANA, ENA, immunofluorescence, hepatitis A, B & C were normal. A renal biopsy showed: Light: 3/16 hypercellular glomeruli - focal glomerular sclerosis & moderate tubular & interstitial sclerosis. IF: completely negative. EM: increased mesangial matrix with focal foot process fusion, thickened basement membranes & no immune deposits. A Ds of FSGS. NOS possibly linked to obesity was made. He was treated with supervised physical therapy & diet, then to 2.3 gm in 2015 when treated with dapagliflozin & valsartan 160 mg a day for 30 years despite retraction of the Lancet COOPERATE trial in 2012. His decrease in gfr was only 1.8 ml/min/hr. His urine protein decreased to 1 gm per day & was only 1 gm/d until 2015 when it increased to 1.5 gm/d & then to 2.2 gm in 2022. His gfr gradually declined to 65 ml/min in 2000, 50 ml/min in 2010, 35 ml/min in 2015 & 29 ml/min in 2023. A Renasight gene panel (Natera, Austin, TX) showed: a c 124G>C (p.Ala42 Pro) mutation, codon 42 missense on exon 3 guanine for cystine.

Discussion: Loss of function mutations in BMP-4 are associated with CAKUT. A BMP4 mutation of function mutation in animal studies shows increased SMAD which inhibits podocyte VEGF leading to shrinkage & immature glomeruli (H.Euda, JASN 2023). Underline represents presenting author.
Molecular Mechanisms of Novel NPHS2 Pathogenic Variants and Proposed Therapeutic Interventions
Asmaa S. Abu-Maziad, The University of Arizona Health Sciences, Tucson, AZ.

Background: The human NPHS2 gene encodes podocin protein, an essential component of GBM. Mutations in NPHS2 causes steroid-resistant FSGS/nephrotic syndrome. Podocin signaling is essential to the structure and function of glomerular podocytes. Defining the molecular dysfunctions of this novel NPHS2 mutations is imperative to improving our understanding of the dynamic roles of podocin protein and potential therapeutic interventions.

Methods: We study the molecular and biochemical properties of the NPHS2 pathogenic variants and podocin protein using patient-derived induced pluripotent stem cell (iPSC) and reprogrammed podocytes. To further study the implications of the W122S mutation, in silico analysis was performed. ColabFold was used to predict the structure of wild-type podocin and W122S mutated podocin.

Results: Try122 is located in podocin’s transmembrane region, where the protein inserts itself into the inner leaflet of the plasma membrane. It is here where podocin recruits neprin and CD2AP into lipid rafts, forming a multiprotein signaling complex. This complex was found to be integral in the formation of the podocyte’s actin cytoskeleton. Given its predicted location on the outer surface of the transmembrane region of podocin, Try122 supports podocin’s ability to embed itself in the plasma membrane.

Conclusions: Distinct differences in lipophilicity and structure of the transmembrane domain are revealed. Further work using our patient’s derived stem cell will allow us to understand the cascade and therapies.

TH-PO475
Molecular Mechanisms of Neonatal-Onset WT1-Related Glomerulopathy
Eli Hildebrandt1, Hei Yang2, Yu Cao2, Xing Zhang2, Xiaodong Cheng,2 Friedrich Hildebrandt,1 Nina Mann,1 Boston Children’s Hospital, Boston, MA; 2The University of Texas MD Anderson Cancer Center Children’s Cancer Hospital, Houston, TX.

Background: Human mutations in WT1, or Wilms’ tumor 1, lead to severe, progressive glomerulopathy marked by heavy proteinuria and progression to end-stage renal disease (ESRD). A subset of patients with WT1 variants present at birth with rapid progression to renal failure. We sought to determine the genotypic spectrum and molecular mechanisms causing neonatal onset WT1-related disease.

Methods: We performed a systematic literature review of neonatal-onset (<1 month of age) WT1-related glomerulopathy and of all cases with the WT1 p.Arg467Trp or p.Arg467Gln variants. Cell biological techniques were utilized to assess the cellular localization, DNA binding, and transcriptional activity of wild type and mutant WT1 proteins.

Results: We identified 21 cases with pathogenic WT1 variants who had disease onset by 1 month of age and ESRD by 6 months. 17/21 (80%) cases had mutations at p.Arg467 variant, which is a common mutational hot-spot. We found that nearly all individuals with the p.Arg467Trp variant had a more variable disease course (median age at ESRD 2.1 months, n=40), while those with the p.Arg467Gln variant had a more variable disease course (median age at ESRD 2.1 months, n=40). In vitro studies showed that the wild-type WT1 protein (in the -KTS isoform) localized diffusely within the cell nucleus, while both the p.Arg467Gln and p.Arg467Trp mutant proteins (in the -KTS isoform) localized to nuclear subdomains and failed to activate transcription. The p.Arg467Gln and p.Arg467Trp mutant proteins also have significantly reduced DNA binding, suggesting that these mutations do not function in a dominant manner via activation of aberrant transcriptional pathways.

TH-PO474
Molecular Mechanisms of Novel NPHS2 Pathogenic Variants and Proposed Therapeutic Interventions
Asmaa S. Abu-Maziad, The University of Arizona Health Sciences, Tucson, AZ.

Background: The human NPHS2 gene encodes podocin protein, an essential component of GBM. Mutations in NPHS2 causes steroid-resistant FSGS/nephrotic syndrome. Podocin signaling is essential to the structure and function of glomerular podocytes. Defining the molecular dysfunctions of this novel NPHS2 mutations is imperative to improving our understanding of the dynamic roles of podocin protein and potential therapeutic interventions.

Methods: We study the molecular and biochemical properties of the NPHS2 pathogenic variants and podocin protein using patient-derived induced pluripotent stem cell (iPSC) and reprogrammed podocytes. To further study the implications of the W122S mutation, in silico analysis was performed. ColabFold was used to predict the structure of wild-type podocin and W122S mutated podocin.

Results: Try122 is located in podocin’s transmembrane region, where the protein inserts itself into the inner leaflet of the plasma membrane. It is here where podocin recruits neprin and CD2AP into lipid rafts, forming a multiprotein signaling complex. This complex was found to be integral in the formation of the podocyte’s actin cytoskeleton. Given its predicted location on the outer surface of the transmembrane region of podocin, Try122 supports podocin’s ability to embed itself in the plasma membrane.

Conclusions: Distinct differences in lipophilicity and structure of the transmembrane domain are revealed. Further work using our patient’s derived stem cell will allow us to understand the cascade and therapies.
Conclusions: WT1 mutations at the p.Arg839 and p.Arg6467 loci are associated with neonatal-onset Alport syndrome. The progression to ESKD in the p.Arg6467Gln variant leads to a more severe disease than the p.Arg6476Trp variant but there was no functional difference between the two mutant proteins with regards to cellular localization or DNA binding. Further studies will be needed to better elucidate the mechanisms of neonatal-onset WT1-mediated glomerulomegaly.

Funding: NIDDK, Support, Other NIH Support - National Institutes of Health. Cancer Prevention and Research Institute of Texas

TH-PO476 Rescue Mechanism for Glomerular Endothelial Lipid Metabolic Dysfunction in Alport Syndrome Hasnol Soloyan,1 Matthew E. Thornton,2 Gereny Clair,3 Janielle M. Cuela,2 Qi Zhang,1 Senta K. Georgia,2 Paolo Cravedi,2 Stefano Da Sacco,1,2 Laura Perin,1,2 Sargis Sargsyakyan.1,21 Children’s Hospital Los Angeles, Los Angeles, CA; 2University of Southern California Keck School of Medicine, Los Angeles, CA; 3Icahn School of Medicine at Mount Sinai, New York, NY; Pacific Northwest National Laboratory, Richland, WA.

Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD). In Alport syndrome (AS, caused by mutations in collagen IVα3α5α4) damage to the glomerular endothelial cells (GEC) occurs before onset of heavy proteinuria and is characterized by altered fenestration size and glyocalyx deposition. Despite this evidence, the role of GEC in Alport progression is poorly understood. Here, we elucidate the role of lipids in GEC injury in an animal model of AS, and the potential of using amniotic fluid stem cell (AFSC) derived extracellular vesicles (EVs) as a rescue strategy to restore glomerular homeostasis.

Methods: The phasor approach to FLIM (fluorescent lifetime imaging microscopy) was applied to study the potential metabolic changes in the kidneys (and particularly in the glomerulus and GEC) of AS and WT mice. GEC isolated by FACS from tdtomato-reporter AS and WT mice at 4-months of age were compared by bulk RNA-seq and lipidomics. In vitro, silencing experiments on primary human GEC were performed to study the role of fatty acid synthesis (FASN) in GEC metabolic dysfunction. FASN-carrying AFSC-EVs and control nanoparticles were applied both in vitro and in vivo to restore lipid homeostasis in GEC.

Results: In AS mice, RNAseq analysis of GEC revealed changes in the metabolic genes, (including FASN) and pathways associated with uptake, synthesis and oxidation of lipids. Fluorescence microscopy showed changes in the metabolic fingerprint of the GEC correlated with increasing age and severity of disease in AS mice. Lipidome analysis found high abundance of triglycerides in GEC isolated from AS. We confirmed accumulation of lipid droplets in the glomeruli of AS mice, as well as in FASN KO human primary GEC. In vivo, genotyping experiments suggest potential metabolic dysfunction in GEC. AFSC-EVs treatment restored lipid homeostasis in GEC, both in vitro and in vivo.

Conclusions: We report for the first time a lipid metabolic dysfunction in Alport GEC, and the ability of AFSC-EVs to rescue this phenotype. Therefore, better understanding of the role of GEC in AS could lead to the development of targeted new therapies for the treatment of this and other forms of CKD.

Funding: Private Foundation Support

TH-PO477 Apolipoprotein M Treatment Restores Kidney Function in Mouse Model of Alport Syndrome Judith T. Molina David,1,2 Matthew Tolerico,1,2 Jin Ju Kim,1,2 Yelena Drexler,1 Sandra M. Merscher,1 Alessia Fornoni,1,2 University of Miami Katz Family Division of Nephrology and Hypertension, Miami, FL; 2Peggy and Harold Katz Family Drug Discovery Center, UM, Miami, FL.

Background: Studies suggest that altered Apolipoprotein M (ApoM) expression is associated with dyslipoproteinemia, atherosclerosis and possibly diabetes, obesity, and inflammation. However, little is known about the role of ApoM in the kidney. We previously reported decreased glomerular ApoM expression in glomerular diseases. ApoM is a protein linking cholesterol and sphingolipid metabolism, which are both important players in the development of glomerular injury in Alport Syndrome (AS) among other glomerular disorders. Here we test the hypothesis that systemic replacement of ApoM in AS protects from the development of kidney failure.

Methods: To study the role of ApoM in the kidney, we analyzed renal ApoM expression in a mouse model of progressive renal disease associated with Alport Syndrome (Col4a3 knockout). We found reduced mRNA and protein expression of ApoM in the kidneys of Col4a3 KO mice. To investigate if APOM replenishment would improve renal function in this mouse model, we injected Col4a3 KO mice with recombinant human ApoM (rh-ApoM). Three groups of mice were studied: (1) Col4a3 −/− (WT) + vehicle, (2) Col4a3 −/− (KO) + vehicle, and (3) Col4a3 −/− (KO) + rh-ApoM. rh-ApoM was administered by weekly intraperitoneal injection starting at 4 weeks of age and until sacrifice at 8 weeks of age.

Results: ApoM mRNA and protein expression were markedly reduced in glomeruli and renal cortex from Col4a3 KO mice compared to WT mice. Treatment of Col4a3 KO mice with rh-APOM normalized renal APOM levels and prevented the development of renal failure (serum BUN and creatinine), proteinuria (urinary albumin/creatinine ratio), and protected from the development of glomerulosclerosis, tubular atrophy and dilatation.

Conclusions: Our results suggest that restoring renal APOM levels could be an experimental model of AS protect from renal failure and that treatment with rh-APOM may represent a novel therapeutic strategy for the treatment of glomerular diseases.

Funding: NIDDK Support

TH-PO478 Exploring the Molecular Basis of Ramipril-Induced Nephroprotection in Alport Syndrome Tomohiko Yamamura, Emily Williams, Mychel R. Morais, Rachel Lennon. Welcome Trust Centre for Cell Matrix Research, Manchester, United Kingdom.

Background: Renin-angiotensin system inhibitors such as angiotensin-converting enzyme Inhibitors (ACEI) play a central role in the treatment of CKD, and they are known to reduce proteinuria and extend kidney survival in Alport syndrome. This beneficial effect has been explained by the reduction of intraglomerular pressure and the inhibition of inflammation and subsequent fibrosis. However, the actual molecular changes induced by ACEI in the kidneys are yet elucidated.

Methods: The ACEI ramipril was administered orally (n=10 each) to a mouse model of Alport syndrome (Col4a5 knockout). Treatment was initiated at five weeks (early treatment group) or ten weeks (late treatment group) and continued until 16 weeks of age, with comprehensive evaluation including functional studies, imaging and mass spectrometry-based proteomic analysis kidney tissue.

Results: The mean urinary albumin-creatinine ratio ± SEM was significantly lower (p<0.01) in both the early treatment group (1417±70.3) and the late treatment group (2984±1116) compared to the no-treatment group (8902±1320). No significant differences were observed between the early and late treatment groups. Although serum BUN was not significantly different between the no-treatment and treatment groups, light microscopy showed that the early-treatment group had less cellular infiltration of the interstitial area than the no-treatment and the late-treatment group. Proteomic analysis revealed distinct proteomic profiles not only between Alport mice and wild-type mice but also between ACEI-treated mice and non-treated Alport mice. With pathway enrichment analysis, we found significant enrichment for terms associated with chaperonin-mediated protein folding, extracellular matrix organisation and glycosaminoglycan metabolism in ACEI-treated mice compared to untreated mice.

Conclusions: Our results suggest that the molecular mechanisms of the nephroprotective effects of ACEIs, such as the reduction of proteinuria and improved histological findings in the Alport mouse, involve proteins related to chaperonin-mediated protein folding, extracellular matrix organisation and glycosaminoglycan metabolism pathways in the kidney.

TH-PO479 Adult Male Patient of Ciq Nephropathy with Heterozygous Pathogenic COL4A4 Variant Karen Kim,1 Takuya Fujimaru,1,2 Chiharu Aizawa,1 Nozomi Kadota,1 Yuji Ito,1 Masahiko Nagahama,1 Fumika Taki,1 Takayasu Mori,1 Eisei Sohara,2 Shinichi Uchida,2 Masaaki Nakayama.1 St. Luke’s International Hospital, Tokyo, Japan; Tokyo Medical and Dental University, Tokyo, Japan.

Introduction: Autosomal dominant Alport syndrome (ADAS) is a disease with heterozygous pathogenic COL4A3 or COL4A4 variants. ADAS is considered to have better renal prognosis than X-linked Alport syndrome and less likely to develop focal and segmental glomerulosclerosis. However, ADAS could predispose to IgA glomerulonephritis (IgAN). We report an adult male patient of Ciq nephropathy with ADAS.

Case Description: A 47-year-old man admitted our hospital for renal biopsy. He had hematuria and proteinuria since childhood. Six years before admission, he had hypertension and chronic kidney disease (serum Cr was around 2.5 mg/dL). His maternal grandfather, maternal aunt, son, and daughter had hematuria. No one, including him, suffered from hearing loss. One year before admission, his renal function deteriorated (Cr 3.37 mg/dL) and severe proteinuria appeared (5–7 g/day). Renal biopsy showed that 25% of glomeruli had global sclerosis and 60% had segmental glomerulosclerosis. Immunofluorescence shows the presence of immune complex and segmental mesangial staining. For Ciq and IgM Electron microscope revealed diffuse intra-membranous deposits with GBM thickening. Genetic analysis showed that he had heterozygous pathogenic variant in COL4A4 (c.2510G>C:p.Gly837Ala). We diagnosed him as Ciq1 nephropathy with ADAS and started 1 mg/kg of corticosteroid for Ciq nephropathy. We added cyclosporine after 1 month of treatment due to refractory proteinuria. However, because cyclosporine worsened renal function and he suffered from avascular necrosis of femoral head, immunosuppressive therapy was tapered.

Discussion: As far as we know, this is the first case of Ciq nephropathy with ADAS. ADAS may also predispose to glomerulonephritis other than IgAN. Additionally, concomitant glomerulonephritises could worsen renal prognosis in ADAS patients.

TH-PO480 Genotype-Phenotype Correlations in Alport Syndrome: A Single-Center Experience Stefan N. Lujinschi, Bogdan Obrissa, Bogdan Sorohan, Roxana A. Jurubita, Alexandra Vorincu, Gener Ismail. Fundeni Clinical Institute, Bucharest, Romania.

Background: Alport syndrome is a common and heterogeneous genetic kidney disease, oftentimes leading to end-stage kidney disease (ESKD). Due to the growing availability of genetic testing, understanding the interplay between genetic and clinical features has become essential for individualized prognostication.

Methods: This is a single-center, retrospective study that included 36 adults with type IV collagen mutations. Our scope was to describe how genetic features influence renal survival, i.e., the age at renal replacement therapy initiation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Results: A total of 28 different mutations were identified, out of which 8 had not been previously described. Mutations affecting each of the type IV collagen α chains were equally prevalent (33.3%). Six patients had multiple mutations. One patient had mutations involving all α chains. Five patients also had mutations involving podocyte and glomerular basement membrane proteins, but with no significant differences regarding proteinuria and renal survival. Most patients had a family history of kidney disease (71%). The most prevalent clinical picture was nephritic syndrome (64%), followed by isolated hematuria (24%). One third of the subjects had extrarenal manifestations, such as hearing loss (28.6%) and eye abnormalities (7.1%). There were no significant differences in laboratory findings at diagnosis between patients with COL4A3, COL4A4 and COL4A5 mutations. Eighteen patients presented with (41.6%) or later developed (8.3%) ESKD at a median age of 25.5 years old (IQR, 21.5-37.25). Six patients underwent kidney transplant. Overall kidney survival was 40.55 years (95% CI, 35.55-45.55). COL4A4 group displayed a significantly better renal survival when compared to COL4A3 (p=0.027). Hearing loss was associated with a significantly poorer renal prognosis (p<0.001). For a subgroup where follow-up data were available (44.4%), the 5-year renal survival was 68.6% and in patients with multiple mutations, a lower renal survival at 27 months was noticed (p=0.014).

Conclusions: In our study, COL4A3 mutations, presence of multiple mutations and a personal history of hearing loss were associated with a poorer renal prognosis.

TH-PO481

The NOX Inhibitor Setanaxib Combined with Ramipril Reduces Glomerular Function Decline and Fibrosis in a Mouse Model of Alport Syndrome

Thierry Christophe,1 Maryline Fresquet,2 Mychel R. Morais,2 Craig Lawless,3 Rachel Lennons.2 Caliditas Therapeutics AB, Stockholm, Sweden; 2Wellcome Centre for Cell-Matrix Research, Division of Cell Matrix Biology and Regenerative Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, and Regenerative Medicine, School of Biological Sciences, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom.

Background: Alport syndrome is a rare genetic disorder, which presents in childhood or adolescence. It is caused by genetic variants affecting type IV collagen, leading to progressive kidney damage. Setanaxib, an NADPH oxidase (NOX) inhibitor, has been shown in preclinical models to reduce inflammation and fibrosis – mechanisms known to play a role in Alport syndrome disease progression. In this study, we assessed the therapeutic potential of setanaxib in a mouse model of Alport syndrome.

Methods: Four-week-old Col4a3+/− mice on 129/SvJ background (n=10 per group) were given 10 mg/kg ramipril (an ACE inhibitor [ACEI]) in drinking water, 60 mg/kg setanaxib once daily by gavage, setanaxib and ramipril combined, or vehicle, over 4 weeks. At the end of the study, kidneys were analyzed by imaging and proteomics.

Results: Setanaxib and ramipril combined also significantly decreased glomerular sclerosis (scored 0-6) at 6 and 8 weeks of age in mice receiving ramipril alone, with a further reduction seen in mice receiving setanaxib and ramipril combined (Figure 1A,B). Histologic analysis indicated that setanaxib and ramipril combined also significantly decreased glomerular sclerosis (scored by a pathologist) and overall fibrosis (Figure 1C-E). Proteomic and in silico analyses also reported increased detection of glomerular basement membrane and collagen proteins with setanaxib and ramipril combined.

Conclusions: These results indicate that setanaxib, when combined with the standard of care ACEI, induced mechanisms that reduced the decline in glomerular function and fibrosis in a well-established mouse model of Alport syndrome.

Funding: Commercial Support - Caliditas Therapeutics

TH-PO482

Beyond COL4A: Combined Renal Histopathology and Genetic Testing Reveals the Genetic Complexity of Thin Glomerular Basement Membrane Disease

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Background: Improved access to genetic testing is changing the diagnostic landscape of chronic kidney disease (CKD). While renal histopathology represents the current gold standard in the differential diagnosis of CKD, the incremental diagnostic yield of genetic testing remains unknown. We aim to investigate the combined diagnostic yield of histopathology and genetic testing, and we seek to identify novel correlations between histopathologies and histogenetic phenotypes.

Methods: We identified 114 patients from two academic medical centers in Boston, MA, who underwent both, kidney biopsy and kidney panel genetic testing between 1/1/2020 and 5/1/2023. We assessed pathologic diagnostic and quantifiable ultrastructural phenotypes. We then analyzed corresponding genotypes for diagnostic variants and variants of uncertain significance (VUS). Variants were grouped by genes associated with CAKUT and podocytopathy (or steroid resistant nephrotic syndrome, SRNS).

Results: Glomerular basement membrane thinning was found in 47/114 patients, representing the most common ultrastructural abnormality. We found 16 COL4A variants in 14 patients with GBM abnormalities (8 diagnostic variants, 8 VUS). The remaining patients with GBM abnormalities had variants in dominant CAKUT genes (14 variants in 12 patients) and dominant SRNS genes (15 variants in 13 patients). 4 patients had exclusively recessive SRNS variants identified. In 8 patients, GBM abnormalities did not correlate with any variant of the above categories. 12/18 patients with COL4A variants had ultrastructural evidence of segmental or diffuse podocyte foot process effacement, and 5/18 had a diagnosis of primary FSGS.

Conclusions: In our retrospective cohort of patients who underwent kidney biopsy and genetic testing, thin glomerular basement membranes represented the most common ultrastructural finding. In only one third of these patients, a COL4A variant was found. Variants in dominant CAKUT and SRNS genes were the next most common findings, reflecting the genetic complexity of TBMD beyond COL4A. We identified alternative mechanisms of disease causation. Genetic testing for COL4A variants alone would have missed the diagnosis of TBMD in 68.9% of cases, while 3.5% of test results were found to be false positive.

Funding: NIDDK Support

TH-PO483

Diagnostic Utility of Characterizing Glomerular Basement Membrane (GBM) Collagen IV Changes by Quantitative Immunofluorescence in Paraffin Sections from FSGS Patients Carrying COL4A3/4/5 Variants

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Background: Variants in COL4A3/4/5 genes are the most common genetic abnormalities associated with FSGS patients without typical Alport syndrome (AS), linking glomerular basement membrane protein (GBM) collagens (collIV) aberrations and podocytopathy. However, variant pathogenicity is often unclear.

Methods: We developed a new method of immunofluorescence staining for collagen α2(IV) and α1(IV) on kidney paraffin sections and used Airyscan confocal microscopy to assess colIV levels in 17 idiopathic FSGS patients with pathogenic/likely pathogenic (P/LP) variants, variants of uncertain significance (VUS), and likely benign (LB) variants in COL4A3/4/5 genes, respectively. Samples from 2 nephrectomies, 3 transplant surveillance biopsies, and 6 biopsies from FSGS patients without COL4A variants were used as controls.

Results: Our approach demonstrated collagen α3(IV) and α1(IV) levels in the GBM as two distinct layers, which enabled quantitative comparisons (Figure 1). The ratios of the mean fluorescence intensities of collagen α5(IV) to α1(IV) (α5:α1 FI ratios) and the ratios of the thicknesses of α5(IV) to α1(IV) (α5:α1 thickness ratio) were calculated to represent the level of collagen α3(IV) and α1(IV) in the GBM collagen (collIV) aberrations and podocytopathy. We identified 3 VUS patients with significantly reduced α5:α1 FI and thickness ratios, suggesting these variants could in fact be pathogenic.

Conclusions: Our approach can serve as a new diagnostic tool to identify the subgroup of FSGS patients with underlying pathogenic COL4A4 variants, which can be confirmed with genetic testing. This may help guide immunosuppressive therapy for FSGS.

Funding: NIDDK Support
Sex Differences in Glomerular Protein Expression in Mice with Autosomal Recessive Alport Syndrome

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Background: Alport syndrome (AS) is a monogenic disorder that leads to progressive kidney disease, ear, and ocular abnormalities. It is caused by pathogenic variants in COL4A3, COL4A4, or COL4A5, which encode the α3, α4, and α5 chains of type IV collagen. COL4A3 and COL4A4 reside on chromosome 2q36, while COL4A5 is on the X chromosome. We evaluated for sex differences in mice with autosomal recessive AS.

Methods: We compared differences in global protein expression in isolated glomeruli between 1-day-old male and female Col4a3 knockout (KO) and wildtype (WT) mice with mass spectrometry (MS). MaxQuant was used for analysis and statistical tests were done on Perseus. Pathway analysis was performed using Gene Ontology.

Results: At postnatal day 1 (P1), we observed more severe disease in male compared to female Col4a3 KO mice, as evidenced by higher urine albumin-creatinine ratios (uACR) (1088 mg/mmol vs. 873.6 mg/mmol, p=0.4). 309 significantly differentially expressed proteins in the glomeruli were identified, of which 208 were downregulated and 101 were upregulated in male Col4a3 KO mice. We also compared P1 WT male and female mice and no differentially expressed protein was detected at baseline. Interestingly, the well-known podocyte apical surface transmembrane sialoglycoprotein, podoculin, was upregulated in males compared to female Col4a3 KO mice. Pathway analysis showed that Col4a3 KO decreased male mice also had decreased biological processes suggestive of impaired glomerular structure maintenance such as actin filament bundle assembly, cell morphogenesis involved in differentiation and endoplasmic reticulum-nucleus signaling pathway. By contrast, pathways including peptide biosynthetic process and ATP biosynthetic process were found to be increased in male Col4a3 KO mice, possibly due to increased compensatory mechanisms.

Conclusions: One day old male compared to female Col4a3 KO mice display more severe disease. Podoculin has been reported to be excrated in urine due to podocye loss and we postulate that its upregulation in male Col4a3 KO mice may represent compensation. Overall, glomerular proteomic comparison highlights biological pathways that can explain phenotypic differences between male and female mice with autosomal recessive AS, though its mechanistic drivers are unclear.

Funding: Private Foundation Support

Mouse and Human Studies Support DSTYK Loss of Function as a Low Penetrance and Variable Expressivity Risk Factor for Urinary Tract Anomalies and Movement Disorders

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Background: Previous work identified rare variant in DSTYK in humans with congenital anomalies of the kidney and urinary tract (CAKUT). DSTYK coding variants exist at low frequency in the general population, complicating genetic interpretation. Mouse and human studies were used to clarify the association, penetrance and expressivity of DSTYK variants.

Methods: We phenotypically characterized Dstyk knockout mice on 3 genetic backgrounds (C57BL/6J, FVB/NJ and C3H/HeJ). We expanded, characterized and re-sequenced the original family segregating the DSTYK c.654+1G>A splice-site variant (referred to “splice variant” below). DSTYK loss-of-function (LOF) and the splice-site variants were annotated in individuals across different phenotypes: a) CAKUT, b) Epilepsy, and c) amytrophic lateral sclerosis (ALS) vs. controls. PhEWS analysis was performed using UKBB data.

Results: C57BL/6J Dstyk-/- mice exhibited a 23% penetrance of obstructive uropathy (OU). FVB/NJ Dstyk-/- mice showed a similarly low penetrance, but with added phenotypes of hypoplasia and partial duplication of the kidney and proximal ureter. C3H/HeJ mutants showed a 40% penetrance of OU, but with mild-to-moderate severity. Expansion, re-analysis and re-sequencing of the original family segregating the rare splice-site variant showed low penetrance and no alternative genetic causes for CAKUT. LOF DSTYK variant burden showed significant excess for CAKUT (OR=9.13, P=6.50x10-3), Epilepsy (OR=6.20, P=1.35x10-2), vs. controls. Enrichment analysis for the splice variant was significant for epilepsy (OR=6.04, P=1.72x10-2). Literature review and exploratory PhEWS supported association with neurological disorders.

Conclusions: Mouse and human data support causality for DSTYK LOF variants. Large sequencing studies (e.g. >200,000 cases) are required to fully assess the contribution of DSTYK rare variants to low-penetrant underlying traits with relatively common population prevalence such as obstructive uropathy. Therefore, while DSTYK LOF variants should not be used to ascertain diagnosis or risk stratification, they may be used in clinical settings when coupled with inheritance information and clinical plausibility.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
TH-PO487

Tofacitinib Suppresses JAK/STAT Pathway Hyperactivity Ex Vivo in Pediatric Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) accounts for approximately 3 to 5% of cases of pediatric nephrotic syndrome. JAK/STAT pathway is an important signaling pathway that plays a critical role in the pathogenesis of FSGS. In this study, we evaluated the extracellular signal-regulated kinase (ERK) and JAK2/STAT3 signaling activities in patient PBMCs.

Methods: PBMCs were isolated from ten healthy controls and five children with isolated FSGS (mean +/- SD age 20.1 +/- 9.3 years). PBMCs were stimulated with patient plasma or control PBMC culture supernatant, and flow cytometry was used to measure JAK2/STAT3 phosphorylation.

Results: Significant basal phosphorylation of JAK2 was observed in control PBMCs (p < 0.01). Stimulation with patient plasma led to a decrease in JAK2/STAT3 phosphorylation, indicating increased JAK2/STAT3 hyperactivity. The JAK1 gain-of-function mutation has not been thoroughly studied. We recently identified JAK1 gain-of-function mutation in a pediatric patient with membranoproliferative glomerulonephritis, and this mutation may be an emerging target for therapy.

Conclusions: Our findings support the involvement of the JAK/STAT pathway in the pathogenesis of pediatric FSGS, and JAK inhibition may be a potential therapeutic approach.

TH-PO488

Validation of Multiple Office Blood Pressure Measurement: A Novel Tool for Evaluating Blood Pressure in Children

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Background: Blood pressure measurement (BPM) is a common procedure in clinical practice, but it can be challenging to obtain reliable values in children. Casual office BPM (gold standard) is all but accurate and ABPM may be difficult to perform or even multiple. Multiple Office Blood Pressure Measurement (mOBPM) was developed at our Institute in 2010 for evaluating BPM with serial and automated measurements (≥10 in at least 30 min) using standard oscillometric devices. BP values were uploaded in a software and coefficient of variation (CV) was calculated after excluding outlier values (≥5th and <95th centiles of the recorded values).

Methods: The present study compares results obtained with mOBPM vs ABPM in children addressed to our Center for suspected arterial hypertension (AH). Given that children develop myocardial hypertrophy soon after the development of AH, Cardiac Mass Index (CMI) was used as gold standard to categorize patients as hypertensive or normotensive.

Results: Twenty-five children were enrolled. AH was confirmed by increased CMI in 5 (20%) of them. ABPM identified 11 (44%) hypertensive children vs 12 (48%) identified by mOBPM. Sensitivity and specificity were 60% and 60% using ABPM vs 100% and 65% using mOBPM. PPV and NPV were 27% and 86% vs 42% and 100%, respectively.

Conclusions: The present analysis shows that mOBPM is more reliable than ABPM in the diagnosis of AH in children. We recommend the routine use of mOBPM for measuring BP since ABPM may lead to wrongful diagnosis, can provide misleading results because of children discomfort and is more time-consuming.

TH-PO489

Evaluating Pediatric Hypertension According to Different Guidelines Using the Multi-Institutional Electronic Health Record Database

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Background: Childhood hypertension is associated with cardiovascular morbidity and adult mortality. However, the burden of pediatric hypertension in Taiwan remains unclear. By using the multi-institutional electronic health record database, we aimed to evaluate the hypertension prevalence and treatment patterns in children.

Methods: We conducted a cross-sectional study using outpatient blood pressure (OBP) measurements obtained in routine care visits from the Chang Gung Research Database between 2009 and 2018 to evaluate guideline defined hypertension and patient-related factors of pediatric hypertension. Additionally, we examined the agreement on hypertension between the American Academy of Pediatrics (AAP) guidelines and the pediatric hypertension in the study setting ranged from 0.78–0.95 per 1000 persons between 1 and 17 years of age. Perfect agreement existed between the thresholds of the two guidelines for defining hypertension in 1–7, 8–17 and 18–17 years of age groups (all k static >=0.85), but the use of AAP threshold classified more children as having hypertension. Children and adolescents with hypertension often had complex chronic diseases and required substantial healthcare services in outpatient, emergency, and inpatient settings.

Conclusions: The present study provides evidence of guideline-based pediatric hypertension. The study results highlight the importance of regular blood pressure monitoring to identify and management of hypertension in children and adolescents. Further research is required to investigate the new thresholds on the identification of target organ damage in pediatric age.

Funding: Private Foundation Support

TH-PO490

Hypertension Associated with Hyper-Reninemic Hyperaldosteronism After COVID-19 Infection in a Pediatric Patient

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Introduction: COVID-19 was a leading cause of death among children and adolescents from Aug 2021 through Jul 2022, ranking 8th for all causes and 1st for infectious causes [Kompaniyets, 2022]. Children and adolescents are at risk for certain post-COVID complications. [Tadeo, 2023] [Flaxman, 2023]. In a prospective multicenter study in Turkey, 28% of the children ages 10-18 yrs had abnormal blood pressure 8 weeks after a mild COVID-19 infection, of whom 39.2% had stage 1 HTN [Uysal, 2022]. The pathophysiology of SARS-CoV-2 associated hypertension (HTN) remains unclear [Kukarni, 2022].

Case Description: A 13-yr-old male with no significant past medical history presents to the pediatric nephrology clinic for evaluation of HTN. He had COVID infection 9 mths ago and was noted to be hypertensive since then. He was asymptomatic. Vitals notable for BP 142/87 mmHg, BMI 31 kg/m². Exam was normal. Labs revealed normal CBC, urinalysis, electrolytes, creatinine, TSH, serum metabolite levels. Renin [4.2ng/mL/h] and aldosterone [717.5 ng/dL] levels were elevated. Renal US with doppler was unremarkable. MRA abdomen was negative for renal artery stenosis. 24-hour ABPM showed a daily average 135/70 mmHg and night average 140/73 mmHg. He was started on lisinopril with improvement in BP.

Discussion: Angiotensin converting enzyme 2 (ACE2), which is utilized by SARS-CoV-2 for entry into host cells, is widely expressed in the lungs, kidneys, testes, gut, adipose tissue, and brain. Infection within host cells mediates RAS overactivation. One hypothesis is that the increased activity of the ACE/Ang1/AT1 axis or the decreased activity of the ACE2/Ang-(1-7)/Mas Receptor axis generates pulmonary and neurogenic HTN [3]. We were able to rule out secondary causes in our patient with hyper-reninemic hyperaldosteronism and clinical response to lisinopril further supports this proposed mechanism. In a retrospective and prospective cohort study of adult patients, 21% of patients had unresolved HTN requiring treatment, 23 days post-discharge from the hospital or ER for COVID infection [Wrona, 2022]. In a cross-sectional study in Korea, an increase in the prevalence of HTN was observed among youths during the pandemic [Song, 2019]. There are limited studies available in pediatric patients in comparison to adults assessing prevalence and risk factors for HTN post COVID infection.
Melorheostosis and Renal Artery Stenosis in Solitary Kidney: A Pediatric Case

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Introduction: Melorheostosis is a rare bone dysplasia characterized by irregular hyperostosis of bones, diagnosed by typical radiological signs. Additionally, soft tissue changes have been described. We present a patient with melorheostosis and severe hypertension due to angioplasty-resistant renal artery stenosis (RAS) of the solitary kidney.

Case Description: A 7-years-old girl presented with severe hypertension. She had a history of stroke, absence of left kidney and scoliosis. In 2022, due to severe RAS she underwent percutaneous cutting balloon angioplasty with improvement on blood pressure control. Few days later the occurrence of subacute thrombosis was treated by drug eluting stent. MRI imaging of the spine revealed evidence of bony aspects compatible with melorheostosis. She was considered not suitable for vascular surgery and proposed to our Institution for nephrectomy or renal transplant. In our Institute she was treated with 9 antihypertensive drugs without reaching pressure control. Kidney ultrasound demonstrated in-stent fracture with severe restenosis. Two additional percutaneus angioplasties were attempted with no significant improvement. Then we introduced ACE inhibitor (ACEi) titrated to benefit on blood pressure control without compromising kidney function. Her blood pressure is now acceptable.

Discussion: Melorheostosis is associated with different malformation of soft tissue: we present the first case of melorheostosis with RAS in solitary kidney patient. RAS causes activation of RAAas to increase renal blood flow, leading to high blood pressure. The use of ACEi in patients with RAS is controversial: it acts directly on the causative mechanism of hypertension, but it leads to a reduction in the kidney blood flow, with the risk of developing acute kidney damage. Given the poor response to several angioplasties, we started with Ramipril at very low dose progressively increased until 0.11 mg/kg/die. She is treated now with 5 antihypertensive drugs, with better pressure control.

Renal Autotransplant in a Pediatric Patient with Neurofibromatosis Type 1 (NF1) and Renal Artery Stenosis (RAS)

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Introduction: Patients with NF1 are at increased risk for developing HTN, with RAS being the most common etiology. When medication fails, surgery may be indicated. We present the case of a 6-year-old boy with NF1 and RAS whose HTN was refractory to medical therapy and balloon dilation, but successfully treated with renal autotransplant.

Case Description: A 6-year-old boy with NF1 presented to our nephrology clinic with HTN. While his laboratory findings were unremarkable, computed tomography angiography (CTA) of the renal vessels revealed high-grade stenosis of the proximal right renal artery. He subsequently underwent arterial dilation and balloon angioplasty performed with IR. Following this, he presented in hypertensive urgency on dual-medical therapy. Repeat CTA redemonstrated severe right-sided stenosis; IR deemed the patient inappropriate for re-intervention. With 45% function of the right kidney on MAG-3 scan, our surgical colleagues offered renal autotransplant for consideration, which the family accepted. Six months postoperatively, his antihypertensive burden decreased from four-drug therapy to amlopidine monotherapy, with home blood pressures averaging 100/60 mmHg.

Discussion: Patients with NF1 are at increased risk of developing HTN. In those with RAS, a stepwise treatment approach from least-to-most invasive is preferred. If multidrug therapy and endovascular interventions fail, nephrectomy is then considered. Because stenosis may recur in the remaining kidney, renal autotransplant can be a preferred intervention for the treatment of refractory HTN with RAS in patients with preserved renal function. While more technologically challenging in pediatric patients, this intervention confers the benefit of retaining the native kidney.

Clinical Characteristics of Korean Pediatric Renovascular Hypertension According to Underlying Diseases


Background: Previously, Moyamoya disease (MMD) has been suggested as the most common cause of renovascular hypertension (RVH) in Korean children. The ring finger protein 213 (RNF213) has also been reported to be a causative gene of systemic vasculopathy in East Asia which results in MMD and RVH. This study aimed to evaluate the clinical characteristics of RVH and to compare the outcomes according to underlying diseases in Korean children.

Methods: A retrospective study was performed in patients who were diagnosed RVH at age under 18 years in Samsung Medical Center from 2010 to 2022. Medical records including sex, age, gene study, location of vascular lesion, treatment modalities and response to treatment were reviewed. RNF213-related vasculopathy designates systemic vasculopathy involving intracranial, renal, and pulmonary arteries with defined RNF213 mutation. According to underlying diseases, patients were grouped as RNF213-related vasculopathy (group 1, n=17), atypical vasculopathy (group 2, n=14), and others including congenital anomalies of kidney and urinary tract (CUTAK) and solid tumor (group 3, n=10).

Results: A total of 41 pediatric patients (19 males and 22 females, mean age of 10.1±4.8 years) were included. The mean value of initial blood pressure (BP) was 162/96 mmHg. Twenty five children were incidentally detected hypertension without symptoms while 15 patients showed neurological symptoms. Five patients were diagnosed RVH prior to MMD. Twenty patients underwent percutaneous transluminal angioplasty (PTA), 3 patients received bypass surgery, and 3 patients were done nephrectomy. Target organ damage was found in 15 patients (36.6%). Ostial vascular involvement was notably prevalent in group 1. For response to treatment, BP and stenotic lesions were poorly controlled in group 1 and 2 while overall outcome was relatively favorable in group 3. However, no statistical differences were revealed for the location and level of stenosis, treatment modalities, and outcomes between 3 groups.

Conclusions: The RNF213-related vasculopathy including MMD is the most common cause of RVH in Korean children in association with ostial vascular lesions. PTA and bypass surgery are mostly performed for patients with RNF213-related or atypical vasculopathy and clinical outcomes are relatively poor in these patients compared to other underlying diseases such as CUKAT or solid tumor.
Blood Pressure Control in Pediatric Hemodialysis: Data from the SCOPE Collaborative

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Background: The Standardizing Care to Improve Outcomes in Pediatric End Stage Kidney Disease (SCOPE) Collaborative is a quality improvement initiative focused on improving care of children on dialysis. Accurate blood pressure (BP) measurement is a focus of SCOPE as hypertension and cardiovascular disease is a leading cause of morbidity and mortality for children on dialysis.

Methods: Twenty centers collected two post-hemodialysis (HD) BP measurements per week for two weeks of each month using a standardized procedure (BP measurement bundle) to characterize the BP of children on HD from 4/1/2019-3/31/2022. The measurements were conducted via either oscillometric or manual methods. Hypertension was classified using the 2017 AAP hypertension guidelines.

Results: A total of 2,390 BP evaluation forms from 294 HD patients ≥3 years of age have been submitted to date. There were 4,713 weekly BP measurements. 1,457 (31%) measurements were from patients aged 3-12 years and 3,256 (69%) measurements were from patients aged 13 years and older. BP medications were prescribed at the time of 56% of measurements. Overall, 2,432 (52%) of the BP readings were abnormal. The majority (58.5%) of measurements in the 3-12 year olds were consistent with either Elevated, Stage I or Stage II hypertension. In the patients 13 years and older, 48.5% of measurements were abnormal, with 35% of the readings in Stage 1/II hypertension. More than 70% of the abnormal readings were based only on oscillometric measurement. 891 (18.9%) of all BP measurements were manual. In 41% of instances when a manual BP was repeated after an oscillometric reading, the BP classification changed, in 33% there was an increase in the BP classification, while the classification improved in 67% of cases.

Conclusions: The prevalence of elevated BP-hypertension is high amongst pediatric HD patients in the SCOPE collaborative when using a standardized BP measurement procedure and despite the use of antihypertensive therapy. While most of the BP classifications were based on oscillometric measurements instead of manual readings, the latter may help inform treatment decisions. Additional efforts by SCOPE will help to further define a clinically practical strategy for BP assessment in children on HD as a prelude to addressing therapeutic BP management.

Prevalence of Masked Hypertension and Its Association with Target Organ Damage in Children: A Systematic Review and Meta-Analysis

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Background: We investigate the prevalence of pediatric masked hypertension (MH) in children with various comorbid conditions and compare the risk of target organ damage in children with MH and normotensive children.

Methods: A systematic literature search on 9 databases included English publications from 1974-2022. MH was defined based on ambulatory blood pressure monitoring. LVMI was indexed to subject height and body surface area (g/m²). LVH was defined by the 95th percentile pediatric reference range, or a pediatric or adult cut-off. Correlation coefficients were transformed and pooled using a random effects model.

Results: Of 896 screened studies, 12 studies and 2028 children were included. MH prevalence was highest among those with chronic kidney disease (CKD) (18%), congenital cardiac conditions (24%), obesity (18%) and solid-organ or stem-cell transplant (24%). LVMI was elevated in the MH group (mean=35.48 g/m²) compared to the normotensive group (mean=31.10 g/m²), with a mean difference of LVMi was 4.06 g/m² (95% CI: 2.78-5.33) (fig). MH children were at 2.37 (95% CI: 1.41, 3.97) increased odds of LVH compared to normotensive children.

Conclusions: MH is common among children with congenital cardiac conditions, solid organ or stem-cell transplant, CKD, and obesity, and is associated with increased risk of LVH. These findings emphasize the importance of early screening, diagnosis, and treatment of hypertension in these high-risk children.

Risk of Target Organ Damage in Pediatric CKD Patients with Ambulatory Hypertension: A Systematic Review and Meta-Analysis

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Background: The objective of this systematic review is to determine the association between ambulatory hypertension and left ventricular mass index (LVMI) as well as ambulatory blood pressure monitoring (ABPM) parameters in youth with CKD.

Methods: A systematic literature search on 9 databases included English publications from 1974-2022. LVMI was indexed to subject height and body surface area (g/m²). Correlation coefficients were transformed and pooled using a random effects model.

Results: Of 1,128 screened studies, 16 studies and 2,254 children and adolescents were included. LVMI was elevated in the hypertensive group compared to the normotensive group (mean difference: 6.22 g/m², 95% CI: 4.80-7.65). Hypertensive children were at 3.34 (95% CI: 2.38-4.68) increased odds of left ventricular hypertrophy compared to normotensive children. Estimates of pooled correlation coefficients demonstrated nighttime systolic (r=0.46, 95% CI=0.36, 0.56) and daytime systolic (r=0.45, 95% CI=0.33-0.53) BP to have the strongest positive linear relationship to LVMI.

Conclusions: Pediatric CKD patients with ambulatory hypertension especially during nighttime are at significant risk of increased LVMI. Adequate blood pressure control among children with CKD is imperative to avoid the risk of target organ damage and future cardiovascular disease.
Association of Isolated Nocturnal Hypertension (INH) and Target Organ Damage in Light of the 2022 American Heart Association (AHA) Pediatric Ambulatory Blood Pressure Monitoring (ABPM) Guidelines


Background: Pediatric INH, previously defined by the 2014 guidelines as sleep blood pressure (BP) >95th%ile for sex and height, is associated with increased risk of target organ damage (TOD). In 2022, AHA guidelines lowered sleep BP thresholds to 110/65mmHg. The aim was to determine the association of INH and TOD according to the new guidelines.

Methods: A retrospective chart review of ABPMs from adolescents 13-21 years old between 2015-2022 was performed. ABPM phenotypes were normotension, INH, isolated daytime hypertension (IDH), and sustained day-night HTN. The primary outcome was left ventricular hypertrophy (LVH), defined as LVMI >95th%ile. Pearson's chi-squared, Wilcoxon rank-sum, and logistic regression were utilized as appropriate.

Results: Of 353 ABPM reports (median age 16, 73% male), 25% (N=89) classified as INH by 2014 guidelines, while 45% (N=115) classified as INH by 2022 guidelines. Hypertensive sleep BPs bordered the 110/65mmHg cutoff; median systolic BP was 116mmHg [IQR 112,122] and median diastolic BP was 62mmHg [58,68] (Table 1). Echos performed within 6 months of ABPM were reviewed. The primary outcome was LVH as compared to normotension.

Conclusions: Lack of association between INH and LVH may reflect the increased sensitivity of 2022 AHA guidelines to diagnose nocturnal HTN. LVH was less prevalent among INH as compared to other hypertensive phenotypes. While the cohort was small, these findings may inform future studies of how clinicians should manage INH.

Sleep-Disordered Breathing, Risk of Target Organ Injury, and Role of Obesity in Youth Referred for Hypertension Disorders

Donald J. Weaver,1 Rahul Chanchlani,2 Stefan Kiesling,1 Margaret Murphy,3 Sandeep K. Riar,4 Christine B. Sethna,5 Iuyo Yamaguchi,2 Andrew M. South,1 Levine Children’s Hospital, Charlotte, NC; 2McMaster University, Hamilton, ON, Canada; 3University of Oklahoma Health Sciences Center, Oklahoma City, OK; 4Wake Forest University School of Medicine, Winston-Salem, NC.

Background: Sleep-disordered breathing (SDB) has adverse consequences on blood pressure regulation in adults, but its relationship with target organ injury (TOI), especially in youth, is less clear. Our objective was to determine if SDB is associated with higher risk for TOI in youth referred for hypertension disorders and if obesity magnified this risk.

Methods: Interim cross-sectional analysis of baseline data from the multisite Study of the Epidemiology of Pediatric Hypertension Registry (SUPERHERO) which retrospectively collects electronic health records data using biomedical informatics scripts. Inclusion criteria were initial visit for hypertension disorder between 1/1/2015 and 12/31/2022 and age <19 years. Exclusion criteria were kidney transplant, dialysis, or pregnancy per ICD-10 codes at the index visit. Exposures were ICD-10 code-defined SDB, and obesity by body mass index percentile was our effect modifier. Outcomes were ICD-10 code-defined heart and kidney TOI at the index visit. We used unadjusted and adjusted linear models.

Results: In this analysis of 11,580 participants, mean age was 12.0 ± 5 years, 52% had obesity, 4% has SDB, and 8 % had TOI (Table). Compared to participants without SDB, those with SDB had a 57% lower risk of TOI (RR 0.43, 95% CI 0.26 to 0.69). Obesity was associated with a lower magnitude of association, though not significantly (interaction p-value 0.08).

Conclusions: In a large multisite registry of youth referred for hypertension disorders, participants with an ICD-10 code for SDB at baseline had a lower risk of TOI by ICD-10 code. Next steps include better defining our exposure and outcome. Further studies are needed to determine if clinical interventions that impact sleep health can mitigate future cardiovascular risk in youth.

Funding: Other NIH Support - NIH K23-HL-148394, L40-HL148910, UL1-TR001420
The relationship was stronger in girls for both BW and z-score (r = -0.10, p = 0.036) than in boys (r = -0.007, p = 0.003). There was no correlation between maternal urinary protein/creatinine ratio and levels of urinary biomarkers in their infants.

Conclusions: This cross-sectional study on urinary biomarkers among infants born to preeclampsia mothers has shown high urinary protein in the study group over control. Urinary klotho levels were also significantly lower in the study infants mirroring the existing knowledge of low klotho levels with acute renal injury and advanced CKD. Levels of urinary nephrin urinary KIM-1 and cystatin C were not statistically different between the two groups. Further prospective studies tracking renal function, proteinuria and blood pressure measurement can provide clues to the significance of these urinary biomarkers as early screening tools for CKD in infants born to mothers with preeclampsia.

Urinary biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Mothers Preeclampsia (n = 38)</th>
<th>Mothers Preeclampsia (n = 34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein (mg/dL Median (IQR))</td>
<td>2.1 (1.4) to 3.5</td>
<td>2.7 (1.7) to 3.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Creatinine (mg/dL Median (IQR))</td>
<td>0.4 (0.3) to 0.6</td>
<td>0.6 (0.4) to 0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Cystatin C (mg/dL Median (IQR))</td>
<td>0.6 (0.5) to 1.0</td>
<td>0.7 (0.5) to 1.0</td>
<td>0.05</td>
</tr>
<tr>
<td>KIM-1 (ng/mL Median (IQR))</td>
<td>0.03 (0.004) to 0.20</td>
<td>0.04 (0.005) to 0.40</td>
<td>0.06</td>
</tr>
<tr>
<td>Nephrin (ng/mL Median (IQR))</td>
<td>0.56 (0.5) to 1.0</td>
<td>0.5 (0.5) to 0.8</td>
<td>0.05</td>
</tr>
<tr>
<td>Klotho (ng/mL Median (IQR))</td>
<td>0.8 (0.6) to 1.0</td>
<td>0.7 (0.6) to 0.8</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Association Between Birth Weight Z-Score and Blood Pressure in 9- to 10-Year-Old Icelandic Children

Asdis J. Hrafnskóldsdottir, Olafur S. Indridason, Sigurdur S. Stephensen, Thoríður J. Hrafnkelsdóttir, Vidar O. Edvardsson, Landspítali, Reykjavík, Iceland; Haskóli Íslands, Reykjavík, Iceland.

Background: Low birth weight has been associated with adverse cardiovascular outcomes, including an increased risk of hypertension later in life. The aim of this study was to examine the association between birth weight (BW) indices and blood pressure (BP) in a cohort of healthy 9- to 10-year-old Icelandic school children.

Methods: Icelandic children aged 9-10 years underwent 4 seated BP measurements in 2009. BP percentiles and z-scores were calculated from the average of the 4 measurements. Height and weight were measured, and information on birth weight and gestational age was obtained from the Icelandic Birth Registry. Birth weight z-score was calculated based on a standardized growth chart by Niklasson & Alberstsson-Wikland. Pearson correlation coefficient and multivariable linear regression were used for statistical analysis.

Results: Of 892 children with complete data, 458 were girls (51.3%). The mean BP in girls was 111/63 mm Hg and 112/64 mm Hg in boys. The mean BW was 3688 ± 586 g for girls and 3750 ± 644 g for boys. A significant negative correlation was observed between BW and systolic BP z-score (r = -0.09, p = 0.001), and between BW z-score and systolic BP z-score (r = -0.09, p = 0.006). There was a negative correlation between the diastolic BP z-score and both BW and BW z-score (r = -0.09, p = 0.005, and r = -0.10, p = 0.003). The relationship was stronger in girls for both BW and z-score (r = -0.11, p = 0.024 and r = -0.10, p = 0.036) than in boys (r = -0.07, p = 0.04 and r = 0.08, p = 0.11). When adjusted for body mass index (BMI) z-score, there was a significant association between BW z-score and systolic BP z-score (beta = -0.12, p = 0.001) and diastolic BP z-score (beta = -0.08, p = 0.001) in girls. In boys the adjusted association was significant for BW z-score and systolic BP z-score (beta = -0.07, p = 0.024), but the association with diastolic BP z-score was of borderline significance (beta = -0.04, p = 0.05). Neither BW nor the BW z-score significantly correlated to absolute blood pressure values in children.

Conclusions: This study suggests that low birth weight may be an important predictor of elevated BP in children and indicates the importance of BP follow-up of low-birth-weight infants.
**TH-PO503**

**Association Between Epigenetic Age Acceleration at Extremely Preterm Birth and Systolic Blood Pressure in Adolescence**  
Anish Saral, Kyle R. Roell, Katelyn Huff, Michael O’Shea, Rebecca Fry, Keia Sanderson. The University of North Carolina at Chapel Hill, Chapel Hill, NC.

**Background:** Epigenetic age deviation from chronologic age is associated with poor cardiovascular (CV) outcomes in adults. No studies have evaluated this association in children born preterm, who are at risk for advanced epigenetic gestational age (eGA) and poor CV outcomes. Our objective was to examine the association between epigenetic gestational age acceleration (eGA) and adolescent systolic blood pressure (SBP) in individuals born extremely preterm.

**Methods:** This is a secondary analysis of the Extremely Low Gestational Age Newborn study. Participants were born <28 weeks’ gestation and had placental DNA quantification at birth and 3 manual blood pressures measured during follow up at 15-17 years old. eGA was estimated using the Robust Placental Clock (RPC). eGA was calculated as residuals from a linear regression of predicted RPC eGA on chronologic gestational age (GA). Mixed effects models were fit to assess association between eGA and average adolescent SBP. A minimally sufficient adjustment set, identified using a directed acyclic graph, included maternal factors (health insurance, years of education, marital status, prenatal smoking, pre-pregnancy body mass index (BMI) > 30 kg/m², diabetes, hypertension) and birth weight for GA.

**Results:** 202 study participants had data for eGA and adolescent SBP. 34% had elevated SBP > 120 mmHg, and 52.6% were male. 67% with elevated SBP were male, 27.8% had mothers with hypertension, and 25% had mothers with BMI > 30 kg/m². In the overall sample, we found no association between eGA and adolescent SBP (p=0.539). When stratified by sex, for every 1 week increase in eGA, adolescent males had an increase of 3.32 mmHg in SBP (p=0.04; Table 1).

**Conclusions:** Epigenetic gestational age acceleration at birth is associated with significant increase in SBP in adolescent males but not females who were born extremely preterm. The kidney is key in regulating blood pressure, so future research includes evaluating kidney-specific epigenetic changes at preterm birth and CV outcomes.

**Funding:** NIDDK Support, Other NIH Support - NIDDK support was provided through Grant T32DK007750-24. The ELGAN study was supported by grants from the National Institute of Neurological Disorders and Stroke (5U01NS040069;2R01NS040069). The ELGAN-ECHO study is supported by the Office of the National Institutes of Health Director (5U33OD023348-04).

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Male, unadjusted</td>
<td>2.396</td>
</tr>
<tr>
<td>Male, adjusted</td>
<td>2.320</td>
</tr>
<tr>
<td>Female, unadjusted</td>
<td>-1.122</td>
</tr>
<tr>
<td>Female, adjusted</td>
<td>-1.06</td>
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</tbody>
</table>

**Table 1. Association between eGA and adolescent SBP by sex**

**TH-PO504**

**Disparities in Medication Fill Duration in Pediatric Hypertension**  

**Background:** Medication nonadherence is a barrier to blood pressure control. The CDC recommends prescribing 90-day fills for maintenance medications yet antihypertensives are often dispensed as 30-day fills due to insurance limits. This increases the burden of pharmacy visits, a contributor to nonadherence. We observed how often antihypertensives are dispensed as a 30-day supply despite a prescription for longer duration and the impact of 30-day vs 90-day fills on adherence.

**Methods:** This retrospective cohort study included patients with hypertension (HTN) seen in our Pediatric Nephrology Clinic over a 3 year period. For each patient, antihypertensive medication days prescribed was compared to days dispensed using pharmacy refill and insurance claim data. Proportion of days covered (PDC) was calculated to estimate medication adherence.

**Results:** A total of 449 patients (61% primary HTN, 39% secondary HTN) had 4,492 prescription orders and 8,800 dispenses over the 3-year period. While 36% of prescriptions were ordered for a 90-day fill, only 25% of patients had at least one prescription for a 90-day fill. In addition, 35% of patients had a fill discrepancy (prescribed but never received a 90-day fill). There was no difference in likelihood of being prescribed a 90-day fill by insurance type (public vs private, OR = 0.82, p = 0.35) but patients with public insurance were less likely to be dispensed a 90-day fill (OR = 0.126, p < 0.001) and more likely to have a fill discrepancy (OR = 6.02, p < 0.001). Patients who received at least one 90-day fill had better adherence rates (median PDC, 77.5% vs 58.1%, p < 0.001).

**Conclusions:** Longer fill duration is associated with better adherence with antihypertensive medication in pediatric patients. However, patients are often dispensed only 30-day fills despite a 90-day prescription. Patients with public insurance are markedly less likely to be dispensed 90-day fills, a modifiable barrier to improving adherence in disadvantaged youth.

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

*Underline represents presenting author.*
Th-Po506

Abstract Withdrawn

Th-Po507

Phosphate-Containing vs. Phosphate-Free Solutions in Pediatric Continuous Renal Replacement Therapy: A WE-ROCK Study

Background: Hypophosphatemia is common in patients on continuous renal replacement therapy (CRRT), and is associated with adverse outcomes (prolonged mechanical ventilation (MV) and longer ICU stay). We aimed to compare outcomes between commercially available phosphate-containing (1 mmol/L, PHOS+) and phosphate-free (PHOS-) solutions in pediatric CRRT patients.

Methods: The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) is a 32-center registry of patients aged 0-25 years treated by CRRT for acute kidney injury or fluid overload (FO). This analysis excluded patients with incomplete CRRT fluid data or those receiving pharmacy-compounded solutions with variable phosphate concentrations. Primary outcomes were 28-day MV- and ICU-free days. Multivariable regression analyses were conducted for outcome comparisons.

Results: We included 410 patients; median age 8 years (IQR 1.6-14.1) y. Of these, 43.4% (176/401) received PHOS+. The PHOS+ group had a higher %FO (7.2% vs. 5.4%, p=0.009) and lower MV rate at CRRT initiation (64% vs. 82%, p<0.001). There was no difference in PELOD and vasoactive inotropic score between the groups. Both groups received a similar dose of CRRT (42 vs 48 ml/kg/h, p=0.4) although the duration was longer for the PHOS+ group (7 vs 4 d, p=0.001). The PHOS+ group had less incident hypophosphatemia (<2.5 mg/dl) during CRRT compared to the PHOS- group (20% vs. 33%, p=0.007). However, there were no differences in 28-day MV- and ICU-free days and 90-day mortality between the 2 groups in unadjusted and adjusted analyses (Table).

Conclusions: PHOS+ (1 mmol/L) CRRT solutions reduced incident hypophosphatemia in this pediatric cohort but did not associate with reduction in 90-day mortality or less ventilator or ICU resource utilization.

Table: Variable & ICU-free days

<table>
<thead>
<tr>
<th>Variable</th>
<th>ICU-free days</th>
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<tbody>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>Sepsi</td>
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<tr>
<td>Podor</td>
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<tr>
<td>Np dor</td>
<td></td>
</tr>
<tr>
<td>V/s</td>
<td></td>
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<tr>
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<td></td>
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<tr>
<td>P/36 d</td>
<td></td>
</tr>
<tr>
<td>V/s</td>
<td></td>
</tr>
<tr>
<td>Hbol</td>
<td></td>
</tr>
<tr>
<td>MV time</td>
<td></td>
</tr>
<tr>
<td>Inf cit</td>
<td></td>
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<tr>
<td>CRRT cr</td>
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<tr>
<td>Dose cr</td>
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<td>CI cr</td>
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<td>Inf cit</td>
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<td>CRRT cr</td>
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<td>Dose cr</td>
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<tr>
<td>CI cr</td>
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</tbody>
</table>

*F and % are defined as follows: *F is the percentage of patients with the specified variable, while % is the percentage of patients without the specified variable. CI cr is the confidence interval for the difference in mortality between PHOS+ and PHOS- groups, calculated using the Wald chi-square test (confidence level 95%).

**Significance marked in bold.

Multivariable analysis for 28-day ventilator- and ICU-free days

Th-Po508

Regional Citrate Anticoagulation in Continuous Renal Replacement Therapy in Children: Opportunities for Optimization

Background: Regional citrate anticoagulation (RCA) is based on blood citrate concentration of 3-4 mmol/L to reach post filter ionized calcium (CaI) of 0.25±0.40 mmol/L in continuous hemodialfiltration (CVVHDF). However, it can lead to metabolic complications of citrate accumulation.

Methods: From May 2019 to Dec 2022, 5.5% (109/1970) of patients admitted in a PICU were submitted to CVVHDF using RCA with 2.2mmol/L of citrate. 25 patients were excluded for CVVHDF <24h, and 3 others for prior CVVHDF. Data related to minimum magnesium was analyzed to sensitize the results.

Results: From the 81 patients included, 56.8% were girls, the age was 4.2 years (1.1-36.3) and the weight 13 kg (8.1-36.3). Organic dysfunctions were cardiovascular in 64.2%, pulmonary in 70.4% and hepatic in 65.4%, and the mortality rate was 51.9%. Hypomagnesemia (Mg<1.7mg/dL) was observed in 64% of patients, and the minimum magnesium was 1.6mg/dL (1.4-1.8), where blood flow rate was 6ml/kg/min (3.4-7.5), the replacement/dialysate fluid rate of 65 ml/kg/h (47-92), blood citrate concentration of 1.7 mmol/L (1.4-2.6), citrate dosage of 0.66mmol/kg/h (0.35-0.85), reaching CaI/Cai (citrate GAP) of 2.01 (1.89-2.03). Only 4 patients presented citrate accumulation (citrate GAP >2.5). Patients <1 years of age reached larger blood flow rate [7.7 (6.7-11.7) vs 4.8 (3-6.5), p=0.001], smaller blood citrate concentration [1.5 (1.4-1.9) vs 1.9 (1.4-2.80), p=0.048], larger citrate dosage [0.75 (0.64-1.09) vs 0.53 (0.32-0.77), p=0.008], and larger citrate GAP [2.14 (1.96-2.33) vs 1.96 (1.79-2.09), p=0.035]. Blood citrate concentration tended to be smaller in the circuits with <36 hours of duration (48.7%), [1,7mmol/L (1.3-2.0) vs 1.9 (1.4-2.8) vs p=0.062], and no difference was observed in the citrate dose (p=0.117) or post filter Cai (p=0.385).

Conclusions: The low citrate patency obtained is probably associated with the low blood citrate concentration used. Children <1 year of age presented good tolerance to high doses of citrate, with a low rate of citrate accumulation. It is possible that children tolerate citrate doses of 0.6-0.85 mmol/kg/h, reaching blood citrate concentration of 3mmol/L by adjusting the blood flow rate to 2.5-5 ml/kg/min, improving circuits patency without major metabolic consequences.

Th-Po509

Longitudinal Trends in Pediatric Hospitalizations Complicated by AKI in the United States

Background: There are limited national data describing longitudinal trends of pediatric acute kidney injury (AKI) and AKI requiring dialysis (AKI-D) We aimed to characterize rates of pediatric AKI and AKI-D across the United States over a 20-year period.

Methods: We analyzed data from the Kids Inpatient Database (KID) from 1997 to 2016. AKI was identified using International Classification of Diseases Clinical Modification (ICD-CM) codes, 9th Revision (1997-2012) and 10th Revision (2016). Use of dialysis during hospitalization was assessed using procedure codes. We excluded pediatric hospitalization for uncomplicated, term newborn birth. Weighted data was used to estimate national yearly incidence totals and rates.

Results: Over the study period, there was a weighted total of 49,228,048 pediatric discharges, 22,659,242 of which were included in the final analysis. Nationwide, the yearly incidence of AKI and AKI-D increased from 1997 (AKI: 8340 cases/year, AKI-D: 1049 cases/year) to 2016 (AKI: 43,053 cases/year, AKI-D: 1656 cases/year). The rates of hospitalizations with AKI and AKI-D also increased from 1997 (cases/10k discharges: AKI: 20.7[20.2,21.1], AKI-D: 2.6[2.4,2.8]) to 2016 (AKI: 111[110,112], AKI-D: 4.2[4.0,4.5]) (Figure 1).

Conclusions: This analysis of KID shows an increase in the absolute number, and the rate of pediatric hospitalizations complicated by AKI and AKI-D from 1997 to 2016. While some of the increase may be explained by an increase in awareness and documentation, there is a near 3-fold increase in rates of AKI-D. More detailed analysis are needed to evaluate the reasons behind this. Given our understanding of the long-term impact of AKI, it is important to assess for preventable causes and to optimize care of those with AKI and AKI-D.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO510
Long-Term Outcomes After Pediatric Non-Dialysis-Treated AKI: A Population-Based Cohort Study
Cal Robinson,1 Nivethika Jayakumar,2 David J. Askennazi,3 Akash Deep,4 Amit X. Garg,3 Stuart Goldstein,3 Jason H. Greenberg,3 Cherry Mammen,3 Danielle M. Nash,5 Rulan S. Parekh,6 Samuel A. Silver,7 Ron Wald,8 Michael Zappitelli,9 Rahul Chanchlani10 1 The Hospital for Sick Children, Toronto, ON, Canada; 2ICES Western, London, ON, Canada; 3 The University of Alabama at Birmingham, Birmingham, AL; 4King’s College London, London, United Kingdom; 5Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 6Yale University, New Haven, CT; 7BC Children’s Hospital, Vancouver, BC, Canada; 8London Health Sciences Centre, London, ON, Canada; 9Women’s College Hospital, Toronto, ON, Canada; 10Queen’s University, Kingston, ON, Canada; 11St Michael’s Hospital, Toronto, ON, Canada; 12McMaster Children’s Hospital, Hamilton, ON, Canada.

Background: Acute kidney injury (AKI) is common in hospitalized children. Dialysis-treated AKI is associated with long-term chronic kidney disease (CKD), hypertension, and death. We aim to evaluate the outcomes after non-dialysis-treated AKI, which are uncertain.

Methods: Retrospective cohort study of all hospitalized children (0-18yr) surviving non-dialysis-treated AKI from 1996-2020 in Ontario, identified via provincial administrative health databases. Children with prior kidney replacement therapy (KRT; dialysis or transplant), KDK, or AKI were excluded. Cases were matched with up to four hospitalized controls without AKI by age, neonatal status, sex, index year, ICU admission, cardiac surgery, malignancy, hypertension, and a propensity score for AKI. Children were followed until death (2.9%), provincial emigration (5.3%), or March 2021 (91.8%). The primary outcome was major adverse kidney events (MAKE; composite of death, chronic KRT, or de novo CKD).

Results: A total of 4173 pediatric AKI survivors were matched to 16,337 hospitalized controls. Baseline covariates were well-balanced after propensity score matching. Median age was 8yr (IQR 1-15); 706 (16.9%) AKI cases were neonates. During median 9.7-year follow-up, 17.6% of AKI survivors developed MAKE vs 4.6% of controls (HR 4.3, 95%CI 3.9-4.8, p<0.001). AKI cases had higher rates of chronic KRT (2.2% vs 0.2%, HR 12.8, 95%CI 8.5-19.4), CKD (15.9% vs 2.0%; HR 8.8, 95%CI 7.7-10.0), hypertension (16.8% vs 7.7%; HR 2.4, 95%CI 2.2-2.7), and subsequent AKI (5.7% vs 1.5%; HR 4.0, 95%CI 3.4-4.8), but no mortality difference (2.7% vs 2.9%; HR 1.0, 95%CI 0.78-1.16).

Conclusions: Children with non-dialysis-treated AKI are at increased long-term risk of CKD, chronic KRT, hypertension, and subsequent AKI vs hospitalized controls.

Funding: Private Foundation Support

Figure. Cumulative incidence of MAKE

TH-PO511
Reducing AKI in Critically Ill Pediatric Patients: An Improvement Project Targeting Nephrotoxic Medication Exposures
Natalie R. Carperuta,1 W. Joshua Frazier,1 Jeffrey Lutter,1 Cheryl Sargel,1 Lindsay Kalata,2 Robert J. Gajarski,1,3 Diana Zepeda-Orozco1 1 Nationwide Children’s Hospital, Columbus, OH; 2 The Ohio State University, Columbus, OH.

Background: Acute kidney injury (AKI) occurs commonly in critically ill hospitalized pediatric patients, is associated with nephrotoxic medication exposure and is independently associated with worse clinical outcomes. Our pediatric intensive care unit (PICU) utilized the multicenter Nephrotoxic AKI (NAKI) quality improvement project to increase awareness of nephrotoxic medication exposures, develop interventions, and reduce NAKI.

Methods: A multi-phased approach was used to increase education and recognition surrounding nephrotoxic medication exposures in the PICU and their role in subsequent AKI. Monthly resident physician education was provided by our unit-based clinical pharmacist, and an informational handout was created and reviewed monthly during resident PICU orientation. A third phase included a clinical pharmacist notification to attending physicians of patients meeting exposure criteria with acceptable alternatives to nephrotoxic drugs and suggestions for AKI monitoring.

Results: Our cohort included 39,181 patient days admitted to the PICU at our institution between October 1st 2019 and April 30th 2020. A total of 225 unique patients met nephrotoxic exposure criteria leading to 21 AKI episodes. We reduced nephrotoxic medication exposure rates by 25% from 36.73 to 27.39 per 1000 patient days and NAKIs by 51% from 5.43 to 2.64 per 1000 patient days.

Conclusions: Interventions to decrease AKI successfully in critically ill patients required a multi-phased approach including recurrent education efforts and pharmacy-driven daily physician alerts. Organizational implementation of these interventions is ongoing.

TH-PO512
GUIDANCE: Primary Results of a Prospective, Observational Clinical Study Evaluating the Performance of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the Risk Assessment of AKI in Pediatric ICU Patients
Stuart Goldstein1, Shina Menon,2 Katja M. Gist,3 Megan Soochoo,3 Natasha Afonso,1 David M. Kwiatkowski,1 Christopher W. Mastroproietto,4 David J. Askennazi,5 Hostensia M. Beng,3 Sarah J. Kizilbash,3 Abhy M. Basaale6, Avi Traum,11 Julie C. Fitzgerald,13 The GUIDANCE Investigators.2 1 Cincinnati Children’s Hospital, Cincinnati, OH; 2 Seattle Children’s Hospital, Seattle, WA; 3 Children’s Hospital of Colorado, Aurora, CO; 4 Texas Children’s Hospital, Houston, TX; 5 Lucile Packard Children’s Hospital School, Palo Alto, CA; 6 Riley Hospital for Children at Indiana University Health, Indianapolis, IN; 7 Children’s of Alabama, University of Alabama at Birmingham, Birmingham, AL; 8 East Carolina University Brody School of Medicine, Greenville, NC; 9 Oklahoma City University Medical Center, Oklahoma City, OK; 10 Cohen Children's Medical Center, Queens, NY; 11 The Children’s Hospital of Philadelphia, Philadelphia, PA.

Background: Acute kidney injury (AKI) has been associated with prolonged hospital stays, future progression to chronic kidney disease, and a 25-80% risk of in-hospital death in critically ill patients. Our ability to treat this condition is lacking, partially due to our inability to detect AKI early. We sought to validate the clinical cut-off value for neutrophil gelatinase-associated lipocalin (NGAL) in pediatric patients. Here, we report the clinical performance of NGAL as a risk assessment marker for AKI in GUIDANCE, a validation study completed in support of an FDA submission.

Methods: Children (aged ≥ 90d to 22 yr) admitted to an adult or pediatric common unit (ICU) with a urine sample collected within 24 hours of admission were eligible. Eligible patients must have had either mechanical ventilation, vasoactive medication administration, solid organ or bone marrow transplantation, OR hypotension within 24 hours of admission. Urine NGAL was measured using a particle-enhanced, turbidimetric, NGAL assay. Serum creatinine (SC) was measured on days 1,2, and 3 to determine stages 2 or 3 AKI per KDIGO guidelines. Independent adjudication by three clinical experts assessed for AKI within 48-72 hours using SC measurements and clinical information but did not have access to NGAL results. NGAL positivity was defined as a urine concentration ≥125 mg/mL based on a prior derivation study.

Results: Six hundred sixty patients were screened, and 514 were evaluable per the study protocol. Forty-seven patients (9.1%) developed stage 2 or 3 AKI; 36 of these patients were NGAL-positive. The sensitivity, specificity, negative predictive value, and positive predictive value for the NGAL test ≥125 mg/mL was 76.6% (36/47), 86.5% (406/468), 97.6% (406/416), 36.7% (36/98), respectively. The diagnostic performance of NGAL as demonstrated by an area under the ROC was 0.86 (95%CI, 0.80-0.92).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: These data demonstrate that a particle-enhanced, turbidimetric, NGAL assay performs well early in ICU course to aid in risk assessment for stage 2 or 3 AKI in critically ill children.

Funding: Commercial Support - BioPorto Diagnostics

Disclosures: To our knowledge we are not aware of any reports studying kidney echogenicity as a marker for kidney recovery and raises the possibility that it may improve before other markers. EI as an early indicator of kidney recovery needs to be prospectively evaluated compared to other markers such as urine NGAL and, in oliguric patients, increasing urine output.

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

TH-PO513

Does Kidney Echogenicity Correlate to eGFR in Pediatric AKI?
Shreya Goswami, Michelle C. Starr, Daniel Cater, Andrew L. Schwaderer. Indiana University School of Medicine, Indianapolis, IN.

Background: Kidney ultrasound echogenicity is a subjective finding reported by radiologists however it may be more clinically useful if quantified. The objective is to investigate if ultrasonographic parameters of the kidney correlates to estimated glomerular filtration rate (eGFR) in pediatric AKI.

Methods: Retrospective study in a tertiary children’s hospital. Ultrasounds of 35 subjects were identified with AKI at the time of CKRT initiation. Three distinct areas of the kidney cortex and liver were cropped. Using Adobe Photoshop software a gray scale pixel density value was quantified. An inverse ratio of the kidney to liver mean pixel density value was quantified. An inverse ratio of the kidney to liver mean pixel density value was quantified. The difference between the mean measured and predicted right and left kidney lengths was the kidney length ratio (KLR). The mean measured kidney length was the mean of both kidneys.IMAL

Results: 35 subjects were analyzed. The median age was 10 years (range 2-16) and 54% were male. Heatmap correlation analysis revealed statistically significant negative correlations for mean EI with eGFR and BMI (r = -0.36 [p-value 0.03]; and -0.35 [p-value 0.04], respectively). KLR showed negative correlation with BMI and age (r = -0.46 [p-value 0.005] and r = -0.38 [p-value 0.0025], respectively). The % of FO significantly correlated with decreasing size and BMI. The AUC for EI with eGFR <90ml/min/1.73m² and <60ml/min/1.73m² was 0.7 (p-value 0.08 and 0.02, respectively). EI < 1.17 predicted eGFR < 90 with sensitivity of 55.0% (CI 34%-74%) and specificity of 86.7% (CI 62%-98%). AUC for KLR was 0.6 and statistically insignificant.

Conclusions: Increased kidney echogenicity appears to be a more accurate correlate with decreased kidney function than increased kidney size.

Correlation plot for data. Significant values highlighted in yellow.

TH-PO514

Is Kidney Echogenicity an Early Indicator of AKI Recovery?
Shreya Goswami, Michelle C. Starr, Daniel Cater, Andrew L. Schwaderer. Indiana University School of Medicine, Indianapolis, IN.

Introduction: Kidney ultrasound echogenicity is a subjective finding reported by radiologists however it may be more clinically useful if quantified. We present a case report of a 15-year-old girl with acute kidney injury (AKI).

Case Description: 15-year-old girl was diagnosed with AML requiring treatment with a tyrosine kinase inhibitor, gilteritinib. Within two weeks of receipt of this agent she developed severe non-oliguric AKI, likely from medication induced thrombotic microangiopathy. Her baseline serum creatinine was 0.40 mg/dL with a peak of 6.83 mg/ dL, necessitating CKRT for 5 days. She was receiving serial abdominal ultrasounds for concerns for venous occlusive disease at the same time. Mean echogenicity (EI) was obtained by quantifying the gray scale pixel density value of the right kidney cortex compared to the liver using adobe photoshop software. Serial echogenicity index (mean EI) of the kidney cortex, weekly urine output (ml/kg/hour) and estimated glomerular filtration rate (eGFR) was collected during hospitalization. It appears that mean EI peaked on day 4 while eGFR was the lowest. Subsequently EI improved on day 7 while the eGFR had sustained improvement between days 21-42.

Discussion: To our knowledge we are not aware of any reports studying kidney echogenicity as a marker for kidney recovery and raises the possibility that it may improve before other markers. EI as an early indicator of kidney recovery needs to be prospectively evaluated compared to other markers such as urine NGAL and, in oliguric patients, increasing urine output.

TH-PO515

Epidemiology and Outcome of AKI in Hospitalised Children in Australia
Madeleine S. Didsbury,1,2 Ben Gelbart,1,3 Peter R. Summers,1,2 Daryl R. Cheng,2,3 Thomas A. Forbes,1,2,3 Catherine Quinlan,1,2 Joshua Y. Kausman,1,2 Emily Sec.1,2
1Department of Nephrology, The Royal Children's Hospital, Melbourne, VIC, Australia; 2Centre for Health Analytics, The Royal Children’s Hospital, Melbourne, VIC, Australia; 3Murdoch Children’s Research Institute, Parkville, VIC, Australia; 4Paediatric Intensive Care Unit, The Royal Children’s Hospital, Melbourne, VIC, Australia; 5School of Medicine, University of Melbourne, Melbourne, VIC, Australia.

Background: Available estimates of the burden of acute kidney injury (AKI) in hospitalised children are inconsistent and the prognostic implications of its severity, duration, and frequency are poorly understood. Additionally, lack of hospital data on AKI impacts service provision and planning.

Methods: We used our electronic medical record to capture the epidemiology and outcome of AKI in a cohort of children aged between 1 month and 18 years who were hospitalised for at least 24 hours at a quaternary paediatric centre in Melbourne, Australia, between 1 January 2017 and 31 December 2021. AKI was defined according to phenotype in terms of KDIGO stage, duration (transient <48 h, persistent 48 h to 7 d, or acute kidney disease), and frequency. The primary outcome was 30-day mortality. Secondary outcomes included resource utilisation, hospital outcome, and major adverse kidney events at 30 days (MAKE30).

Results: A total of 4,214 AKI episodes occurred, involving 3,134 admissions for 1,540 children (incidence 16%; 17.77 episodes per 1000 patient-days). Most AKI was stage 1, transient, and occurred as a single episode. AKI was associated with an increased risk of 30-day mortality (aOR 3.93, 95% CI 2.77 to 5.58). Compared to children without AKI, children with AKI had a higher odds of ICU admission (aOR 3.40, 95% CI 3.13 to 3.69), mechanical ventilation (aOR 2.05, 95% CI 1.76 to 2.41), vasoactive drugs (aOR 3.76, 95% CI 3.28 to 4.30), and extracorporeal membrane oxygenation (aOR 32.37, 95% CI 15.73 to 66.60). Children with AKI were also more likely to die in hospital (aOR 5.98, 95% CI 4.29 to 8.35), be discharged to rehabilitation (aOR 2.03, 95% CI 1.66 to 2.47), or develop a MAKE30 (aOR 40.35, 95% CI 29.63 to 54.94) compared to children without AKI, when adjusted for ICU status and age. Most adverse events had a graded association with AKI stage and AKI duration; the association between AKI frequency and outcome is less clear.

Conclusions: AKI occurs commonly in hospitalised children and is associated with increased mortality and, among survivors, greater hospital resource utilisation. There was a graded increase in the magnitude of the association with increasing AKI severity and duration. This analysis could be automated and repeated over time to measure the impact of interventions to detect and reduce AKI.

TH-PO516

Predictors for the Development of CKD Stage 2 or Higher in Repeat Pediatric Heart Transplant Recipients
Melvin Chon, University of Colorado, Denver, CO.

Background: There is little data on the risk factors for developing chronic kidney disease (CKD) in repeat pediatric heart transplant recipients.

Methods: All repeat heart transplants (RT) at our center from 1995-2021 were reviewed. Renal function was determined by estimated glomerular filtration rate (eGFR) derived from CKID U25 calculator using creatinine at each hospital and clinic visit.
The stages of acute kidney injury (AKI) were in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria. Independent samples t-test was conducted on the development of CKD stage 2 or higher and the following variables: pre-transplant eGFR; post-transplant eGFR at 1-3 months; ages at first heart transplant (FT) and RT; time between transplants; gestational age; weight category prior to transplant; and number of AKIs between FT and RT. Multivariate logistic regression was performed for significant variables.

**Results:** A total of 43 RT were included in this cohort, with a majority being Caucasian and mean age of 14 years old. Median follow-up time was 3 years. Univariate analysis showed significant associations between development of CKD stage 2 or higher and the following variables: pre-transplant eGFR, post-transplant eGFR at 1-3 months, the number of stage 2 and 3 AKIs between FT and RT. Multivariate logistic regression showed that post-transplant eGFR at 1-3 months (OR 0.92) and number of stage 2 and 3 AKIs (OR 21.5) remained significant, with an AUC of 0.91, sensitivity of 0.97, and specificity of 0.60.

**Conclusions:** Our preliminary data shows the post-transplant eGFR at 1-3 months and number of stage 2 and 3 AKIs are predictors for the development of chronic kidney disease stage 2 or higher. More research is needed to look at predictors for development of advanced chronic kidney disease to inform transplant teams when a repeat heart transplant or a dual heart and kidney transplant can be done.

**TH-PO518**

**Outcomes of Simultaneous Heart-Kidney vs. Sequential Heart-Kidney Transplantation in Children**

Ruchi Mahajan, Michael D. Evans, Sarah J. Kizilbash. University of Minnesota Twin Cities, Minneapolis, MN.

**Background:** Heart transplant (HTx) recipients frequently require kidney transplantation for concomitant advanced chronic kidney disease. Data on simultaneous (HTx and Kidney Transplantation (KTx) at the same time) versus sequential (HTx performed before KTx) HTx and KTx in children are limited. Herein, we compare KTx outcomes between the two groups.

**Methods:** We used the Scientific Registry of Transplant Recipients (SRTR) to identify all pediatric (age < 21 years) HTx recipients who also received a KTx within 10 years of the HTx. We divided the study cohort into two: simultaneous heart/kidney and sequential heart/kidney recipients. We compared continuous and categorical variables using the Wilcoxon rank sum test and chi-square test. We compared patient and death-censored graft survival between simultaneous and sequential KTx recipients using the Cox regression, adjusting for age at the KTx, sex, race, pretransplant dialysis, donor type, and prior KTx. All analyses were performed in R, and a p-value of <0.05 was considered statistically significant.

**Results:** Our analysis cohort included 165 recipients (79 for simultaneous and 86 for sequential). Table 1 is baseline characteristics of the cohort. We found no difference in patient survival (aHR: 0.97; 95% CI: 0.39, 2.41; p = 0.95) but better death-censored graft survival in simultaneous heart/kidney recipients compared with simultaneous heart/kidney recipients (aHR: 4.26; 95% CI: 1.21, 14.9; p = 0.02).

**Conclusions:** Pediatric HTx/KTx recipients who receive the KTx after their HTx have a better death-censored kidney allograft survival compared with those who receive KTx simultaneously with the heart transplant. Children with less significant kidney dysfunction at the time of HTx evaluation should be considered for a sequential heart/kidney transplant.

**Baseline Characteristics of Patients undergoing Sequential versus Simultaneous Heart Kidney Transplantation.**

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Simultaneous</th>
<th>Sequential</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age at kidney Tx years</td>
<td>17.00 (15.00, 21.00)</td>
<td>16.00 (12.00, 18.75)</td>
<td>0.118</td>
</tr>
<tr>
<td>Female</td>
<td>44 (57.7)</td>
<td>44 (57.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Race - Asian</td>
<td>6 (7.8)</td>
<td>7 (8.8)</td>
<td>0.909</td>
</tr>
<tr>
<td>Black</td>
<td>10 (13.2)</td>
<td>17 (21.0)</td>
<td>0.061</td>
</tr>
<tr>
<td>Multi</td>
<td>2 (2.6)</td>
<td>0 (0.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Native</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>White</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.000</td>
</tr>
<tr>
<td>Transplant type-dialysis &gt;N</td>
<td>16 (21.5)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor Type - Donor Living</td>
<td>34 (43.2)</td>
<td>84 (100.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Delayed graft function (DGF) &gt;N</td>
<td>72 (97.3)</td>
<td>0 (0.0)</td>
<td>0.017</td>
</tr>
<tr>
<td>eGFR at Heart Transplant (median 17.73)</td>
<td>87 (11.7)</td>
<td>0 (0.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart Transplant (median 17.73)</td>
<td>73 (15.6, 18.36)</td>
<td>29.4 (17.18, 45.81)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**New Treatments, New Challenges: Nephrotoxicity-Associated Naxitamab in Pediatric Patients with High-Risk Neuroblastoma.**

Alvaro Madrid Aris, Pedro Arango Sancho.1,2 Hospital Sant Joan de Deu, Barcelona, Spain; 1Pediatric Cancer Center Barcelona, Barcelona, Spain.

**Background:** Neuroblastoma is the most common extracranial solid tumor in pediatrics, having a poor survival in high-risk (HR) tumors. Naxitamab (Hu3F8) is a humanized monoclonal antibody anti-dysialoganglioside (GD2) approved for treatment
of > 1 year-old and adults with refractory/relapsed HR-neuroblastoma limited to bone or bone marrow. Our hospital is the first center (2017) worldwide use it (clinical trials/comparative use), obtaining excellent results.

Methods: Retrospective descriptive study including 244 patients (41% female-101-and 59% male-143-) using Naxitamab (monotherapy and/or associated with chemotherapy) from June 2017 to current day (6 years) in whom renal involvement and/or hypertension (HT) was evaluated.

Results: Mean age was 8 years, presenting nephropotoxicity of some type up to 26.6% (65-HT(11.9%-29), acute renal damage (ARD10.2%-25) and proteinuria(5.3%-13), developed in them during the infusion or the first 3 cycles. In case of IIT, only in 6 patients an ABPM was performed, observing 2 nocturnal-HT 2 diurnal-HT without specific-pattern and 2 disautonomic-pattern, not previously observed. Among the ARD, all cases were tube except for one patient who presented clinical-analytical pattern of acute tubule- interstitial nephritis (AIN). Eight of them(32%) presented possible confounding factors in the development of previous chemotherapy, ibuprofen or radiotherapy). Among patients with proteinuria(none nephrotic range): 38% tubular, 38% glomerular and 23% mixed 2 patients presented ARD+HT and 3 a combination of ARD.+HT+proteinuria. Of these last, all of them received prior chemotherapy, leaving 2 of them with chronic renal damage (CKD stage 2 and 3).67 patients(27%-4%) died due to progression of their underlying disease.

Conclusions: Management of HR-neuroblastoma remains a daily challenge. Naxitamab is an emerging therapy in this type of tumors, although there are few studies describing its AE. Previous studies of our group in mice explain the involvement of the myelin sheaths of the autonomic nervous system with this drug, which could explain, among others, the dysautonomic pattern of blood pressure presented. Short- and long-term follow-up, the systematic performance of ABPM and the use of early markers of renal damage, could lead to a more efficient management of complications derived from this new treatment.

TH-PO520

Incidence of Nephromegaly Following Hematopoietic Stem Cell Transplantation in Children and Young Adults

Racel Bou Matar. Cleveland Clinic, Cleveland, OH.

Background: Hematopoietic stem cell transplantation (HSCT) is an effective treatment for a variety of malignancies, metabolic and autoimmune diseases. Complications of HSCT include infections, veno-occlusive disease, mucositis, hemorrhagic cystitis, and graft-versus-host disease. Nephromegaly, along with other abdominal organomegaly, has been reported in the literature but the incidence and clinical significance is unknown.

Methods: Children and young adults (age ≥ 19 years) who underwent HSCT over a 10-year period (2011 to 2021) were screened for the study. Patients were included if they underwent a kidney ultrasound pre-HSCT and within 3 months post-HSCT. We retrospectively collected data that included demographics, type of HSCT, conditioning regimen and primary diagnosis. Data extracted from ultrasound reports included kidney length, presence, and severity of hydronephrosis and other renal anomalies. Other data points collected included HSCT source, conditioning regimen, and concurrent renal anomalies. The primary outcome of the study was the kidne length percentile for patient’s age as measured by ultrasound before and within 3 months after the HSCT. Paired t-test was used for comparison of continuous data and Chi-Square test for comparing proportions.

Results: Twenty-seven patients met the inclusion criteria for the study. Median age was 7 years (20 months to 19 years) at the time of transplantation. The kidney length percentile was significantly increased post-HSCT (70.4, IQR 51.5 - 87.2) as compared to pre-HSCT (72.4, IQR 44.9 - 97.2, p ≤ 0.03). The percentage of patients with unilateral nephromegaly was 51.8% pre and 59.3% post-HSCT (p = 0.58). The percentage of patients with bilateral nephromegaly was 14.8% pre and 29.6% post-HSCT (p = 0.19). No statistically significant differences were detected when groups were stratified by age, sex, primary diagnosis, HSCT source, conditioning regimen, and presence of other renal anomalies.

Conclusions: In this cohort of children and young adults, kidney length percentiles for age significantly increased post-HSCT. The mechanism and clinical significance of this increase requires further investigation.

TH-PO521

Epidemiology and Outcomes of AKI and Dialysis After Bone Marrow Transplantation in Pediatric Patients

Omer S. Ashraf,1 Zara C. Orozco,1 Imad U. Haq,1 Zaid Ashraf,1 Sidharth K. Sethi,1 Rupesh Raina,2,4 ‘Northeast Ohio Medical University, Rootstown, OH; 3Cleveland Clinic Akron General, Akron, OH; 4Medanta The Medicity, Gurgaon, India; 5Akron Children’s Hospital, Akron, OH.

Background: Acute kidney injury (AKI) is a common post-operative complication of bone marrow transplantation (BMT) in pediatric patients, with high mortality and morbidity. However, little is known about the epidemiologic characteristics. We assessed the characteristics, risk factors, and outcomes of BMT-induced AKI and the incidence, prevalence, and mortality of dialysis in the pediatric population.

Methods: Using patient data from TruNyx, a commercial database of health record data from 101 healthcare organizations, two cohorts were identified using ICD-10/lab/procedure prescription codes: <18y/o patients with AKI within 30 days of BMT, and <18y/o patients who underwent BMT excluding AKI. Cohorts were 1:1 propensity matched for age significantly increased post-HSCT. The mechanism and clinical significance of this increase requires further investigation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: 49.8% of the cohort were males and median age at diagnosis was 4.8 (IQR = 3.0-9.0) years. By end of treatment, HTN and a history of kidney injury (AKI) were present in 15.3% and 34.2% of patients respectively. Stage 1 AKI represented 77.8% of all AKI episodes. Initial ultrasound findings suggestive of leukemic kidney infiltration (LKI) and tumor lysis syndrome (TLS) were associated with higher AKI risk. HTN risk was higher among children younger than 5 years old (OR 2.3, 95% CI 1.4-4.8), those with LKI (3.5, 1.5-7.9), and who had AKI (2.5, 1.2-5.2). Median length of follow-up was 15.0 (11.6-19.7) years, with median age of 21.4 (16.8-25.9) years old. High blood pressure values suggesting HTN were recorded in 11.5% of patients. Mean eGFR was 100.3 ± 15.7 ml/min/1.73 m2. Nearly, with no difference between patients who had previous severe AKI episodes versus not, 27.1% of the cohort met criteria for stage 2 CKD (eGFR < 90 ml/min/1.73 m2). CKD at long-term follow-up was not associated with number of AKI episodes, AKI severity, or HTN prior to end of treatment. Prior severe AKI episodes were associated with high blood pressure at follow-up (5.1; 1.7-5.2).

Conclusions: Attention may be warranted for patients with ultrasound findings suggestive of LKI and TLS prior to end of treatment. CALL survivors who had severe AKI would benefit from long-term blood pressure monitoring. All eCALL survivors should have their kidney function monitored as over 1 in 4 had stage 2 CKD by early adulthood, regardless of previous AKI or HTN diagnoses.

TH-PO523
Severe AKI and CKD Are Common in Children with Veno-Occlusive Disease Following Bone Marrow Transplantation
Kylie Culley, April Rahrig, Courtney M. Rowan, Jodi L. Skiles, David S. Hains, Michelle C. Starr. Indiana University School of Medicine, Indianapolis, IN.

Background: Veno-occlusive disease (VOD) is a life-threatening complication occurring after bone marrow transplantation (BMT). The prevalence and severity of short and intermediate kidney outcomes is unknown.

Methods: Single center retrospective cohort of children with VOD following BMT from 2010-2020 (N=44). Primary outcome was treatment with kidney replacement therapy (KRT). Secondary outcomes included severe AKI and CKD at 1 year post BMT.

Results: Severe AKI developed in 35 (80%) of children with VOD and KRT was used in 21 (48%). Children receiving KRT were younger (p=0.041) and had lower pre-BMT eGFR (p=0.032). Children receiving tacrolimus for GVHD prophylaxis (p<0.001), shorter therapy (KRT). Secondary outcomes included severe AKI and CKD at 1 year post BMT. 33 (75%) survived to discharge. Of those receiving KRT, 13 (62%) used in 21 (48%). Children receiving KRT were younger (p=0.041) and had lower pre-BMT eGFR (p=0.032). Children receiving tacrolimus for GVHD prophylaxis (p<0.001), shorter therapy (KRT).

Conclusions: Severe AKI would benefit from long-term blood pressure monitoring. All eCALL survivors should have their kidney function monitored as over 1 in 4 had stage 2 CKD by early adulthood, regardless of previous AKI or HTN diagnoses.

TH-PO524
Renal Vein Thrombosis: A 10-Year Review of a Tertiary Pediatric Center Practice
Ashish Patel, Miriam Cynam, Alexander D. Lalyaniis. Birmingham Women’s and Children’s NHS Foundation Trust, Birmingham, United Kingdom.

Background: Renal vein thrombosis (RVT) is a rare diagnosis predominantly affecting neonates. Although uncommon, there is long-term risk of hypertension (HTN) and chronic kidney disease (CKD). RVT tends to be unilateral (70% of cases) but extension of thrombosis is common (52% of cases). There are many risk factors predisposing to RVT including genetic thrombophilia mutations. Current management is based solely on expert opinion or small observational studies with no consensus. The choice and length of anticoagulation, if used, is variable and recommendations vary.

Methods: We reviewed our practice of RVT at a single tertiary pediatric nephrology center in the United Kingdom. We carried out a retrospective review of RVT cases over the past 10 years to evaluate our practice and develop local consensus on management.

Results: 18 patients were screened, with 14 patients eligible for inclusion. Nearly all patients identified were neonates, diagnosed with RVT at a median age of 5.3 days. Our review found a higher proportion of cases having bilateral RVT (57%) compared to unilateral (43%), with associated thromboses occurring in 71% of cases. 86% of cases received anticoagulation initially with low molecular weight heparin (LMWH)/enoxaparin (59%), unfractionated heparin (42%) or aspirin (8%). Long term anticoagulation was predominantly LMWH (62.5%) with others receiving warfarin (25%) and one case receiving rivaroxaban. Duration of anticoagulation varied between 1 week to 6 months. Most children (79%) were investigated with a thrombophilia screen, and 45% of those investigated had a gene mutation identified (2 with prothrombin mutation and 3 with factor V Leiden mutation). Mortality was high (21%) with long term outcomes of HTN (50% of cases) and CKD (43% of cases) being common at 3 and 6 month follow up.

Conclusions: Our review, although small, highlighted the variability in RVT presentation and management. There were more cases of bilateral RVT with a high index of associated thrombus formation in our population. Most cases received anticoagulation, but we recognise the variation in practice and length of therapy. We highlight the need for thrombophilia screening as well as monitoring for long-term sequelae like HTN and CKD. We recommend that larger international studies or an RVT registry are needed to achieve consensus on management between pediatric haematology and nephrology.

TH-PO525
Congenital Single Kidney, Inferior Vena Cava Abnormality, and Bilateral Ileo-Femoral Deep Vein Thrombosis: A Case of KILT Syndrome
Amy Hearn,1 Smita Gunda,2 Queen Elizabeth Hospital King’s Lynn NHS Foundation Trust, King’s Lynn, United Kingdom; 1Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom.

Introduction: KILT (kidney and inferior vena cava (IVC) abnormalities with leg thrombosis) syndrome is a rare condition comprising of renal defects, IVC abnormalities and venous thrombosis. There is limited knowledge about its pattern of presentation, management, and prognosis.

Case Description: We present a 30-year-old lady who was referred to us with microscopic haematuria, single kidney on recent imaging and normal renal function. She later developed bilateral ileo-femoral DVT. In 2016, she presented to her General Practitioner with bilateral loin pain and positive urine dip. Computed tomography (CT) program was performed due to pyelonephritis revealing a solitary left hypertrophied kidney, hence referred to our renal clinic. She had normal renal function, no proteinuria or hypertension so renal biopsy was not clinically indicated. Renal function and urine parameters were therefore monitored annually. She presented to the Accident & Emergency department in August 2022 with pelvic inflammatory disease then developed a rigid left calf. Ultrasound Doppler demonstrated extensive DVT involving the popliteal femoral axis and anti-coagulation was commenced. Haematology screen was negative. She re-presented with right thigh pain in September 2022. CT abdomen-pelvis showed bilateral DVTs extending into the iliac veins and IVC as well as an IVC anatomical variant. In view of her having a single kidney, IVC abnormality and leg thrombosis a diagnosis of KILT syndrome was made. She has since developed a pulmonary embolism despite oral anti-coagulation.

Discussion: Most reported cases present with leg thrombosis and are later found to have absent/hypoplastic kidney. Our patient presented with a single kidney and no known history of thrombosis. The presentation therefore seems to be varied and a high degree of clinical suspicion is necessary. Could we have prevented DVT if we had imaged her...
I.VC anatomy as workup for the single kidney? Perhaps. We feel KILT syndrome should be included in the differential diagnosis of young patients with renal defects to prompt consideration of CT imaging of the I.VC. Early detection may prevent renal hypoplasia with vascular intervention. There is no consensus of prevention or management of DVTs in KILT syndrome. Therefore, long-term anticoagulation and more follow up is required.

TH-PO526
Res(e)et and Relaxation: Intractable Hypernatremia
Rishik Patel, Nithiakishna Selvathesan, Subhrata Verma, Caomhhe Costigan, Mathieu J. Lemaire. The Hospital for Sick Children, Toronto, ON, Canada.

Introduction: Sodium and water homeostasis is regulated by vasopressin (AVP) release from the anterior pituitary and its antidiuretic action on the kidney. Osmoreceptors detect changes in plasma tonicity. The osmotic threshold (or osmostat) for AVP release is ~285 mOsm/kg H2O.

Case Description: A 3-y-old boy with global developmental delay, cerebellar palsy and G-tube dependence presented with pneumonia. The plasma sodium (PNa) improved from 154 mmol/L to 151 mmol/L with increased water intake. On follow up, PNa was 157 mmol/L; he was admitted for further investigations. There was persistent sialorrhea and diaphoresis, but no medication changes, excess water losses or increased salt intake. He had stable vitals, 100g drop in weight and unremarkable examination. With no intervention, repeated bloodwork showed PNa 150 mmol/L, plasma osmolality (POsm) 309 mOsm/kg, H2O, urine osmolality (UOsm) 1019 mOsm/kg and FeNa 0.5%. All other serum electrolytes and renal indices were unremarkable. Active increase in free water intake above his usual total fluid intake resulted in a PNa nadir of 146 mmol/L, with urine osmolality of 187 mOsm/kg. These data show evidence of free water loss while still hypertonic.

Discussion: We describe a case of hypertonic hypernatremia and concomitant highly concentrated urine, indicating excellent urinary concentrating ability and adequate ADH production, effectively ruling out diabetes insipidus. Once PNa dropped below 150 mmol/L (but never less than 146), enhanced free water excretion was invariably observed. We hypothesized that these findings are in keeping with an osmostat that is reset at a higher POsm to trigger ADH release: a rarer form of reset osmostat (RO), which has remained stably high ever since.

Conclusion: There was no evidence of anterior pituitary dysfunction, and perhaps the osmostat for ADH release in this patient was reset at a higher POsm. We hypothesize this is a rare form of reset osmostat (RO). The etiology remains unclear with no hypothalamic lesion and no evidence of anterior pituitary dysfunction, and perhaps long term high osmolal diet.

Figure-1

TH-PO527
Prediction of Ionized Hypocalcemia by Anion Gap and Its Components in Children Admitted to the Intensive Care Unit: A Retrospective Cohort Study
Jmal Alhaj, Anil K. Mongia, Olutwotyon F. Bamgbola. SUNY Downstate Health Sciences University, New York City, NY.

Background: The diagnosis of ionized hypocalcemia based on total serum calcium can be misleading. Correction of total calcium for hypoalbuminemia may be erroneous because calcium binds to other anions outside of the serum albumin. In this study, we tested the hypothesis that a correction of total serum calcium for albumin and its components would improve the accuracy of a non-invasive diagnosis of ionized hypocalcemia in pediatric patients admitted to the ICU.

Methods: This is a retrospective study of patients aged 1 month to 21 years who were admitted to PICU at SUNY Downstate Medical Center between 2016-2020. All patients who had measurements of basic metabolic panel and blood gas analysis respectively taken within 60 minutes of each other were included. Logistic regression analysis for the prediction of ionized hypocalcemia using either the anion gap (AG) model, its ion components (Na, Cl, and CO2; ion model), total serum calcium, and serum albumin as independent variables was performed.

Results: Compared with the AG model, the ion model was a better predictor of ionized hypocalcemia. The value of area-under-the-curve (ROC) was 0.85 (p < 0.005) for AG model and 0.97 (p < 0.005) for the ion model (Figure 1). Both parameters were more predictive of ionized hypocalcemia than the albumin-adjusted calcium method with the value of the ROC of only 0.8 (p > 0.05), Figure-1.

Conclusions: A correction of the total serum calcium for the anion gap and its components [sodium, chloride, and CO2] respectively improved the ability to diagnose ionized hypocalcemia non-invasively in pediatric patients admitted to ICU.

TH-PO528
Clinical Features of Cystinosis and Practice Patterns: A Report of the NAPRTCS Cystinosis Registry
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Background: The NAPRTCS Cystinosis Registry was established to describe the clinical features of cystinosis in children and young adults and the associated practice patterns of providers.

Methods: Subjects ≤ 25 yrs of age with cystinosis at any NAPRTCS center are eligible for enrollment. Demographic and clinical data from time of diagnosis, time of registry enrollment, and every 6 months thereafter are collected.

Results: To date, data from 91 subjects from 30 centers diagnosed between 12/1999 and 8/2022 are available. Patient demographics and clinical features are shown in Table 1. Reported medications at diagnosis included cystine lowering medications (81.3%), cysteamine eye drops (35.2%), and phosphorus and potassium supplementation (42.9%, 40.7%) (Table 2). Procybci use progressively increased following FDA approval in 2013. Median creatinine at registry entry and 36 months post enrollment was 0.64 mg/dL (1.6gF 76.4 ml/min/1.73m²) and 0.79 mg/dL (66.1 ml/min/1.73m²), respectively. At registry entry, almost half the patients (48.9%) had a g-tube and photophobia was reported in 25.3%. Over 90% of patients were at grade level with 34.1% receiving special services. The most common subspecialty visits were ophthalmology (28.9%), endocrinology (25.6%), and GI (17.8%).

Conclusions: Children with cystinosis present early in life with the majority diagnosed before 2 years of age. Patients typically experience 5 months of symptoms prior to diagnosis, with failure to thrive present in more than 50%. Children and young adults with cystinosis have complex care needs which are often met through multispecialty care providers.

Funding: Commercial Support - Horizon, Leadiant
Updates on Renal Amyloidosis in Children and Adolescents

Suceena TH-PO529

Background: Amyloidosis affects individuals with eastern Mediterranean ethnicity; however, worldwide manifestation is frequent because of worldwide human migration. Although renal amyloidosis (RA) is a potentially fatal disease, it is relatively rare in children and adolescents. Its early manifestation as nephrotic syndrome may be mistaken for a minimal change disease. Familiarity with its geographical spread and pattern of presentation may enhance diagnostic awareness. For this purpose, we embarked on a PubMed search for articles on pediatric RA.

Methods: We searched the PubMed and Embase databases from 1960 to 2022 for relevant original articles including case reports and case series on RA in children and adolescents.

Results: RA occurred (n = 679) commonly among a population affected by familial Mediterranean fever (FMF) (n = 2812) who were mostly residents of Turkey (n = 1907) and Lebanon (n = 836). The second most common cause of RA was idiopathic juvenile arthritis (JIA) (n = 139). Other reported causes were tuberculosis (TB) (n = 10) and epidermolysis bullosa (EB) (n = 13). In general, there was often renal remission following early diagnosis and treatment of FMF, JIA, and TB. The poor response to treatment in EB frequently resulted in end-stage kidney disease and fatal outcomes. There were only 6 cases of hereditary RA, three of which were due to ALyS amyloid deposition. There was a single report of ALECT2 disease.

Conclusions: Most cases of pediatric RA were due to auto-inflammatory syndromes. Acquired causes were mostly due to JIA. Early treatment frequently resulted in renal remission. Finally, resources for modern genetic diagnosis most likely influenced the prevalence and geographical spread of the disease. Ref Picken MM. Current Understanding of Systemic Amyloidosis and Underlying Disease Mechanisms. Am J Cardiol. 2022;185: S2-S40.

Elevated Serum Gd-IgA1/s.IgA Levels and Not Serum Gd-IgA1 Alone Is an Independent Risk Factor for Composite Outcome in South Asian IgA Nephropathy (IgAN)

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Background: The role of serum Gd-IgA1 in a prospective longitudinal South Asian IgAN cohort (GRACE-IgAN1) and the impact of immunosuppression is not known.

Methods: We measured serum galactose-deficient IgA1 (s.Gd-IgA1) levels in 170 IgAN patients, 40 disease controls, and 27 healthy controls by K/M5 ELISA (Biotrin International, Dublin, Ireland). s.Gd-IgA1 levels were assayed at baseline. Longitudinal measurements were made at 1 year and 2 years in a subgroup of 117 IgAN patients who received a short course of immunosuppression. The baseline associations and the usefulness of s.Gd-IgA1 as a diagnostic and prognostic biomarker was assessed.

Results: s.Gd-IgA1 had significant positive correlation with serum immunoglobulin A (s.IgA) (r=0.6, n=1170, p=0.001). Neither s.Gd-IgA1 nor s.Gd-IgA1/s.IgA ratio was a diagnostic marker for IgAN. s.Gd-IgA1/s.IgA ratio had stronger baseline and longitudinal associations than s.Gd-IgA1 alone. Elevated s.Gd-IgA1/s.IgA ratio was significantly associated with baseline clinical and histopathological indices of activity and chronicity. In the subgroup that received immunosuppression, there was significant decrease in both s.Gd-IgA1 and s.IgA at 1 year. The mean time to the composite outcome was significantly shorter for each quartile increase in s.Gd-IgA1/s.IgA ratio by Kaplan-Meier survival analysis (<1.3 vs. 1.3-1.7 HR 3.3 (95% CI 1.2-9.1), 1.7-2.3 HR 4.3 (95% CI 1.6-11.9), >2.3 HR 6.2 (95% CI 2.4-16.2), p<0.001). Higher median s.Gd-IgA1/s.IgA ratio was an independent predictor for composite outcome by Cox proportional-hazards (HR 2.3, 95% CI 1.2-4.5, p=0.01) model and outperformed 24-hour urine protein.

Conclusions: We have shown for the first time in IgAN with South Asian ethnicity, the relevance of proportion of s.Gd-IgA1 to total serum Iga for risk stratification, its association with prognosis and its longitudinal changes with immunosuppression. The results need to be externally validated.

Funding: Government Support - Non-U.S.
TH-PO532

Elevated Levels of IL-6 in IgA Nephropathy Patients Are Induced by an Epigenetically Driven Mechanism Medulated by Viral and Bacterial RNA

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**Background:** Immunoglobulin A nephropathy (IgAN) is the most frequent primary glomerulonephritis characterized by the presence of IgA immune complexes in the glomeruli. Newly, the role of IL-6 in pathogenesis is becoming increasingly important, but reason why levels of IL-6 are elevated in IgAN patients is not well understood. One attainable hypothesis comes out from our recent whole genome DNA methylation screening in IgAN patients, that identified, among others, a hypermethylated region containing Vinculin (VNL-2-1) (VTRNA2-1), a non-coding RNA.

**Methods:** Total RNA were isolated from PBMCs of IgAN patients, transplanted IgAN patients (TP-IgAN), non-IgAN transplanted patients (TP) and healthy subjects (HS). VTRNA2-1, CREB and PKR transcripts were evaluated by RT-PCR. Total and phosphorylated PKR, CREB and IL-6 proteins were evaluated by ELISA. Poly (I,C), a synthetic analogue of dsRNA, and Pfizer-BioNTech COVID-19 vaccine were used to transfacet patient PBMCs. PKR inhibitor Iovinex (C16) 1 µM was used to stimulate patient PBMCs.

**Results:** Here we confirm that VTRNA2-1 is low expressed in IgAN subjects compared to HS and we found that also in transplanted IgAN patients (TP-IgAN), compared to non-IgAN transplanted patients (TP), the VTRNA2-1 transcript was expressed at level very low. We found that in IgAN patients with downregulated VTRNA2-1, PKR is overactivated, coherently with the role of the VTRNA2-1 that binds to PKR and inhibits its phosphorylation. The loss of the VTRNA2-1 natural restraint caused the activation of CREB by PKR, a classical AMP-activated CRE-binding factor interacting with a region of the IL-6 promoter and leading to IL-6 production, both in IgAN and in TP-IgAN patients. PKR is normally activated by bacterial and viral RNA and we found that both the RNA polyc(C) and the COVID-19 vaccine stimulation significantly increase the IL-6 levels in PBMCs from HS but had an opposite effect in those from IgAN patients.

**Conclusions:** In conclusion, the discovery of the upregulated VTRNA2-1/PKR/CREB pathway in IgAN patients may provide a novel approach to treat the disease and may be useful for development of precision nephrology and personalized therapy, possibly by checking the VTRNA2-1 methylation level in IgAN patients.

**Funding:** Private Support Foundation

TH-PO533

Topological Analysis of High-Resolution Spatial Transcriptomics Reveals Immune Glomerular Architecture of Lupus Nephritis

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**Topological Analysis of High-Resolution Spatial Transcriptomics Reveals Immune Glomerular Architecture of Lupus Nephritis**

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**TH-PO534**

ACE in Granulocytes Has a Protective Role in Crescentic Glomerulonephritis via Complement Lectin Pathway Independent of Angiotensin II

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**Background:** ACE is a well-known enzyme to regulate blood pressure and inflammation, and structurally has two enzymatic domains: N-domain and C-domain. Its C-domain regulates blood pressure by producing angiotensin II in renin-angiotensin system. We recently reported a novel function of ACE: ACE overexpressed neutrophils have a protective role in immune complex (IC)-mediated crescentic glomerulonephritis (GN) via complement C3b-CR1/2 axis, efficiently removing IC deposits. Here, we show that ACE-C-terminal catalytic domain is responsible for the renoprotective role in myeloid cells in crescentic GN via lectin pathway.

**Methods:** We induced the nephrotoxic serum nephritis (NTN) in C57Bl/6 (WT), Jw mice that overexpressing ACE in myeloid cells (neutrophils and monocytes/macrophages), Jc mice that overexpressing C-domain knockout ACE in myeloid cells, and Jn mice that overexpressing N-domain knockout ACE in myeloid cells, and evaluated renal function and histology (crescent formation and fibroinoid necrosis). In addition, we examined complement pathway activation in vitro and blood angiotensin II level.

**Results:** 7 days after induction of NTN, Jw mice showed less severe proteinuria and mild histological glomerular damages, showing overexpressed ACE in neutrophils and monocytes/macrophages has the protective role in IC-mediated crescentic GN. When we induced NTN in Jc mice and Jn mice, Jc mice lost the renoprotective effects and Jn mice showed the severe glomerular damage. These data clearly showed that ACE C-domain, but not N-domain, has the renoprotective role. Regarding complement activation, recombinant ACE activated lectin pathway, but not classical and alternative pathways. Given the normal blood pressure level and the normal plasma angiotensin II level in all these mouse strains, the ACE C-domain mediated renoprotective effect is independent of angiotensin II.

**Conclusions:** ACE C-domain in granulocytes has a protective role in crescentic glomerulonephritis via complement lectin pathway independent of Angiotensin II.

**Funding:**

TH-PO535

Integrin β6 Regulates Tubuloglomerular Feedback Through the NKC22-COX2/nNOS Pathway

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**Background:** Integrin β6 (β6) is a protein expressed in some tubules and macula densa cells, which mediates transpressing growth factor-β (TGF-β). Our previous studies showed that β6+ mice exhibit milder tubulointerstitial fibrosis but more severe glomerulosclerosis than wild type (WT) after 5/6 nephrectomy. This study aimed to explore the involvement of macula densa integrin β6 in the dysfunction of tubuloglomerular feedback.

**Methods:** We first knocked down β6 in mouse macula densa cells (MMDD1) and exposed them to high salt. The expression of Oxidative Stress Responsive Kinase 1 (OXS1), a regulator of NKC22 activity, was assessed by qPCR. The protein

**Results:**

**Acknowledgments:** This work is supported by NIH grants (DK070093, DK039282, and GM117298) awarded to A. Fogo.

**Conclusions:** Our study adds an additional layer to the complex interplay between TGF-β and tubuloglomerular feedback. The role of β6 in the TGF-β system warrants further study to understand its precise role in glomerulosclerosis.

**Funding:**

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

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expressions of NKCC2, COX2, and nTOS were analyzed by western blot. We then measured renal clearance before and after acute volume expansion in β6 and WT mice. 

Results: Immunostaining showed that integrin β6 and NKCC2 colocalized on the cell membrane of MMD1. Knockdown of β6 significantly increased the expression of OXSR1 and NKCC2 and induced more nTOS and less COX2 compared to WT cells. High salt reduced COX2 and increased nTOS protein expression in WT, which was not changed in β6 knockdown cells. In vivo, following acute volume expansion with 3% of body weight volume of isotonic saline over 5 min, blood pressure decreased minimally and similarly in both groups at 15 min and recovered to the baseline level at 30 min after volume expansion. GFR of WT mice increased at 30 minutes and returned to baseline at 90 min. In contrast, integrin β6 knockout mice reached peak GFR at 60 min, but ultimately returned to baseline at 90 min.

Conclusions: These findings suggest that integrin β6 regulates tubuloglomerular feedback through the NKCC2-COX2/nTOS pathway. The dysfunction of tubuloglomerular feedback induced by β6 knockout on macula densa cells may contribute to the observed mismatch in tubulointerstitial fibrosis and glomerulosclerosis in β6−/− mice after 5/6 nephrectomy.

Funding: NIDDK Support

TH-PO536

Lambda Light Chain Predominance Links C1q Deposition to Endocapillary Hypercellularity in IgA Nephropathy

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Background: Involvement of the complement system is a key driver of immune complex-mediated nephritogenicity in immunoglobulin A nephropathy (IgAN), being the most prevalent primary glomerulopathy worldwide. Despite growing insights on the implications of glomerular complement deposition remain largely elusive. Therefore, we here aimed to systematically assess the correlative pattern of clinicopathological findings and glomerular C1q and C3c deposits by means of multivariable linear regression.

Methods: A total of 37 patients with biopsy-proven IgAN obtained between 2016 and 2021 were retrospectively included in a single center observational study. Clinical data assessment comprised age, sex, serum creatinine levels, blood urea nitrogen, eGFR, complement C3/ C4 and proteinuria. Oxford-scored lesions mesangial (M) and endocapillary hypercellularity (E), segmental sclerosis (S), tubular atrophy (T), crescentic formation (C), and other lesions scored analogous to the Banff classification were evaluated. Immune histochemistry-detected glomerular deposits of complement factors C1q/ C3c and kappa (κ)/λ LCs were semiquantitatively scored. Two groups were formed according to the λ-LC status: λ-LC positive (n=29) and λ-LC negative (n=17). Clinicopathological correlations were analyzed in both groups regarding glomerular C1q and C3c deposits by means of multivariable linear regression.

Results: Enrolled patients featured a median creatinine level of 1.5 mg/dL. Cλ and C3c deposition featured no significant association with serum parameters indicative of kidney injury or proteinuria. We identified endocapillary hypercellularity to feature the strongest association with glomerular C1q deposition in the λ-LC positive group (p=0.7, β=0.745, p<0.001). In the λ-LC negative group, a significant correlation of C3c deposition and mesangial hypercellularity was identified (p=0.6, β=0.762, p<0.001).

Conclusions: We here show a correlative pattern of λ-LC-associated deposition of complement factors C1q and C3c in distinct histopathological features of IgAN implying an involvement of the classical pathway in the preset of λ-LC predominance.

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Classical Monocyte-Derived and Lipid-Associated TREM2+ Macrophages Orchestrate Inflammatory and Fibrotic Processes in ANCA-Associated Glomerulonephritis

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Background: ANCA-associated glomerulonephritis (AGN) associates with a high risk of end-stage kidney disease. Kidney macrophage infiltration is one of the main histological hallmarks of vasculitic lesions and is strongly linked to disease activity. The role of kidney macrophages in local inflammation remains unclear. Here we investigate kidney macrophage diversity and function.

Methods: Single cell transcriptome analysis of CD45+ immune cells from freshly retrieved kidney biopsies of 5 AGN patients, 1 disease-control with class 2 lupus nephritis (LN), and 1 nephrectomy control (NC) was performed using 10X Genomics technology. Myeloid cells were selected and subsequently reclustered to identify disease-specific macrophage subtypes and functionality was assessed by a gene set enrichment analysis (GSEA). Validation studies were performed using flow cytometry and immunohistochemistry.

Results: Focused analysis identified 2 monocyte-derived macrophage (MDMs) clusters and 2 new TREM2+ lipid-associated macrophage (LAMs) subtypes, C1q- and SPP1+ Osteopontin+ LAMs (panel A). GSEA revealed increased interferon responses in MDMs compared to LAMs (panel B), and increased TNFα signaling via NFκB in classical MDMs compared to non-classical MDMs. SPP1+ LAMs showed upregulation of gene sets related to fibrosis and cell cycle. Evaluating kidney macrophage subsets between diseases revealed increased % classical MDMs and LAMs in AGN (respectively, 52% and 38%) compared to NC tissue (18% and 24%) (panel C). Flow cytometric analysis identified a similar increase in peripheral blood classical monocytes during active disease (P<0.0001).

Conclusions: Classical MDMs and LAMs are the main kidney macrophage subsets present in AGN. Classical MDMs drive inflammation, whereas SPP1+ TREM2+ LAMs orchestrate fibrosis. Targeting these specific macrophage subsets may potentially reduce acute kidney injury and long-term fibrosis.

TH-PO538

Evaluation of Intrarenal Plasmacytid Dendritic Cells in Active Lupus Nephritis

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Background: Interferon-alpha (IFNα)-responsive gene expression is highly upregulated in the kidneys of patients with active lupus nephritis (LN). Infiltrating plasmacytid dendritic cells (pDCs) have been postulated to be a source of intrarenal IFNs. In this study we quantified intrarenal pDCs in patients with LN and correlated infiltration with histologic activity and chronicity.

Methods: Immunohistochemistry (IHC) for BDCA-2, a marker of pDCs and a subset of plasmacytoid dendritic cells (pDCs) was used to evaluate intrarenal pDCs. All pDCs within a biopsy were counted and the average number of glomeruli and the number of tubulointerstitial pDCs per unit area were determined. The NIH activity and chronicity indices were calculated. IHC for MX1, an IFNα-inducible protein was used to characterize the interferon response.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Results: We studied 18 patients with proliferative (70% (n=12)) or proliferative + membranous glomerulonephritis (30% (n=6)) with at least a LN diagnosis for 1-6 years. Patients were biopsied for suspected LN flare. pDCs were found mainly as individual cells within the tubulointerstitium in these kidney biopsies, and were seldom seen within glomeruli. In some biopsies, aggregations of pDCs were observed in areas of tubulointerstitial inflammation or surrounding glomeruli. A median (range) of 0 (0-0.62) pDCs/glomerulus and 2.7 (0.77-49) pDC/mm² of tubulointerstitial tissue were found. There was no evidence of an association between tubulointerstitial pDCs and serum creatinine, proteinuria, activity index, or chronicity index. MX1 immunoreactivity was found within the kidney, including glomerular and tubulointerstitial epithelial cells, glomerular and tubulointerstitial endothelial cells, vascular wall smooth muscle cells, and infiltrating inflammatory cells.

Conclusions: pDCs are thought to be the major source of IFNα in the kidneys of patients with LN. If this is true, our data suggest that very few infiltrating pDCs are needed to initiate a robust IFNα response within the kidneys.

Funding: Commercial Support - Biogen

TH-PO539

The Balance Between STAT3 and Glutathione Metabolism Is Required for PARal Cell Activation and Proliferation in Proliferative Glomerulopathies

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Background: STAT3 signalling is activated in podocytes and parietal epithelial cells (PECs) in murine models of proliferative glomerulopathy and in human RGN and subtypes of FSGS. We previously showed that podocyte-specific loss of STAT3 preserves podocyte loss and reduces proteinuria in PECs. However, the mechanism by which STAT3 activation triggers PEC activation, proliferation, and crescent formation and whether its inhibition as a therapeutic target in proliferative glomerulopathies remains poorly understood.

Methods: PECs were treated with increasing doses of IL-6 (5, 10, 20, 40ng/ml) to express a range of STAT3 activation in cell viability. We generated mice PECs as a deletion of STAT3 using Crisper/Cas9. MT assay was performed on Cas9 (wildtype) and STAT3 knockout (STAT3-/-) PECs. Cell migration of Cas9 and C7 cells were measured using a scratch assay. Mitochondrial respiration, glycolytic rate, and ATP production were performed on PECs. Glutathione, superoxide, and reactive oxygen species (ROS) levels were measured. RNA sequencing was conducted in the Cas9 and STAT3-/- PECs. PEC-specific STAT3-/- mice were generated as well as STAT3 inhibitor treatment in mice in n-potsheroxie serum (NTS) administration.

Results: STAT3-/- PECs exhibited reduced cell proliferation, activation, oxygen consumption, and ATP production. RNAseq demonstrated a downregulation of differential expressed genes (DEGs) involved in glutathione metabolism with an upregulation in focal adhesion DEGs. STAT3-/- PECs had reduced cellular glutathione pool leading to increased levels of superoxide levels leading to increased oxidative stress and DHE expression. In silico analysis showed that pSTAT3 occupies the promoter region of key glutathione synthesis genes, suggesting potential direct regulation. PEC-specific STAT3-/- mice or treatment with STAT3 inhibitor reduced proteinuria, PEC activation (CD44, Akap12), crescent formation with increased oxidative stress (8-endo-G, OGG1) as compared to their respective controls post-NTS treatment.

Conclusions: To date, this is the first study to demonstrate the mechanism by which STAT3 activation in PECs enhances glutathione metabolism to maintain a balance in ROS and ATP levels in PECs and associated crescent formation in proliferative glomerulopathies.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO540

Association of a New Variant of Complement Regulator FHR2 with C3 Glomerulopathy

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Background: C3 glomerulopathy (C3G) is caused by a dysregulation of the complement system leading to C3 deposition and formation of glomerular deposits. Several C3 patients harbor mutations or copy number variations in the human Factor H (FHR) gene (FHR1, FHR2, and FHR3) genes. Therefore, FH and FHRs are emerging immune targets for inhibition of the complement cascade, as well as markers to monitor patients on complement regulator drugs to test their efficiency.

Methods: Here, we focused our study on FHR2, known to inhibit in vitro formation of the terminal complement complex. We identified new variants for the FHR2 gene in a cohort of C3G patients and performed detailed functional studies on the novel variant FHR2_L46. We sequenced the Pro at position 46 replaced by Leu. Patients with FHR2_L46 variant presented increased FHR2 plasma levels, as compared to controls and displayed FHR2 deficiency. We generated a recombinant FHR2 mutant protein to gain insight into the effect of this novel FHR2 variant on complement regulation.

Results: As the amino acid exchange occurred in the first short consensus repeat (SCR1), we first tested if the Leu at position 46 altered FHR2 homodimerization and FHR2 with FHR1 and FHR5. We observed that FHR2_L46 mutant forms stable oligomers with FHR5 and enhanced complement activities.

Conclusions: Taken together, the present study identified a novel FHR2_L46 variant in a C3G patient and suggests that the FHR2_L46 mutant forms stable oligomers with FHR5 and enhanced complement activities.

TH-PO541

An Integrated Proteome-Transcriptome Organoid Atlas Illuminates Core Concepts of Kidney Disease

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Background: The use of kidney organoids as a model for studying kidney disease shows great promise, but their potential is limited by our limited understanding of the proteins they express and their functional profiles. In this study, we aimed to address this limitation by examining the proteome and transcriptome of organoids throughout their culture period and in response to TNFα, a cytokine stressor.

Methods: In our study, we employed proteomic analysis to compare kidney organoids with other established model systems (mainly mice) including native glomeruli and cultured podocytes. We examined the developmental trajectory of organoids and explored their innate immune responses, thereby expanding the applicability of organoids as a valuable model system in the field of nephrology. Additionally, we performed a comprehensive comparison of our proteomic data with both bulk and single-cell transcriptomics data, providing a more comprehensive understanding of the molecular landscape of kidney organoids.

Results: We found that older organoids displayed increased accumulation of extracellular matrix while showing decreased expression of glomerular proteins. By integrating mRNA-seq and single-cell transcriptomic data, we discovered that most changes in the proteome were localized to podocytes, tubular cells, and stromal cells. Treatment of the organoids with TNFα resulted in the differential expression of 322 proteins, including cytokines and complement components. Importantly, the transcript expression of these 322 proteins was significantly higher in individuals with poorer clinical outcomes in proteinic kidney disease. Notably, key proteins associated with TNFα (C3 and VCA1M) were found to be increased in both human tubular and organoid kidney cell populations, indicating the potential of organoids to advance the development of biomarkers. VCA1M was localized to the descending thin limb (DTL) of proteinuric patients with kidney disease.

Conclusions: By integrating various ‘omic’ layers of kidney organoids, incorporating a relevant cytokine stressor, and comparing with human data, we highlight the significance of kidney organoid modeling in understanding and studying complex human kidney disease.

Funding: NIDDK Support, Other NH Research Support - The Nephrotic Syndrome Study Network (NEPTUNE) is part of the Rare Diseases Clinical Research Network (RDCRN), which is funded by the National Institutes of Health (NIH) and led by the National Center for Advancing Translational Sciences (NCATS) through its Division of Rare Diseases Research Innovation (DRDRI), Government Support - Non-U.S.

TH-PO542

Identification of Conserved Gene Expression Changes Across Common Glomerular Diseases by Spatial Transcriptomics

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Background: Glomerular diseases encompass a group of kidney diseases that may share common gene expression pathways. We aimed to analyze glomerular-specific gene expression profiles across various glomerular diseases.

Methods: We performed spatial transcriptomic profiling using formalin-fixed paraffin-embedded kidney biopsy specimens of controls and patients with five types of glomerular diseases using the GeoMX Digital Spatial Profiler. We identified common differentially expressed genes (DEGs) across glomerular diseases and performed Gene Ontology (GO) annotation using the TopGene suite.

Results: A total of 35 DEGs were consistently downregulated in glomeruli across the disease compared to the control, while none of the DEGs were consistently upregulated. Twelve of 35 downregulated DEGs, including the two hub genes FOS and JUN, were annotated in the molecular function GO terms related to DNA-binding transcription factor activity. The annotated biological process GO terms included response to lipid-related (C3 and VCAM1) responsive to lipid-related (C3 and VCAM1), response to steroid hormone (12/35 DEGs), or cell cycle regulation (10/35 DEGs).

Conclusions: Identifying common DEGs by spatial transcriptomic analysis provides insights into underlying molecular mechanisms of glomerular diseases and may lead to novel assessment or therapeutic strategies.

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**TH-PO544**

Comparing Different Pathogenic Patterns Between Immunoglobulin A Nephropathy and Lupus Nephritis Using Integrated Bioinformatics

**Analysis**

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**Background:** Immunoglobulin A nephropathy (IgAN) and lupus nephritis (LN) are the most common primary and secondary glomerular diseases, respectively, sharing several similarities in clinical presentations. Common pathogenic mechanisms in IgAN and LN have been well established by previous studies. However, it is confusing how these two independent diseases carrying distinct pathological features are manifested, or if the similarities between them. Therefore, different mechanisms of the pathogenesis between IgAN and LN were compared in this study.

**Methods:** Glomerular gene expression profiling data were acquired from the Gene Expression Omnibus (GEO) database. R packages were used for the data processing. Least Absolute Selection and Shrinkage Operator (LASSO) regression analysis and multivariate logistic regression analysis were used to construct models predicting IgAN and LN. Cibersort processed the analysis of immune cell infiltration in IgAN and LN. RT-qPCR was used to validate the gene expression in the human renal mesangial cells (HRMC).

**Results:** In the regressing models generated on differentially expressed genes (DEG) and weighted correlation network analysis (WACNA), retinoic acid receptor γ (RARG) and prolactin releasing hormone (PRLH) were independent risk factors for IgA1- and C4d-TET domain containing 1 and CX3CR1-expressing T regulatory cells. Differences in the expression data might represent a promising point of action to increase renal migration of these Tregs in vitro and in vivo. Ultimately, the therapeutic potential in attenuating NTN will be assessed.

**Conclusions:** The expression of CX3CL1 is upregulated in nephritic kidneys and might therefore represent a promising point of action to increase renal migration of ex vivo induced T regulatory cells. A viral vector was successfully cloned to generate CX3CR1 expressing Tregs. Future experiments will validate the suppressive function of these Tregs in vitro and in vivo. Ultimately, the therapeutic potential in attenuating NTN will be assessed.

**TH-PO545**

Characterization of Cell Surface Glycophenotypes of IgA1-Secreting Cells Reveals Distinct Subpopulations and Correlation with Glycosylation of Galactose-Deficient IgA1 in IgA Nephropathy

**TH-PO545**

**Generation of CX3CR1-Expressing T Regulatory Cells Using Retroviral Transduction**

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**Background:** T cells play a central role in the pathogenesis of acute glomerulonephritis. Studies in rodent models as well as observations in patients suggest an imbalance of pro-inflammatory T effector cells and anti-inflammatory T regulatory cells (Treg), resulting in autoimmune-mediated glomerular injury. Increasing the T regulatory cells in the inflamed kidney might restore the T cell balance and, thus, attenuate disease. This could be achieved by transfection of Tregs equipped with specific chemokine receptors to increase their migration into the inflamed kidney. In this regards, the CX3CR1-CX3CL1 axis represents a promising target, as it has been implicated in a variety of inflammatory diseases in the kidney.

**Methods:** The nephrotoxic nephritis model (NTN) is used to assess the distribution of CX3CL1 in the kidney using IHC stainings. The expression of CX3CR1 on renal and splenic immune cells during homeostasis and NTN is analysed using flow cytometry. Standard cloning techniques are used to design a retroviral vector for transduction of naive murine T cells.

**Results:** Flow cytometry analysis after 7 days of nephrotoxic nephritis reveals CX3CR1 expression mostly on macrophages and classical dendritic cells Type 2 in the kidney and spleen. Renal and splenic T cells, on the other hand, express less CX3CR1, with about 20% of cytotoxic T cells and 10-15% of Tregs and Th17 cells expressing the receptor. Immunohistochemistry reveals increased Fractalkine expression in nephritic kidneys compared to healthy controls. To generate induced Tregs expressing CX3CR1, the protein coding sequences for CX3CR1 or eGFP were linked with a P2A site to the sequence for Foxp3 and introduced into a MSCV retroviral vector system. This vector will be used for transfection of the Phexin-Eco packaging cell line to produce virions for subsequent transduction.

**Conclusions:** The expression of CX3CL1 is upregulated in nephritic kidneys and might therefore represent a promising point of action to increase renal migration of ex vivo induced T regulatory cells. A viral vector was successfully cloned to generate CX3CR1 expressing Tregs. Future experiments will validate the suppressive function of these Tregs in vitro and in vivo. Ultimately, the therapeutic potential in attenuating NTN will be assessed.
Conclusions: We found an inverse correlation of cell-surface GalNAc sialylation with non-sialylated in PNA-high cells. This observation suggests that some glycosyltransferase pathways are regulated by distinct mechanisms with different impact on cell-surface glycophenotypes and IgA1-glycosylation.

Funding: NIDDK Support

TH-PO546

Nucleotide-Sensing TLR9/TLR7 System Is a Potential Therapeutic Target for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Galactose-deficient IgA1 (Gd-IgA1) is a key effector molecule in the pathogenesis of IgAN. Previous reports indicated that toll-like receptor (TLR)9/7 and TLR8 are involved in synthesizing Gd-IgA1. TLR9 and TLR7 recognize bacterial DNA and RNA, respectively. Several clinical trials suggested that hydroxychloroquine (HCQ), known to suppress TLR9/TLR7, might effectively treat IgAN. The present study aimed to clarify whether TLR9/7LR7 could be therapeutic targets for IgAN.

Methods: We first divided the 60 mice, the spontaneous IgAN model, into the control group, HCQ administered group, CpG-ODN (ligand of TLR9) nasally administered group, CpG-ODN + HCQ group, Imiquimod (ligand of TLR7) nasally administered group, and Imiquimod + HCQ group, respectively. We analyzed the serum aberrantly-glycosylated IgA, IgG-IgA immune complexes (IC), proteinuria, and renal pathology. Next, we cultured the splenocytes of the mice with CpG-ODN or Imiquimod. We analyzed the effect on the synthesis of aberrantly-glycosylated IgA. Finally, we cultured tonsillar mononuclear cells (TMCs) from IgAN patients with CpG-ODN or Imiquimod. We analyzed the cellular expression of C1GaLG1, an enzyme involved in IgA glycosylation, and the supernatant Gd-IgA1 levels.

Results: The mice administered with CpG-ODN or Imiquimod showed elevated serum levels of aberrantly-glycosylated IgA and IgG-IgA IC. Furthermore, these mice showed aggravated proteinuria. Renal pathological findings further confirmed glomerular mesangial proliferation accompanied by significant IgA/1G/C3 deposits. The mice co-administered with HCQ did not show the changes that CpG-ODN or Imiquimod induced. The splenocytes of the mice significantly elevated IL-6, known to affect IgA glycosylation, and promoted aberrantly-glycosylated IgA when stimulated by CpG-ODN or Imiquimod. In the human studies, stimulation with CpG-ODN or Imiquimod let the cultured TMCs promote IL-6 synthesis, downregulated C1GaLG1 and consequently enhanced the production of Gd-IgA1.

Conclusions: Present data suggested that nucleotide-sensing TLR9/7LR7 are involved in the pathogenesis of IgAN and might be the candidates for disease-specific therapeutic targets.

TH-PO547

Differentiating Lupus Nephritis Classes Using Peripheral Blood DNA Methylation

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Background: Approximately 60% of patients with systemic lupus erythematosus (SLE) develop nephritis. Histologically-determined disease classification provides clinically actionable information including administration of kidney-specific immunosuppression. Given the pivotal role of autoimmunity in SLE, we hypothesized that DNA methylation patterns of immune cells could distinguish between the different lupus nephritis classes.

Methods: We identified 25 participants from the Yale Kidney Biobank with biopsy-confirmed lupus nephritis. DNA was extracted from blood buffy coat. DNA methylation was analyzed using Illumina MethylationEPIC V2.0, surveying > 935,000 CpG loci. β-values (percent methylation) were derived using the R Sesame package. KEGG pathway enrichment and differential methylation analyses were performed, comparing class II participants to those with more advanced nephritis (III, IV, V).

Results: We identified 3 participants with class II disease, and 22 participants with classes III, IV, or V disease. Enrichment analysis identified differential methylation in Rap1 signaling, focal adhesion, and MAPK signaling pathways between the two groups (q-values < 0.05). Participants with advanced lupus nephritis exhibited ERK hypermethylation and Rap1 hypomethylation compared to those with class II. We identified 5 CpG loci that were differentially methylated between the two groups (adjusted p-values < 0.045). Unbiased hierarchical clustering based on the top 25 differentially methylated loci revealed that those with class II nephritis have distinct methylation profiles as compared to those with more advanced nephritis (Figure 1).

Conclusions: Our findings suggest that DNA methylation patterns in immune cells may distinguish between lupus nephritis classes, potentially guiding the decision to conduct a kidney biopsy. The observed methylation differences in ERK and Rap1 pathways, which are involved in SLE pathobiology, among advanced lupus nephritis classes may provide valuable insights into disease pathogenesis.

Funding: NIDDK Support, Private Foundation Support

TH-PO548

Deciphering the Contribution of Inflammatory Macrophages to Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) refers to a histologic pattern of glomerular injury that can result from heterogeneous disease entities, which in turn respond differently to therapeutic regimens. Causes for FSGS include immunological diseases that respond to immunosuppressive treatments. Modern biotechnological tools allow us to characterize diseases resulting in an FSGS pattern in detail with the prospect of providing pathophysiology-based precision medicine for the patients.

Methods: We used a genetic model (heterozygous compound mutations in Nphp2) that causes a slowly progressive FSGS phenotype with a strong intraglomerular immune cell infiltrate. In order to characterize these immune cells in depth and to identify glomerular communication patterns, we employed bulk and single nucleus RNA sequencing of glomerular isolates, flow cytometry, and immunohistochemistry.

Results: We identified myeloid cells to be the most abundant immune cells in diseased glomeruli. A macrophage subpopulation with an M2-like, tissue-remodeling transcriptomic signature significantly expanded over time, which correlates with proteinuria. We confirmed such intraglomerular infiltration of macrophages by immunohistochemistry, and detected macrophages in the tubulointerstitium at a later stage of the disease. snRNA-seq-based ligand-receptor-target gene network analysis indicated progressively altered signaling between glomerular cells resulting in a pro-fibrotic inflammatory milieu characterized by strong signaling activity of the TGFβ-superfamily and upregulation of CC-chemokines and matrix metalloproteinases. Intriguingly, fractalkine (CX3CL1), a macrophage recruiting chemokine, was strongly upregulated at an early stage of the disease. Immuno-staining localized fractalkine to glomerular endothelial cells while flow cytometry showed significant upregulation of its receptor CX3CR1 on macrophages.

Conclusions: In this model, a mutation in a slit-diaphragm protein results in a glomerular fibro-inflammatory phenotype with strong macrophage infiltration that may be linked to fractalkine. Based on these results, our project might provide the rationale for new therapeutic approaches in FSGS.

Funding: Government Support - Non-U.S.

TH-PO549

Identifying Targetable Renal Immune Pathways in Lupus Nephritis


Background: Lupus nephritis (LN) is characterised by renal immune-complex (IC) deposition, how these deposits trigger inflammatory mediators, and signalling between resident and recruited cells is unclear. Mouse lupus models share clinical features of human disease including renal involvement. Using single-nucleus RNA sequencing (snRNA-seq), we compared two models of early LN, to identify disease drivers, potential therapeutic targets, and to establish an approach translatable to human kidney.

Methods: Kidney sections from autoimmune MRL/lpr mice aged 15-weeks, or Balb/c mice treated for 8 weeks with topical TLR7 agonist (IMQ) and respective controls, were processed for histology, immunofluorescence (IF), flow cytometry and snRNA-seq.

Results: IMQ kidneys showed IC deposition, mesangial expansion, and endothelial proliferation consistent with class-II LN. MRL/lpr mice additionally developed crescents, and class-III LN. Transcriptomic data from 92k nuclei identified clusters corresponding to resident and immune populations. Early S1/S2 proximal tubule segments were identified as interferon (IFN) susceptible targets in both models. Intrarenal T, B, and myeloid cells were enriched in diseased mice. MRL/lpr mice had the largest immune infiltrate, indicating RNA and CD8 T cells expressing markers of cytotoxicity and exhaustion (Gzma, Pdcd1). Integrated analysis with human immune LN single cell data (Arazi et al., 2019), showed overlap with MRL/lpr phenotype with cytotoxicity and exhaustion

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Mechanistically, CD11b activation reduced TLR7-dependent activation of NFκB to suppress Gal-3 expression.

**Conclusions:** We demonstrate that CD11b activation reduced TLR7-dependent suPAR levels in models of LN. These studies provide further support for CD11b activation as a therapeutic strategy for LN.

**Funding:** NIDDK Support

**TH-PO552**

**In Vitro Expansion of Regulatory T Cells Restores Functional Capacity in ANCA Vasculitis**

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**Background:** ANCA vasculitis is an autoimmune disease characterized by loss of tolerance to one of two main ANCA autoantigens, myeloperoxidase or proteinase 3.

**Methods:** Tregs defined as CD4+, CD27low, CD25high, and CD45RA+ were identified using mass spectrometry of uEV we identified potential non-invasive biomarkers for treatment response to voctosporin in patients with LN. In addition, we were able to characterize the altered processes in the patients responding to voctosporin, which included complement and a specific change in neutrophil-associated proteins.

**Funding:** Commercial Support - Aurinia Pharmaceuticals

**TH-PO551**

**Autoantibodies Against Laminin-521 Are Pathogenic in Anti-Glomerular Basement Membrane Disease**

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**Background:** We previously demonstrated that laminin-521 is a novel autoantigen within the GBM and that antibodies to laminin-521 are present in about one-third of patients. However, definitive evidence for a pathogenic role of these antibodies has lacking.

**Methods:** In a study, a rare case of atypical anti-GBM disease whose serum was negative for anti-α3(IV)NC1 and phosphate-buffered saline, respectively. Data was analyzed with Spectronaut and proteins with a log2-fold change >1 and q-value <0.05 considered significant. Pathway analysis was performed using the Reactome database.

**Results:** We identified 3708 proteins in uEV. At baseline 545 proteins were different in patients who progressed to vescicular. Pathway analysis linked these proteins to neutrophil degranulation, selenoamino-acid metabolism, and Robo-receptors. Previous work on Robo-signaling showed it controls leukocyte infiltration and podocyte function in kidney injury and is increased in LN, while selenoamino acids are key to cellular antioxidant responses (Carnitine).

**Conclusions:** Using mass spectrometry of uEV we identified potential non-invasive biomarkers for treatment response to voctosporin in patients with LN. In addition, we were able to characterize the altered processes in the patients responding to voctosporin, which included complement and a specific change in neutrophil-associated proteins.

**Funding:** NIDDK Support
Mice with a Pax2 Missense Variant Are Susceptible to Experimental FSGS and Display Impaired Glomerular Repair

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Background: FSGS is a form of chronic kidney disease characterized by podocyte loss. Our team previously reported that Pax2 pathogenic missense variants account for 4% of adults with FSGS. Pax2 regulates glomerular development and expression persists in adult parietal epithelial cells (PECs), postulated to serve as a reservoir for cells including podocytes. We hypothesize that in humans and mice with pathogenic Pax2 missense variants, PEC-mediated podocyte regeneration is impaired.

Methods: FSGS induced by Adriamycin was performed on wildtype mice and mice with Pax2 missense variant (termed Pax2246). Kidney tissue were analyzed by histology, and immunostaining. Glomeruli were isolated and subjected to mass spectrometry (MS), and immunostaining. Glomeruli were isolated and subjected to mass spectrometry (MS), and analysis by Gene Ontology (GO) Enrichment Analysis. Kidney tissue from relatives with FSGS and Display Impaired Glomerular Repair

Results: At embryonic day 16.5, mouse wildtype kidney showed overlapping expression of Pax2 and WT-1 in the condensed mesenchymal cells until PEC and podocyte differentiation, supporting a close lineage relationship. Pax2246 had reduced nephron number but displayed only minor differences in glomerular function at baseline. Adriamycin-induced Pax2246 mouse showed more severe FSGS compared to wildtype, including decreased podocyte numbers and increased albuminuria. Adriamycin-injected Pax2246 mice showed Pax22-expressing glomerular tuft cells, which were rarely observed in injured wildtype and were similar to histological findings from Pax22-associated FSGS patients. Podocyte loss was associated with increased podocyte apoptosis, focal adhesion, and cytoskeleton dynamics, and in-utero embryonic development; while GO terms of normal processes obtained from isolated glomeruli demonstrated maladaptive repair in Pax22-expressing glomerular tuft cells, decreased cell adhesion, and actin cytoskeleton organization were enriched in wildtype.

Conclusions: Our findings support decreased glomerular regeneration in Pax22-expressing mice compared to wildtype. We are next pursuing glomerular single-cell RNA sequencing to characterize the role of PECs in this process.

Funding: Government Support - Non-U.S.

Enhanced Growth of Gut Bacteria Muribaculaceae Reduces Inflammation and Kidney Injury in an Experimental Model of Anti-Neutrophil Cytoplasmic Antibody Vasculitis

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Background: The gut microbiome is a critical factor influencing immune homeostasis. Reduced microbial diversity in the gut has been associated with the increasing prevalence of autoimmune diseases. Notably, the family Muribaculaceae has declined within the human microbiome in the industrialised world, and studies have linked its reduced abundance to disease. We investigated the role of the declining Muribaculaceae family in ANCA-associated vasculitis (AAV). We hypothesized that dietary supplementation with resistant starch (RS) a fermentable substrate for gut bacteria would enhance the growth of anti-inflammatory short chain fatty acid (SCFA) producing bacteria (including Muribaculaceae) which would mitigate neutrophil activation and ameliorate kidney inflammation in AAV.

Methods: Using an experimental model of ANCA vasculitis, we assigned mice to treatment groups receiving a diet supplemented with 15% RS (n = 8) or a calorie-matched control diet (n = 8). Additionally, another cohort of mice was randomized to receive either a control vehicle (n = 8), or SCFAs acetate (n = 8), butyrate (n = 8), or propionate (n = 8) orally.

Results: 16S RNA analysis (Illumina miseq) analysis of the caecal contents revealed that the RS diet induced significant alterations in the gut microbiota composition, characterized by a notable expansion of SCFA-producing bacteria from the Bacteroidaceae and Muribaculaceae families. The ratio of firmicutes/bacterioidota an indication of gut dysbiosis was reversed in the mice on the RS diet. RS treated mice had all significant diminution of inflammation, with a reduction in glomerular injury, neutrophil, macrophage and CD4 T cell recruitment. Mice in the RS treatment group had significantly reduced dendritic cell activation in the draining lymph nodes with a decrease in MHCII and CD80 expression. Albuminuria was significantly decreased in the RS group (p < 0.05). SCFAs alone were not as efficient as RS supplementation in reducing glomerular injury and leukocyte infiltration.

Conclusions: Our findings highlight the therapeutic potential of SCFA production through RS fermentation or direct administration of SCFAs in ANCA vasculitis. These interventions represent possible novel adjunct therapies for reducing inflammation in vasculitis.

Funding: Government Support - Non-U.S.

Targeting Tissue-Specific T Cell Plasticity by Pooled Single-Cell CRISPR Screening in Preclinical Mouse Models


Background: Treatment of autoimmune diseases demands a shift from unspecific immunosuppression towards targeted therapies. This could be achieved by turning pro-inflammatory T helper cells into anti-inflammatory subsets. However, the molecular
pathways involved in T cell plasticity and stability are not fully understood. Single cell CRISPR-screening are a powerful tool to simultaneously analyze the impact of multiple genes on cellular phenotypes.

Methods: By combining single cell gene expression analysis and T cell receptor sequencing, we uncover Th17 to Th1 cell plasticity in the human kidney in renal autoreactivity. To investigate the molecules involved in T cell plasticity in disease settings, we established in vivo single cell CRISPR droplet sequencing (iCROP-seq).

Results: By applying this technique to in vivo models of inflammatory diseases in the kidney and intestine, we demonstrate that CRISPR-induced alterations in T cell polarization can be identified and ranked according to corresponding transcriptional perturbations. In particular, we targeted pro-inflammatory Th17 cells in models of immune-mediated diseases and quantified polarization biases into Th1 and regulatory T cells.

Conclusions: iCROP-seq will facilitate the identification of therapeutic targets by highly efficient functional stratification of genes and pathways in a disease- and tissue-specific manner.

Funding: Government Support - Non-U.S.

TH-PO559
Proliferative Glomerulonephritis with Monotypic Immunoglobulin Deposits (PGNMD) and Preeclampsia
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Introduction: We report the case of a pregnant woman presenting with hypertension, nephrotic range proteinuria and hematuria. Kidney biopsy revealed glomerular thrombocytopenic microangiopathy (TMA) and underlying PGNMD with IgG-k deposits.

Case Description: A 33-year-old woman presented at 21 weeks’ gestation with new-onset hypertension. She had a history of prior preterm preeclampsia and obesity s/p gastric sleeve surgery. Physical exam was normal except for blood pressure 141/111 mmHg. Laboratory function was normal. UA showed hematuria and proteinuria, with UPCR of 3.7 g/day. Fetal ultrasound showed severe fetal growth restriction (FGR). ANA, Anti-dsDNA, Anti-PLA2R Ab were negative, and complements were normal. She had persistent proteinuria and microscopic hematuria on multiple UA’s from 5 years prior to pregnancy. Kidney biopsy was done at 23 weeks’ gestation to evaluate for glomerulonephritis vs. preeclampsia. Light microscopy showed glomerular endotheiosis with a membranoproliferative pattern, consistent with preeclampsia. IF showed mesangial and segmental glomerular capillary wall staining for IgG1 and k with negative l, consistent with proliferative glomerulonephritis with monotypic IgG-k deposits (PGNMD). SPEP and immunofixation was negative for a monoclonal protein. Testing for HBV, HCV, and HIV was negative. At 24 weeks, labor was induced for worsening transaminitis. Due to severe FGR, neonatal resuscitation was not attempted. At 3 weeks postpartum, her BP and proteinuria improved (UPCR 1.3 g/day). Kidney function remained normal.

Discussion: To our knowledge, this is the first reported case of PGNMD with preeclampsia. There is 1 report of PGNMD in pregnancy, but without preeclampsia. As in our case, IF showed IgG1-k, and there was no monoclonal protein detected. PGNMD was first described in 2004 as an endocapillary proliferative or membranoproliferative glomerulonephritis related to monoclonal IgG deposition. Most (70%) patients with PGNMD do not have a detectable circulating monoclonal protein in the serum or urine. In such cases, treatment directed at a hypothesized underlying clone may still be considered. In our patient, preeclampsia complicated the clinical presentation and obscured the pathologic findings of PGNMD. Kidney biopsy assisted in confirming the diagnosis of preeclampsia, allowing appropriate management when preeclampsia progressed.

TH-PO561
Scleroderma-Associated Kidney Disease: A Case Series
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Introduction: Scleroderma is a rare multysystem disorder categorised into limited and diffuse subtypes. Recognised renal manifestations of scleroderma include renal crisis (SRC) and ANCA associated vasculitis. We present three differing cases of scleroderma associated renal disease.

Case Description: Case 1: 64 year old normotensive female with systemic sclerosis developed AKI and microangiopathic haemolytic anaemia. ANCA and ANA were negative. IgG Kappa paraprotein detected (97g/L). Bone marrow biopsy showed 72.7% plasma cells. Renal biopsy demonstrated intraglomerular thrombocytopenic microangiopathy, without onion-skinning or involvement of interlobular or arcuate arteries. Treatment was targeted at the plasma cell clone. Case 2: 53 year old female with limited systemic sclerosis complicated with nephrotic syndrome. She was hypertensive but did not tolerate RAAS inhibition. Urinary PCR was 873.6mg/mmol. Renal biopsy demonstrated a cellular form of focal segmental glomerulosclerosis, without tip lesions. Corticosteroids were avoided due to risk of precipitating SRC. She was treated with tacrolimus, which reduced proteinuria to the sub-nephrotic range.

Discussion: These cases demonstrate three different presentations of scleroderma associated renal disease. The intraglomerular distribution of TMA in Case 1 is more consistent with MGRS rather than SRC, in the context of a paraprotein. While there is one published case of SRC in a patient with concurrent scleroderma and monoclonal gammonopathy, SRC is less frequent in seronegative scleroderma. SRC presenting in CREST, as in case 2, is unusual as it is more commonly reported with diffuse scleroderma, and anti-centremere antibodies have a negative association. In the final case, primary FSGS is a highly atypical manifestation of limited systemic sclerosis. The contrasting pathologies highlight the diagnostic value of kidney biopsy in scleroderma patients presenting with renal impairment, and its importance in guiding treatment.

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

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TH-PO562
Unique Case of Silicosis Leading to Several Autoimmunities: Rheumatoid Arthritis and Membranous Lupus Nephritis
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Introduction: Silicosis is a fibrotic lung disease caused by the inhalation of free crystalline silica, and is the oldest pulmonary occupational hazard known. Silica exposure has been linked to several other conditions including infections, malignancies and autoimmunity.

Case Description: A 41-year-old male, marble factory worker, lung silicosis diagnosed by biopsy on 2012. ANA, dDNA, anti-Smith and RF were all negative. In 2017 due to symmetrical arthritis and newly positive RF rheumatoid arthritis was diagnosed, and he was treated with steroids, hydroxychloroquine and methotrexate. Patient currently presented with arthralgia, peripheral edema, and almost 10 Kg gain during a month. He was not taking any medical treatment at that time. Lab results indicated normal renal function, a low serum albumin (23g/L), and nephrotic range proteinuria (7.4 g/g). ANA, anti-Smith, anti-SSA were positive, and C3 was low. Renal biopsy revealed rigid glomerular capillary walls with tiny discrete deposits in the outer aspect of the GBM, a “full house” pattern immunofluorescence, and increased mesangial matrix (M) with numerous electron dense deposits, intramembranous (IM) and subepithelial deposits (SE) interposition of glomerular basement membrane material (spikes), and effacement of foot processes (P) were seen at EM(figure), compatible with membranous pattern injury of SLE. Patient received steroids hydroxychloroquine and MMF treatment.

Discussion: Silicosis is associated with impaired immune system, high risk for pulmonary infections malignancies and more. It is also associated with inflammatory diseases such as RA, scleroderma and mixed connective tissue disease. Autoantibodies as anti-DNA and anti-SSA/B occur in a higher frequency in individuals exposed to silica than general population. Renal involvement secondary to silica has been seen in the past, however this is the first description of membranous lupus nephritis after silica exposure.

TH-PO564
Semaglutide (Ozempic), a Possible Cause of Focal Segmental Glomerulosclerosis (FSGS)
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Introduction: Semaglutide use has been increasing rapidly because of its beneficial effects on diabetes control, cardiovascular protection, and weight loss. Adverse renal events are rare. We present a case of semaglutide-associated FSGS.

Case Description: A 55-year-old nondiabetic female with history of end stage kidney disease secondary to IgA nephropathy treated by kidney transplantation 3 years earlier. Her baseline serum creatinine was 1.2 mg/dL and she had no proteinuria. She was initiated on Semaglutide for weight loss. Soon after starting, 0.5 mg weekly, she developed proteinuria; UPC (urine protein to creatinine ratio) ~400 mg/mg. The association was not suspected and so her dose was increased to 1.0 and then 2.0 mg weekly. The increases in Semaglutide dose coincided with worsening UPC 3300 mg at 2 months and 9 g/4 at 4 months. She was subsequently admitted due to progressive edema and dyspnea; her 24 hour urine protein was 16 g/g now. Her serum creatinine remained at 1.2-1.5 mg/dL while her albumin and LDL levels were 1.7 and 303 mg/dL, respectively. She remained on Tacrolimus, Mycophenolate and Prednisone throughout. Blood tests for HIV, hepatitis, drug use and APOLI gene were negative. A kidney biopsy showed FSGS on light microscopy (figure A), moderate to marked segmental foot process effacement by electron microscopy (figure B).

Discussion: To the best of our knowledge, this is the first case of FSGS that appears to be associated with the Semaglutide use. While we did not establish causality, the time course and progression of proteinuria raise the possibility that Semaglutide was the trigger.

The mechanism is unknown but Semaglutide therapy is known to induce formation of anti-Semaglutide antibodies in up to 1% of patients. The clinical significance of this immune response is unknown but raises the possibility that it could have led to the formation of a circulating glomerular permeability factor that caused the FSGS. Identification of more cases may allow for further investigations into the potential causality and mechanisms of Semaglutide-associated FSGS.

TH-PO565
Type II Cryoglobulinemic Glomerulonephritis in a Patient with Marginal Zone Lymphoma
Devvani Sivakumar, Senin Shah, Manini Vishwanath. Brown University, Providence, RI.

Introduction: Cryoglobulinemia is rare and clinically significant in about 1 in 100,000. Renal involvement is seen in 30-60% cases and is especially associated with type II cryoglobulinemia. In a study of 80 patients with noninfectious biopsy proven mixed cryoglobulinemic/glomerulonephritis, 7 patients had marginal zone lymphoma.

Case Description: A 76-year-old female with history of marginal zone lymphoma since 2019, managed conservatively, presented to the hospital with dyspnea on exertion, fatigue, 20 lbs weight gain and leg edema for 2 months. She had 3 recent hospitalizations for similar complaints and had been managed with diuretics and antibiotics, with no improvement. She was hypertensive to 167/86 mmHg, exam showed bilateral cerebral lymphadenopathy and 2+ pitting pedal edema up to the groin. Labs revealed Cr 1.51 mg/dL [baseline 0.6-0.9 mg/dL], UA positive for protein, albumin 2.4 g/dL and UPCR 9 g. Low complements with C3 at 33 mg/dL and C4 <3 mg/dL. Serology revealed ANA reactive [1:5120] and anti dsDNA negative. HIV, Hepatitis B and C were non-reactive. kappa/Lambda ratio 1.68 with IF positive for monoclonal IgM kappa and potential monoclonal lambda free light chain. Immunoglobulin levels notable for elevated IgM at 1349 mg/dL. Cryoglobulin positive at 790 UL cryo/mL with isotype positive for weak monoclonal IgM kappa. Kidney biopsy showed membranoproliferative glomerular injury pattern with immune complexes which stained for IgM [3+], IgG [2+], C3 [2+], C1q [2+], lambda light chains [1+]. A diagnosis of paraproteinosis...
type II cryoglobulinemia related to marginal zone lymphoma was made. She started treatment with rituximab, cyclophosphamide and dexamethasone and responded well with improvement in symptoms and renal function.

**Discussion:** Noninfectious type II cryoglobulinemic glomerulonephritis associated with marginal zone lymphoma is uncommon. In a retrospective multicenter survey of 242 cryoglobulinemic patients, 22 cases had marginal zone lymphoma and renal involvement was seen in 84 cases. Management and prognosis is dependent on disease severity and involves treatment of underlying cancer. Although our patient responded well to treatment, it was a 2 month delay in diagnosis despite recurrent hospitalizations. It is important to highlight this and the clinical presentation.

**TH-PO567**

**ANCA-Associated Pulmonary Renal Syndrome with Immune Complex Deposition**


**Introduction:** Pulmonary renal syndrome (PRS) is a highly morbid condition in which rapid identification and empiric therapy is critical.

**Case Description:** A 55 year old female with a past medical history of hypertension, rheumatoid arthritis not on any active therapy, and CKD3 diagnosed 6 months ago, presented to the ED for 2 days of hemoptysis and hematuria. She denied any recent upper respiratory symptoms or fevers. She also developed constant, non radiating, epigastric pain with 2 episodes of blood-streaked emesis. She denied any new medications. Because her symptoms were unremarkable and she became dyspneic, she was presented to the ED. On arrival, she was tachypneic at 34 respirations per minute and hypoxic to 84%. She had a hemoglobin of 6.4. Her creatinine was 8.96 with a baseline of 1.5. On urinalysis, she had 3+ protein, 3+ blood, >100 RBCs, no casts or dysmorphic RBCs were noted. A chest x-ray showed severe, diffuse pulmonary infiltrates. Given concern for acute glomerulonephritis (GN) with associated PRS, she was started on empiric pulse dose steroids with 1 gram of methylprednisolone IV daily for 3 days as well as plasmapheresis with FFP and cyclophosphamide. Subsequent workup showed a positive MPO-ANCA serology. Complement c3 and c4 levels were low. Anti-GBM was negative. ANA was positive with anti-DNA and anti-Smith antibodies. Complement c3 and c4 levels were low. Anti-GBM was negative. ANA was positive with anti-DNA and anti-Smith antibodies. Anti-GBM was negative. ANA was positive with anti-DNA and anti-Smith antibodies.

**Discussion:** ANCA associated GN is most often pauci immune and concurrent immune complex GN is unusual but has been reported in 5-14 percent of patients with ANCA associated GN. When ANCA associated GN presents with immune complex deposition, vasculitis involvement is most often exclusively renal. In our case, the patient had both pulmonary and renal involvement. Recognition of MPO ANCA associated GN with concomitant immune complex deposition is important as it has been associated with worse renal outcomes. Moreover, while a link between ANCA positivity and rheumatoid arthritis has previously been established, RA related renal dysfunction is typically not rapidly progressive.

**TH-PO568**

**Infection-Related Glomerulonephritis (IRGN) due to Gordonia Bacteremia in an Immunocompetent Patient with a Femoral Catheter**

Emmanuel A. Aydin-Ghormoz, Andrea R. Lightle, Mauricio Monroy, Albany Medical College, Albany, NY.

**Introduction:** Gordonia species rarely cause human infection, though cases of bacteremia in immunocompromised patients with endovascular devices have been reported. These may be under-recognized as blood cultures (BC) can be negative until 4 or more days after inoculation. We report a case of IRGN secondary to Gordonia bacteremia in an immunocompetent patient with a chronic femoral catheter.

**Case Description:** A 61-year-old woman with complex regional pain syndrome on buprenorphine infusion via femoral catheter presented to our hospital with AKI on outpatient labs. She had been hospitalized 1 year prior with a diffuse macular rash while on Bactrim for cellulitis. At that time, she was febrile with negative BC and low C3/ C4. Skin biopsy showed leukocytoclastic vasculitis (LCV), presumed to be drug-induced. Rash resolved with broad-spectrum antibiotics (Abx). At the current presentation, creatinine was 5.37mg/dl. UA showed 1+ protein and innumerable RBCs. C3 was low and rheumatoid factor (RF) was elevated. Renal biopsy showed diffuse proliferative crescentic immune-complex GN with full house staining pattern suspicious for lupus nephritis, though all serologies (except RF) returned negative. She developed fever after routine femoral catheter exchange and BC were sent. Steroid therapy was started for suspected autoimmune GN when BC were negative for 2 days. Unfortunately, after a sneezing spell she developed a spontaneous left subdural hematoma (SDH) with active bleeding requiring craniotomy. By then, BC (2 sets) grew Gordonia polysacrenivorans at 3 days. Abs were started. Steroids were stopped. She briefly required hemodialysis but had rapid renal recovery with Abx. Unfortunately, she had further intracranial complications including transtentorial herniation and persistent comatose state. Family elected to continue all care. She was discharged to a nursing facility.

**Discussion:** The patient’s AKI and biopsy findings were attributed to IRGN. There was suspicion her spontaneous SDH was secondary to vascular mycotic infection from Gordonia bacteremia, and prior LCV may have been a manifestation of chronic bacteremia. Clinicians should have a high index of suspicion for slow-growing bacterial infections as an etiology of IRGN in unexplained glomerular disease, especially in patients with indwelling central catheters.

**TH-PO569**

**Wunderlich Syndrome with Polyangiitis Overlap: A Diagnostic Challenge**

Christopher Savvides, Komal Paradar, Marguerite Linz, Nishigandha Pradhan,1,2 University Hospitals, Cleveland, OH, 1Case Western Reserve University, Cleveland, OH.

**Introduction:** Spontaneous renal hemorrhage, called “Wunderlich syndrome”, is a rare complication of vasculitides, especially polyarteritis nodosa (PAN). We present a patient with spontaneous renal hemorrhage with polyangiitis overlap syndrome.

**Case Description:** A white male in his 70s presented with leg pain, weakness, and oliguria. He noted worsening bilateral hearing loss and recurrent sinusitis over 6 months and involuntary 30 lb. weight loss over 3 months. Serum BUN/creatinine were 168 mg/dl/11.2 mg/dl and hemodialysis was started. Initial CT scan of abdomen was negative. He developed new onset left sided abdominal pain after 3 days. Repeat CT scan of abdomen showed bilateral renal hematomas (Fig. A) and multiple left renal aneurysms concerning for PAN (Fig. B) on CT angiogram. pANCA titer was 1:320 (<1:20) with anti-MPO titer of 134 AU/ml (0-19). He met classification criteria for both AAV and IgG4-RD. Renal hemorrhage should be considered in patients with ANCA associated vasculitides or polyangiitis overlap previously described in association with Wunderlich syndrome. Renal hemorrhage should be considered in patients with ANCA associated vasculitides or polyangiitis overlap syndrome with abdominal pain.

**Discussion:** We describe a challenging case with features of both PAN and MPA with both palpable subcutaneous renal and mesenteric lesions. The current presentation is most consistent with “polyangiitis overlap syndrome” which has not been previously described in association with Wunderlich syndrome. Renal hemorrhage should be considered in patients with ANCA associated vasculitides or polyangiitis overlap syndrome with acute abdominal pain.

**Table 1**

<table>
<thead>
<tr>
<th>MPO ACRE Classification for PAH (Path)</th>
<th>MPA (Path)</th>
<th>AAV (Path)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated weight loss &gt; 5kg</td>
<td>0.012</td>
<td>0.003</td>
</tr>
<tr>
<td>Myalgia (including sciatica or muscle weakness)</td>
<td>0.015</td>
<td>0.002</td>
</tr>
<tr>
<td>RBC &lt; 50mg/dl or packed cell volume &lt; 35%</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>Characteristic antinuclear abnormalities not from noninflammatory disease process</td>
<td>0.003</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Investigation of standard guideline therapy and the possibility of complete remission require further overall prognosis. Our patient responded well to Rituximab and steroids, but the success through kidney biopsy and initiation of cancer treatment may alter the renal and patient but it’s unclear if this association with MPO ANCA is coincidental. Early identification case has been reported. The association between NELL-1 and malignancy is established, as part of MCL chemotherapy. His renal function improved and dialysis was stopped. Rituximab were used as induction therapy without plasmapheresis. Rituximab continued MPO antibody specificity, low C3 and C4 levels, and normal kappa lambda light chain lymphadenopathy, and normal-sized kidneys. Nephritic labs showed positive ANCA with fever, night sweats, maculopapular rash with bullae, anasarca and a 30 lbs weight loss.

**Case Description:** 61-year-old previously healthy male presented with intermittent fever, night sweats, maculopapular rash with bullae, anasarca and a 30 lbs weight loss. He was hypertensive and labs revealed anemia, thrombocytopenia, Strept. Agalactiae bacteremia, active urinary sediment and severe AKI needing dialysis. Also notable was hypobuminemia 1.9 g/dL with proteinuria 9 g/g. Imaging revealed splenomegaly, diffuse lymphadenopathy, and normal-sized kidneys. Nephritic labs showed positive ANCA with MPO antibody specificity, low C3 and C4 levels, and normal kappa lambda light chain ratio. Bone marrow biopsy confirmed MCL with blastoid features. Renal biopsy showed crescentic GN, polyclonal IgG, C3, C1q, Kappa and Lambda along the tubular basement membrane, positive NELL-1 staining, and lymphomatous infiltration. Steroids and Rituximab were used as induction therapy without plasmapheresis. Rituximab continued as part of MCL chemotherapy. His renal function improved and dialysis was stopped. At 8 months creatinine was 2.9 g/dL with partial nephrosis remission (UPCR 1.3 g/g and albumin 3.3 g/dL).

**Discussion:** We describe a rare AKI in lymphoma presentation with MCL infiltration, MPO positive crescentic GN, and NELL-1 associated GN. To our knowledge no such case has been reported. The association between NELL-1 and malignancy is established, but it’s unclear if this association with MPO ANCA is coincident. Early identification through kidney biopsy and initiation of cancer treatment may alter the renal and patient overall prognosis. Our patient responded well to Rituximab and steroids, but the success of standard guideline therapy and the possibility of complete remission require further investigation.

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

**Underline represents presenting author.**

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**TH-PO570**

A Rare Feature of Myeloperoxidase (MPO)-Positive Crescentic Glomerulonephritis (GN) and Neural Epidermal Growth Factor-Like 1 (NELL-1) Protein Positive Membranous Neoplasia (MN) in Mantle Cell Lymphoma (MCL)

**Erik Mai, Waleed A. ElSheikhMohammed, Milos N. Budisavljevic, Evelyn Bruner. MUSC Nephrology. Medical University of South Carolina, Charleston, SC.**

**Introduction:** MCL is a B-cell non-Hodgkin’s lymphoma that can have renal involvement via infiltration, immune complex (IC), or complement-mediated (CM) GN. Typical IC-positive GN lesions include proliferative GN with mononuclear IgG deposits (PGNMD), C3GN, and MN. Antineutrophilic Cytoplasmic Antibody (ANCA) associated GN is now recognized to link with pericardial or concurrent malignancy. Our case features a rare presentation of acute kidney injury (AKI) caused by MCL infiltration, coexisting MPO-ANCA associated crescentic GN, and NELL-1 positive MN.

**Case Description:** A 75-year-old male with hypertension and alcohol use disorder was admitted for worsening pancytopenia and acute kidney injury. 2 months prior he was diagnosed with seronegative ANCA vasculitis. Results from the cervical lymph node biopsy were consistent with iMCD. The patient was transitioned to siltuximab with a prednisone taper.

**Discussion:** iMCD-TAFRO syndrome can present with proliferative glomerulonephritis. While this patient presented with complete clinical findings of iMCD, renal biopsy results were atypical prior to release of a MPGN or TMA-like histopathology. iMCD-TAFRO syndrome may not always conform to typically seen patterns. Diagnosis requires a high index of suspicion and should be considered for glomerulonephritis with non-specific biopsy findings in the context of a systemic inflammatory disease.

**TH-PO573**

Bacterial Endocarditis with Strongly Positive Anti-PR3 ANCA

**Andrew Slater. University of Florida, Gainesville, FL.**

**Introduction:** ANCA-associated rapidly progressive glomerulonephritis (GN) should be identified and treated promptly. There are however infectious mimickers of ANCA-associated GN that may present only as a lack of anti-p-mercaptoglycine-immunoreactivity on biopsy. When lack of p-mercaptoglycine-immunity is present, it should alert the clinician to a careful search for a causative infectious agent and to reconsider immunosuppressive therapy.

**Case Description:** A 64-year-old man with a mechanical mitral valve presented with dyspnea and acute kidney injury preceded by months of fatigue and weight loss. He was treated as decompensated heart failure. His first blood culture was negative. Subsequently, microscopic urinealysis showed dysmorphorphic red blood cells. Serological testing resulted with anti-PR-3 antibody at 955 AU/el, anti-MPO within the reference range. MPO-ANCA positive biopsy was consistent with crescentic GN, but lacking was complete p-mercaptoglycine-immunity with mesangial staining for IgG (trace), IgM (1+), C3 (2-3+), C1q (2+). It was thought that he had a PR-3 associated RPGN. HCV, HBV, Anti-GBM antibodies and HIV serologies were negative. He began steroids, rituximab and cyclophosphamide. Subsequently, mixed cryoglobulin testing returned positively. The components C3 and C4 were low. Immunosuppression was discontinued and further infectious workup was repeated. QuantiFier GOLD testing was negative. Four of four blood cultures grew Staph. epidermidis. As he’s a cat owner, Bartonella and Coxiella serologies were sent. Bartonella henselae IgM and IgG were both strongly positive, while Q-Fever IgM was less so. Echodacdiogram demonstrated a mitral valve vegetation and CT of the abdomen showed splenic infarction (initial Echo and CT negative). He was started on treatment for S. epidermidis bacteremia and B. henselae, both of which could have been the causative agent of endocarditis. He eventually developed uremia and started kidney replacement therapy. He remains dialysis dependent.

**Discussion:** The decision to initiate immunosuppressive therapy is not light. Bartonella henselae has been shown to present as a rapidly progressive GN that mimics ANCA-associated GN. Through concurrent ANCA antibodies, concomitantly elevated PR-3-ANCA titers and a documented causative agent of mixed cryoglobulinenia. A level of suspicion for infectious disease should be maintained when p-mercaptoglycine-immunity is absent despite clinically rapidly progressive GN in the setting of strong ANCA serological positivity.

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**TH-PO571**

Idiopathic Multicentric Castleman’s Disease (iMCD)-TAFRO Syndrome with Atypical Renal Biopsy Findings

**Carla L. Chen, Karen Strenge, Trevor W. Tobin. Eisenhower Army Medical Center, Fort Gordon, GA.**

**Introduction:** Idiopathic Multicentric Castleman’s Disease (iMCD) is a rare lymphoproliferative disorder characterized by enlarged lymph nodes in HIV-8 negative patients. It is associated with fevers, weight loss, hepatosplenomegaly, cell line dyscrasias, and organ dysfunction. One subtype of iMCD is TAFRO syndrome, characterized by the presence of rheumatoid factor, anasarca, myelofibrosis, renal dysfunction, and organomegaly. We report a patient who presented with a seronegative proliferative glomerulonephritis and was subsequently diagnosed with iMCD-TAFRO syndrome.

**Case Description:** A 47-year-old male with no past medical history presented to the hospital with new-onset lab abnormalities. Vital signs showed tachycardia, tachypnea, and intermittent fevers. Physical exam noted diffuse anasarca. Laboratory investigation revealed elevated inflammatory markers, new anemia, and acute renal injury. He did not have nephrotic syndrome per urine protein quantification. Urine microscopy c- and h microscopics. Glomerulonephritis serologic evaluation was negative. Rapidly progressive renal failure necessitated initiation of renal replacement therapy and pulse dose steroids. Renal biopsy revealed proliferative glomerulonephritis without crescents or segmental necrosis. Immunofluorescence demonstrated trace focal mesangial granular deposits of IgM and C3. Electron microscopy showed moderate foot process effacement without subendothelial or mesangial deposits. Other evaluations included a P/ET/CT scan, bone marrow biopsy, and cervical lymph node biopsy. Pending lymph node biopsy results, IV cyclophosphamide was started for presumed seronegative ANCA vasculitis. Results from the cervical lymph node biopsy were consistent with iMCD. The patient was transitioned to siltuximab with a prednisone taper.

**Discussion:** iMCD-TAFRO syndrome can present with proliferative glomerulonephritis. While this patient presented with complete clinical findings of iMCD, renal biopsy results were atypical prior to release of a MPGN or TMA-like histopathology. iMCD-TAFRO syndrome may not always conform to typically seen patterns. Diagnosis requires a high index of suspicion and should be considered for glomerulonephritis with non-specific biopsy findings in the context of a systemic inflammatory disease.
displayed proliferative necrotizing and crescentic GN with subendothelial deposits and lymphoplasmacytic infiltrate. IF staining: 3+ IgM, 3+ IgA, 1+ IgG, 1- lambda. Review of prior BM biopsy showed cytoplasmic vacuoles in erythroid and myeloid precursors. Genetic screen positive for somatic UBA1 mutation. He was treated with steroids, mycophenolate and tocilizumab with partial response of declining creatinine and proteinuria.

Discussion: Limited data on kidney manifestations in VEXAS include MPO-positive necrotizing and crescentic GN, acute tubulointerstitial nephritis, and isolated interstitial infiltrate with MPO-positive and CD68+ myeloid cells. The present case adds to this data in describing a serology-negative necrotizing and crescentic GN. VEXAS syndrome represents dysregulated immune activation that leads to auto-immune organ injury. The kidney-specific pathological mechanisms of VEXAS syndrome are unknown but proposed theories include: cytokine-mediated tubular injury activating endothelial cells, recruitment of myeloid cells leading to further inflammation, and dysregulated neutrophil extracellular traps. Further research into how VEXAS syndrome involves the kidney is critical to targeted therapies for kidney disease in patients with this multi-system inflammatory syndrome.

TH-PO574
Hepatic Glomerulopathy After Liver Transplant: An Unexplored Clinical Entity
Asael Zhahayer, Ewa Borys, Maria M. Picken, Kavitha Vellanki. Loyola University Health System, Maywood, IL.

Introduction: Hepatic glomerulopathy, also known as hepatic glomerulosclerosis, is a secondary glomerular process that occurs in the context of liver failure and cirrhosis. Pathogenesis involves acquired LCAT (Lecithin–Cholesterol Acyltransferase) deficiency as the enzyme is mainly synthesized in the liver. Deposition of lipid particles in glomerular basement membrane (GBM) similar to those seen in congenital LCAT deficiency is pathognomonic. Here, we present a unique case of persistent hepatic glomerulopathy post liver transplant.

Case Description: A 58-year-old man s/p liver transplant with prior h/o alcoholic cirrhosis complicated by hepatocellular carcinoma presented to nephrology clinic for evaluation of persistent proteinuria post liver transplant. His immunosuppression includes tacrolimus and mycophenolate and BP is well controlled. Work up revealed nephrotic range proteinuria (approx. 4 gm/gm creatinine), rest is shown in Table 1. Kidney biopsy revealed deposition of lipid particles in glomerular basement membrane and metastatic micro-calcifications (Image 1).

Discussion: Hepatic glomerulopathy is an unexplored clinical entity which is characterized by deposition of small, irregular partially electro-lucent lipid particles in the subepithelial, intramembranous, subendothelial and mesangial regions as seen in our patient. The prevalence of hepatic glomerulopathy in liver disease is not known, nor is the clinical course post liver transplantation. To our knowledge, this case is the first to be reported in literature of persistent findings post liver transplantation. We believe raising awareness of the disease entity will help in understanding the clinical course and exploring treatment options.

Table 1

<table>
<thead>
<tr>
<th>Protein</th>
<th>Patient values</th>
<th>Reference range</th>
<th>Patient values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>139</td>
<td>138-144</td>
<td>3.7</td>
</tr>
<tr>
<td>K</td>
<td>4.4</td>
<td>3.5-5.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Cr</td>
<td>2.0</td>
<td>0.6-1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Urea</td>
<td>3.1</td>
<td>0.3-1.5</td>
<td>0.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6</td>
<td>0.4-1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Protein</td>
<td>6.8</td>
<td>6.0-10.0</td>
<td>10.1</td>
</tr>
<tr>
<td>Albumin</td>
<td>2.0</td>
<td>3.0-4.5</td>
<td>1.0</td>
</tr>
<tr>
<td>C3</td>
<td>9.4</td>
<td>8.0-10.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Image 1.

TH-PO575
Mycobacterium simiae: A Rare Cause of Renal AA Amyloidosis
Momen Abbasi, Assaf Potruch, Ophir Eyal. Hadassah University Medical Center, Jerusalem, Israel.

Introduction: Mycobacterium Simiae is a prevalent nontuberculous mycobacterium (NTM) that can become pathogenic to immunocompetent individuals with underlying lung disease. Rarely, untreated chronic NTM infections can result in AA amyloidosis.

Case Description: A 74-year-old male with COPD presented with weight loss, nocturnal fever, elevated ESR and anemia. Cultures, serology tests, and GeneXpert for tuberculosis were negative. Normal FLC ratio. Borderline paraprotein detected only in serum. PET-CT showed increased uptake in upper right lung, small mediastinal and hilar lymph nodes. He was treated pneumonia. M. simiae grew in two sputum cultures after 4 weeks, repeated cultures were advised but not done. 5 months later patient presented with severe nephrotic syndrome, albumin <20 g/L and protein/creatinine ratio 20.8 g/g. Borderline paraprotein reported only in urine. Normal FLC ratio. Kidney biopsy was consistent with renal AA amyloidosis by immunostaining and lack of light chain restriction. PET CT revealed consolidations in right lower lobe and cavitations in both lower lobes. BM biopsy exposed dysplastic changes. Diagnosis of systemic AA Amyloidosis due to untreated M. simiae infection was made. He was treated with azithromycin, ciprofloxacin, cotrimoxazole but succumbed to his disease.

Discussion: NTM rarely cause amyloidosis with 5-8 years interval between NTM diagnosis and amyloidosis development after which mean survival time is 10 months. We believe that M. simiae caused amyloidosis in this case because of longstanding inflammation and negative extensive workup for other causes. We found only one case of AA amyloidosis associated with M. simiae lung infection with renal involvement but no nephritic syndrome described. We present a rare case of nephritic syndrome due to AA amyloidosis associated with M. simiae infection. Despite prolonged inflammation, M. simiae was diagnosed 5 months prior to AA amyloidosis diagnosis. Treatment was started late in the course of the disease and despite that he died within few weeks. This highlights the importance of early diagnosis and treatment of active M. simiae infection.

Congophilic amyloid deposits under polarized light showing apple-green birefringence.

TH-PO576
Looking at ANCA Vasculitis
Saher Aslam, Haris H. Chaudhry, Eric Magliulo, Kirk W. Foster, Felipe S. Naranjo. University of Nebraska Medical Center, Omaha, NE; Creighton University School of Medicine, Omaha, NE.

Introduction: Anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis is a group of autoimmune diseases that can cause inflammation and damage to small blood vessels throughout the body. Inflammatory eye disease is described in 50% to 60% of patients with ANCA-positive vasculitis, and for 8% to 16% of patients, it is an acute manifestations.

Case Description: A 74-year-old man with a history of gout, chronic sinusitis, and chronic kidney disease (G3a) presented to the clinic with worsening kidney function and proteinuria without hematuria. He was seen by Ophthalmology a few months prior for scleritis and was treated with a short course of NSAIDs, with the improvement of his symptoms. The initial workup was unremarkable. Kidney biopsy showed a lesion of focal segmental sclerosis with obliteration of the capillary lumen, mild interstitial fibrosis, and tubular atrophy, immunofluorescence was negative and electron microscopy with rare small dense deposits. The patient was started on SGLT-2 inhibitors. Renal function continued to deteriorate. The patient’s condition was complicated by acute bronchitis, diffuse anterior scleritis, and acute kidney injury, laboratory work was significant for positive ANCA antibodies with elevated PR3 antibodies. A repeat kidney biopsy revealed necrotizing crescentic glomerulonephritis. He was treated with IV steroids, rituximab and ultimately required dialysis.

Discussion: Renal involvement is a significant feature of ANCA vasculitis and can lead to acute kidney injury or chronic renal failure if left untreated. Clinicians should consider ANCA vasculitis in the differential diagnosis of patients presenting with scleritis, especially in those with renal dysfunction even with partial or complete resolution in ocular symptoms. Early diagnosis and treatment are essential in preventing irreversible organ damage and improving patient outcomes.
Membranous Nephropathy Associated with Alemtuzumab

Raj R. Ravender,1 Chaitanya A. Pal,1 Chandra Kumar Mallick Kodavanti,1 Saeid K. Shaffi,1 Darren W. Schmidt,1 J. Pedro Teixeira,1 Tiffany Caza,1 Pablo Garcia,1 UNMH/Arkana Team, The University of New Mexico, Albuquerque, NM; 2Arkana Laboratories, Little Rock, AR.

Introduction: Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved for multiple sclerosis. We present a case of membranous nephropathy associated with alemtuzumab use.

Case Description: A 20-year-old woman with a seven-year history of multiple sclerosis was referred to nephrology due to new-onset nephrotic range proteinuria nine months after receiving her first cycle of alemtuzumab. She took no other medications. Vitals were stable with trace lower extremity edema. Serum albumin was 2.1 g/dL, hemoglobin was 11.7 g/dL, platelets were 251,000/μL, AST was 17 U/L, ALT was 13 U/L, alkaline phosphatase was 141 U/L, total bilirubin was 0.2 mg/dL, direct bilirubin was 0.1 mg/dL, and serum creatinine was 0.4 mg/dL with serum albumin 2.1 g/dL. Hepatitis B and C, HIV, C3 and C4 complement, creatinine ratios were 4.63 g/g and 3481 mg/g, respectively. Serum creatinine was 0.4 mg/dL with serum albumin 2.1 g/dL. Hepatitis B and C, HIV, C3 and C4 complement, kappa/lambda ratio, anti-GBM antibody, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, and anti-phospholipase A2 receptor (PLA2R) antibody were all negative. Renal biopsy revealed membranous nephropathy, with negative immunohistochemical stains for PLA2R, thrombospondin type-1 domain-containing 7A, exostosin 2, and neural epidermal growth factor-like 1. Alemtuzumab was administered as it is effective for membranous nephropathy, with alemtuzumab use.

Discussion: Alemtuzumab depletes B and T lymphocytes and can produce side effects associated with immune reconstitution, with thyroid toxicity seen in up to 30% of patients. However, nephrotoxicity is rare (5/1485 patients, 0.3%). Mechanisms underlying kidney-related side effects from alemtuzumab use are not fully understood but may be linked to the anti-CD52 immune modulatory effect on B and T cell lymphocytes. The autoimmune diseases observed after administering alemtuzumab are predominantly antibody-mediated and appear to respond to B-cell depletion, suggesting that rituximab may be a potentially effective therapy.

Necrotizing crescentic glomerulonephritis seen with Jones silver stain. Active crescents involve 55-60% of non-obsolescent glomeruli sampled for light microscopy.

Truly a Catastrophe: A Case of Severe Anti-Phospholipid Syndrome in the Setting of Lupus

Shilpa Pedapati, Golnanz Vahdani. Banner University Medical Center Tucson, Tucson, AZ.

Introduction: Antiphospholipid syndrome (APS) is characterized by venous or arterial thrombosis in the presence of antiphospholipid antibodies. It can occur as a primary vs secondary condition in which it is associated with inflammatory disorders like systemic lupus erythematosus (SLE). APS related kidney disease can manifest itself in various ways from non-inflammatory occlusive diseases with arterial and venous thrombosis, TMA as well as glomerular diseases. Lupus can affect kidneys in the form of glomerulopathies in addition to TMA. It is important to distinguish inflammatory versus thrombotic lesions in order to ensure timely diagnosis and initiation of emergent management.

Case Description: 49-year-old female with a history of SLE not on any immunosuppression was admitted due to diarrhea and was found to have severe acute renal failure with a creatinine of 13. Serologies demonstrated low C3 and C4, Positive ANA, double-stranded DNA, cardiolipin IgG antibody, beta-2 glycoprotein IgG and c-ANCA. Duplex was negative for renal artery stenosis or renal vein thrombosis. She was initiated on hemodialysis secondary to volume overload. Anticoagulation was also initiated due to new diagnosis of bilateral upper extremity deep vein thrombosis. Kidney biopsy performed demonstrating chronic TMA in the glomeruli, negative for acute thrombi, crescents/features of lupus or a full house pattern on immunofluorescence. MR angiogram was also obtained in the setting of concern for APS showing complete intraluminal thrombus occlusion of aorta at the level of renal arteries due to the bifurcation, with occlusion of the right renal artery and narrowing of left renal artery. Due to concern for catastrophic APS she was promptly started on plasma expanders and steroids. She remained stable with trace lower extremity edema. Spot urine protein- and albumin-to-creatinine ratios were 4.63 g/g and 3481 mg/g, respectively.
diabetes dialysis and had recurrent hospitalizations for pulmonary edema secondary to hypertension, and eventually underwent arteriolysis bypass with improvement of hypertension and remained dialysis dependent.

Discussion: Renal prognosis remains poor in patients affected by SLE in the presence of aPLs and may lead to ESRD. Prompt initiation of anticoagulation, immunosuppression and appropriate management of hypertension is very important to diagnose thrombotic lesions as it affects not only kidney outcomes but also contributes to overall morbidity and mortality.

TH-PO580

Association of Preterm Birth with Adverse Outcomes of Glomerular Disease in Children and Adults in the CureGN Cohort

Jaya Isaac,1 Jonathan P. Troost,2 Yujie Wang,3 Kelly Garrity,4 Rick Kaskel,1 Rasheed A. Gbadegesin,2 Kimberly J. Reidy,1 Children’s Hospital at Montefiore, New York, NY; 2Duke University, Durham, NC; 3University of Michigan, Ann Arbor, MI; 4University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.

Background: While some studies of children with nephrotic syndrome have demonstrated better outcomes in those born preterm vs. term, there is little data on associations of preterm birth with kidney and cardiovascular outcomes in adult-onset glomerular disease.

Methods: We performed a cross-sectional and longitudinal survival analysis of participants in the Cure Glomerulonephropathy (CureGN) cohort with birth history data. Preterm (<37 weeks gestation) was compared to term (≥37 weeks gestation). Baseline characteristics and cardiovascular outcomes were compared using Chi-square and Mann Whitney testing. A survival analysis and adjusted Cox proportional hazards model was used to examine a composite outcome of 40% decline in estimated glomerular filtration rate (eGFR) or progression to End Stage Kidney Disease (ESKD). An adjusted logistic regression model was used to examine remission of proteinuria.

Results: More pediatric than adult participants in CureGN were born preterm: 12.8% (118/919) vs. 7.6% (171/2252) (p<0.001). Adults born preterm had a higher prevalence of Focal Segmental Glomerulosclerosis (FSGS) (35% vs. 25%, p<0.01) and APOL1 high risk genotype (9.4% vs. 4.2%, p<0.01) as compared to adults born term. Pediatric participants born preterm were more likely to have hypertension at enrollment (p<0.001). While there was no difference in eGFR at enrollment, participants born preterm had a shorter time interval to a 40% eGFR decline (developing ESKD after biopsy (p<0.001). In adjusted analysis, preterm participants were 28% more likely to develop 40% eGFR decline/ESKD (p<0.008) and 38% less likely to attain complete remission of proteinuria (p=0.006). There was no statistically significant difference in ever having hypertension or other cardiovascular outcomes between the two groups.

Conclusions: Preterm birth was a risk factor for adverse outcomes in this heterogeneous cohort of children and adults with glomerular disease. Children born preterm were more likely to have baseline hypertension while adults born preterm were more likely to have an APOL1 high risk genotype and FSGS. Even in analyses adjusted for FSGS and APOL1 risk status, there was a faster progression of chronic kidney disease in those born preterm. Low nephron endowment and other perinatal exposures may account for these differences.

Funding: NIDDK, Support, Other NIH Support - Analysis support for Jonathan P. Troost was provided in part by NCATS U1TR004404.

TH-PO581

Inpatient and Outpatient Service Review of a Greek Reference Centre for Glomerular Diseases

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Background: The glomerulonephritis (GN) is a rare and complicated disease with high demand of hospitalization, while the glomerular disease and end-stage renal disease present increased prevalence in these patients.

Methods: We retrospectively assessed the inpatient and outpatient service for patients with GN, who have been followed-up at a Greek reference centre for GN, during the Covid-19 period.

Results: 267 patients (median age 65±23 years) included. All patients underwent a kidney biopsy by the nephrologist without complications. ANCA associated GN (18%), Focal Segmental Glomerulosclerosis/Minimal Change Disease (17.5%), IgA nephropathy (17%), Membranous Nephropathy (12.6%), Lupus Nephritis (5%), Membranoproliferative GN (3%), Fibrillary GN (3%), Monoclonal Gamopathy of Renal Significance (3.3%) and IgG4-related disease (2%) were encompassed. We reported median 75 new patients per year. Regarding the inpatient service, we observed an increasing trend to the hospitalizations during this period (274, 452, 461 hospitalizations in 2018, 2019, 2020 respectively). The AAV was the most common disease of hospitalized patients through this period (53% in 2018, 33% in 2019, 39% in 2020), whereas the second most common was the FSGS (28% in 2018, 13% in 2019, 23.8% in 2020). The outpatient’s service review also revealed an increasing number of visits per person per year (279, 456 and 464 total visits in 2018, 2019 and 2020 respectively). The disease with the highest number of visits per person was reported the AAV (median 3.25 visits per patient per year). All the participants treated in collaboration with a multidisciplinary team, consisting of nephrologists, rheumatologists, cardiologists, and pathologists. Finally, we reported complete response at 76% of the patients and in terms of renal improvement, 46% presented eGFR>60ml/min/1.73m², 45% eGFR<60ml/min/1.73m² and only 9% progressed to ESRD after the first year of treatment.

Conclusions: The patients with GN present an increased need for hospitalization and regular outpatient visits. In addition to the medical treatment, the favourable outcome depends on a well-organized inpatient and outpatient service provided by a multidisciplinary team.

TH-PO582

Histopathology Findings and Outcomes of Non-Nephrotic Range Proteinuria in Adults and Children

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Background: While there are clinical practice recommendations for nephrotic syndrome (NS), the approach to diagnosis and management of non-nephrotic range proteinuria (NNP) is not well defined. We hypothesized that histopathologic diagnosis would differ between subjects with NNP compared to NS, and that renin-angiotensin system (RAAS) blockers would be associated with complete or partial remission in subjects with NNP.

Methods: This is a secondary analysis of the Nephrotic Syndrome Study Network (NEPTUNE) cohort. We included adult and pediatric NEPTUNE participants who did not receive treatment for NS prior to screening, and who presented with protein creatinine ratio (UPCR) ≥ 0.5 g/g in children and < 2 g/g in adults at the time of screening. A NS comparison group was identified using clinical diagnoses of NS and/or UPC ≥ 2 g/g in children and untreated adults with UPC ≥ 2 g/g at screening. The histopathologic diagnoses were compared by Chi-Square test between NNP and NS cohorts. In longitudinal analyses, we examined the associations of covariates with complete or partial remission and eGFR decline during the follow up period in NNP using generalized estimating equation.

Results: More than half of adult and children presenting with NNP were classified as overweight/obese and had high blood pressure. Subjects presenting with NNP were more likely to have FSGS than those presenting with NS [In adults, 37.1% in NNP vs 29.3 % in NS (p=0.002). In children, 41.2% in NNP vs 18.1% in NS (p<0.0001)]. In those with NNP, histopathologic diagnosis was different in some cases of other diagnoses of other ESRD [OR=3.27, p<0.03] and/or presence of NNP at baseline [OR=0.51, p<0.02] predicted decreased rate of remission. In those with NNP, histopathology diagnosis of IgAN (vs FSGS) and/or overweight/obesity at baseline predicted eGFR decline [2.63 ml/min/year (p=0.028), -7.04 ml/min/year (p=0.021) respectively]. While this study had a limited sample size, RAAS therapy was not statistically significantly associated with either remission or eGFR in this cohort.

Conclusions: This study supports the need for kidney biopsy in subjects presenting with NNP. Further study/case trials are needed to identify the effective therapies for subjects with NNP.

TH-PO583

Edema and the Risk of Thromboembolic Complications in Nephrotic Syndrome: A Cohort Study

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Background: Nephrotic syndrome (NS) is defined by severe albuminuria, proteinuria, hyperlipidemia, and edema; however, the prevalence of edema with nephrotic range albuminuria and the associated risk of complications is unclear. We examined edema prevalence and the association between edema, mortality, and thromboembolic events (TE) in a cohort of NS patients.

Methods: A cohort study including patients being hospitalized or treated in outpatient clinics with a urine albumin-creatinine ratio (<uACR) > 2,200 mg/g and plasma-albumin < 30 g/l in the Central Denmark Region between 2015-2022. Patients were identified from the central laboratory database by screening all recorded <uACR and p-albumin measurements. We further collected demographics and outcomes and reviewed all medical records to examine if edema was present at time of NS diagnosis. Patients were followed until death or end of study.

Results: Among 806 included patients with nephrotic range albuminuria, 459 (61.4%) had edema at time of diagnosis. A total of 34 (4.2%) arterial TE (ATE) and 23 (2.6%) venous TE (VTE) were observed during follow-up (Table 1). Patients with edema
Corticosteroid Dose and Risk of Infection in Children and Adults with Glomerular Disease: An Analysis of the CureGN Study
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Background: Corticosteroid (CS) exposure is associated with risk of infection leading to increased morbidity and mortality in patients with glomerular disease (GD). We describe longitudinal CS exposure and measure its association with risk of infection in the Cure Glomerulonephropathy (CureGN) study.

Methods: CureGN is a prospective cohort study of patients with biopsy-proven primary GD. CS dose and duration were abstracted from participant medical records at interval study visits and harmonized to prednisone (oral) and methylprednisolone (IV) dose equivalents. Marginal structural models (MSM) were used to estimate effects of CS dose (see Figure), with or without other IS exposure, on hazards of first infection-related hospitalization or ED visit, adjusting for baseline age, race, sex, ethnicity, GD subtype, comorbid conditions, and time-varying markers of disease activity [eGFR, UPCR, and serum albumin].

Results: Of 2586 participants (43% female, 35% <18 years), 446 (17%) experienced a first infection over a median follow-up of 8 months (IQR 32-77). Children and adults were exposed to CS for 14% and 9% of their follow-up time, respectively. Median daily exposure to oral and intravenous CS was 13 mg (IQR 5-32) and 65 mg (IQR 40-500) in children and 10 mg (IQR 5-22) and 125 mg (IQR 125-125) in adults. In a multivariable MSM model, low, medium, and high dose CS exposure was associated with 1.22 (95% CI 0.53-2.84), 3.06 (95% CI 1.84-5.10), and 3.03 (95% CI 1.64-5.59) times higher hazards of infection without concurrent IS, and 2.30 (95% CI 1.40-3.77), 2.71 (95% CI 1.75-4.21), and 3.66 (95% CI 2.35-5.71) times higher hazards of infection with concurrent IS, compared to no IS exposure.

Results: Medium and high dose CS independently increase risk of infection when used alone. When used in combination with other IS, all doses of CS increase risk of infection. These results can inform clinical care and highlight the importance of CS sparing medication regimens for patients with GD.

Funding: NIDDK Support, Other NIH Support - NIAID

TH-PO584

Influenza Vaccine Administration and Effectiveness Among Patients with Glomerular Disease
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Background: Influenza contributes to excess healthcare utilization and morbidity in individuals with glomerular disease (GD). Immune responses to influenza vaccination in individuals with GD may be attenuated by immunosuppression and immunosuppressant use. We used the effectiveness of influenza vaccination among patients with GD.

Methods: Individuals with primary GD were identified within the Merative MarketScan Claims & Encounters database and followed across annual influenza seasons until disenrollment or 2020. Influenza vaccination, influenza and influenza-like infections, and covariates were ascertained using ICD-9/10-CM-based definitions from medical and prescription claims. Influenza seasons (2010-2019) were analyzed individually by comparing the incidence rates of infection in vaccinated and unvaccinated individuals. Despite potential confounding by indication and unascertained vaccinations and infections, Cox proportional hazards models were used to estimate vaccine effectiveness (VE=1-hazard ratio). We then compared years with a close match between vaccine composition and circulating influenza strains (2010-2013, 2015-2018), with a mismatched “control” season (2014). We used a weighted Cox model with an interaction term between vaccination status and vaccine match to estimate the relative VE in matched vs. mismatched seasons.

Results: 46,010 influenza person-seasons were analyzed from 17,219 individuals (median age 45 years (SD 17), 43% female), including 10,535 and 35,475 person-seasons in matched vs. mismatched seasons. Propensity weighting was used to balance the distribution of potential confounders across vaccination status. Cox proportional hazards models were used to estimate vaccine effectiveness (VE=1-hazard ratio). We then compared years with a close match between vaccine composition and circulating influenza strains (2010-2013, 2015-2018), with a mismatched “control” season (2014). We used a weighted Cox model with an interaction term between vaccination status and vaccine match to estimate the relative VE in matched vs. mismatched seasons.

Conclusions: Rates of influenza vaccination are suboptimal among patients with GD. Despite potential confounding by indication and unascertained vaccinations and infections, these data suggest that protection from influenza after vaccination may be poor, leading to excess infection-related morbidity in this vulnerable population.

Funding: Other NIH Support - NIAID

TH-PO586

Patterns of Disease Progression Among Children and Adults with IgA Nephropathy/Vasculitis in CureGN
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Background: IgA nephropathy (iGAn) is the most common glomerular disease worldwide. Identifying demographic and clinical characteristics that place patients at increased risk for disease progression is critical for optimizing therapeutic interventions and targeting clinical trials.

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Methods: CureGN is a multi-center cohort study of children and adults with biopsy-proven glomerular disease, including 823 patients with IgA nephropathy/vasculitits with nephritis (IgAN/IgAVN). We used latent class analysis to segregate 316 incident and prevalent patients, with at least 4 UPCR measurements within the first 2 years of their follow-up, into 3 groups based on longitudinal UPCR trajectories over 2 years. Using Cox proportional hazard models, we then modeled disease progression, defined as the composite outcome of 40% eGFR decline or kidney failure (initiation of dialysis, transplant, or 2 eGFR <15ml/min/1.73m²), as a function of UPCR trajectory group while adjusting for age, eGFR at enrollment, use of immunosuppression, RAAS blockade, and IgAN/IgAVN status.

Results: 149 incident and 167 prevalent patients (enrolled >6 months and > 6 months from biopsy (max 5 years), respectively) were followed for a median of 6.1 (IQR 4.5,6.9) years. Three groups were identified based on UPCR trajectories (Figure). Among incident patients, those with the highest UPCR (Group 3) had 3.9-times higher hazard of progressing to the composite outcome (p=0.0049). No association between immune suppression use and the composite outcome was detected.

Conclusions: In both incident and prevalent IgAN/IgAVN cohorts proteinuria trajectories define patients into distinct clinical groups and are a strong independent predictor of disease progression.

Funding: NIDDK Support

TH-PO587
Frequency and Risk Factors for Glucocorticoid-Induced Diabetes Mellitus: The Japan Nephrotic Syndrome Cohort Study
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Background: Glucocorticoid (GC)-induced diabetes mellitus (GIDM) is one of the major complications of glucocorticoid treatments. The study aims to examine the incidence and risk factors for GIDM among patients (pts) with primary nephrotic syndrome in Japan.

Methods: We conducted a post-hoc analysis of the Japanese Syndrome Cohort Study (JNSCS), a nationwide prospective study of primary nephrotic syndrome. 374 pts who received renal biopsy between 2009 to 2010 were enrolled in JNSCS. After excluding 151 pts (no data for baseline HbA1c, no GC use, and already diabetes at baseline), 223 pts (104 male) were included. GIDM was defined when pts started diabetes medication while ≥ 254 years. There was no significant difference between groups in proteinuria or GFR at baseline level, however serum albumin was lower in the steroid treated group (25g/L vs 32g/L). 47% (14) of participants received corticosteroids, while the remainder (non-steroid treated) were divided into 2 groups: patients with or without GIDM during within 6 months of GC treatment.

Results: Baseline clinical data were as follows: mean age 54.6±20.0 years, mean body mass index 23.4±3.6, eGFR 65±8.7 ml/min/1.73m², and HbA1c 5.2±0.4%. GIDM was developed in 50 pts (22.4%) in 223 total pts, 14 pts (14.2%) in 98 minimal change diseases pts, 27 pts (30.3%) in 89 membranous nephropathy pts, 9 (33.3%) in 27 focal segmental glomerulosclerosis pts, and 0 pts (0%) in 9 other diseases pts. Multiple logistic regression analysis revealed age>65 years and HbA1c>5.6% before treatment are risk factors for the development of GIDM (Figure). Among 43 GIDM pts whose data were available, 15 pts (34.9%) discontinued diabetes medications within 2 years. There were no significant differences for adverse events (death, infections, vascular thrombosis, cardiovascular) and renal outcomes (complete remission, relapse, renal function deterioration) between patients with or without GIDM during 2 years after renogram.

Conclusions: About 20% of patients developed GIDM during the treatment of primary nephrotic syndrome in Japan. Older age and higher HbA1c levels at baseline are the risk factors for GIDM. One-third of GIDM patients could discontinue diabetes medications during 2 years after treatment.

Funding: Clinical Revenue Support

TH-PO589
Humanization and Telehealth for Improving Patient-Reported Outcomes in Glomerular Diseases: The Human-C Project
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Background: Glomerular diseases (GD) encompass rare diseases that predominantly affect young and working-age individuals, often requiring off-label therapies. These conditions necessitate personalized and ongoing monitoring, which can impact patients’ quality of life (QoL). The implementation of telehealth should be tailored to individual patient profiles, while nurse coaching support can identify patients’ personal and occupational needs, and reinforce effective communication. This study reports the outcomes of implementing telehealth and nurse coaching support (Humanization Coaching Project: Human-C Project) in a glomerular disease unit.

Methods: Objective: Evaluate the effect of the Human-C Project on patient-reported outcomes (PROs) and patient-reported experience measures (PREMs) in GD patients, including during the COVID-19 pandemic. Telehealth via WhatsApp and nurse coaching support were introduced in November 2019, incorporating virtual visits. A nurse conducted interviews using Promis-29 and SF-36 questionnaires. In February 2023, an online survey with 15 items (including questions from Promis-29, SF-36, and nurse coaching) was administered to 233 patients.

Results: In 2019, 2,432 visits were recorded, reducing by 7% in 2020 (2,251 visits), with 37% being virtual. Eighty-nine patients responded to the questionnaire. The questionnaire covered domains such as employment status, disease knowledge, social

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function, psychological health, medical appointments, and therapy preferences. Key findings included: working-age patients (87%), inadequate disease knowledge (10%), fatigue (53%), sleep issues (50%), dissatisfaction with work performance (40%), and reduced activity due to emotional problems (34%). Following the Human-C Project, 85% reported adequate healthcare team access during the pandemic, and 72% reported improved QoL.

**Conclusions:** Glomerular disease patients face QoL challenges, but the Human-C Project, along with telehealth, provides specific care perspectives and improves QoL. These findings have important implications for healthcare systems, even in crises like the COVID-19 pandemic.

**TH-PO590**

**Adverse Educational Outcomes in Glomerular Disease**

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**Background:** Research on kidney disease’s cognitive impacts in youth has largely focused on CAKUT patients due to the extent of brain development in the first 5 years of life. Our prior research found decreased high school diploma/GED attainment in those with adolescent Glomerular Disease (GD) onset. However, school impacts range beyond diploma attainment. No studies have analyzed the likelihood of patients with renal disease onset solely after age 5 reporting any adverse educational impact. Objective: Determine the prevalence of any educational impact on GD patients diagnosed between ages 5-19 and which factors might contribute.

**Methods:** CureGN prospective cohort study participants with Minimal Change Disease (MCD), Focal Segmental Glomerulosclerosis (FSGS), Membranous Nephropathy (MN), or IgA Nephropathy (IgAN) diagnosed between ages 5-19 (n= 817) were included in the analysis, with the outcome defined as any self-reported educational impact. Odds ratios (OR) based on General Estimating Equations were used to determine predictors of educational impact. Predictors of interest included race-ethnicity, child (5-12) vs adolescents (13-19) GD onset, parental education, adherence, APOL1 high risk allele, disease type, sex, and number of coexisting conditions.

**Results:** 43% (348/817) reported GD ever impacted their education. Table 1 shows OR of the educational impact of predictors.

**Conclusions:** GD impacts a high percent of patients’ educations, even with onset after age 5. Having coexisting conditions and Black race (reference White) increased the likelihood while IgAN (reference MCD) decreased the likelihood of reporting an educational impact. The racial disparity in educational outcomes and the underlying factors may help improve educational outcomes.

**TH-PO591**

**Assessment of Medication Adherence Among Adults with Glomerular Disease**

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**Background:** Patients with glomerular disease (GD) face challenges taking complex and potentially toxic medication regimens. This study assessed medication adherence in adults with GD and associations with demographic, socioeconomic and disease-related factors.

**Methods:** CureGN is a multinational prospective cohort study of prevalent patients with biopsy proven GD. Nonadherence is assessed at enrollment and follow-up visits. We compared patient and disease characteristics at enrollment and probability of nonadherence during follow-up across self-reported racial and ethnic groups. We used multivariable mixed effects logistic regression models to explore associations between race and ethnicity and odds of nonadherence, serially adjusting for potential confounders.

**Results:** In 1,550 adults with GD (66% White, 15% Black, 10% Asian, 9% Hispanic, 56% male, median age 42 years; 64% privately insured (US); at enrollment, median estimated glomerular filtration rate 73.2mL/min/1.73m2, median urine protein-to- creatinine 1.5g/g, 914 (59%) reported at least one non-adherence response over a median 53 (28, 72) months follow-up time where a median 4 (2, 6) surveys were completed. Odds of non-adherence were higher for Black vs. White adults (OR 1.70, 95% CI 1.24-2.33), for public insurance (US) (OR 1.45, 95% CI 1.06-1.98), and for moderate or greater edema (OR 1.45, 95% CI 1.13-1.86). While forgetfulness was the most common stated reason for medication non-adherence (60%), Black adults were most likely to cite side effects (23% for Black adults vs 17% for overall cohort), cost (7% vs 3%), and feeling well (12% vs 8%) as reasons for non-adherence.

**Conclusions:** Non-adherence to medication is common in adults with GD. Black compared to White adults had higher odds of non-adherence, with side effects, cost, and feeling well all 12% more commonly indicated as reasons. Interventions to target these reasons across racial and ethnic groups may help improve medication adherence.

**Funding:** NIDDK Support

**TH-PO592**

**A New Mexico-Based Kidney Biopsy Registry Data Analysis**

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**Background:** The frequency of biopsy-proven renal parenchymal diseases in the U.S. Southwest is unknown which is summarized in this study.

**Methods:** The University of New Mexico Kidney biopsy registry is a data repository from 2002 to 2019. We abstracted the primary diagnoses from the biopsy report with natural language processing and reviewed them to ensure data accuracy. We reported the initial primary diagnosis if the subsequent diagnoses were congruent in patients with multiple biopsies. Continuous and categorical data were reported as median (QR) and n (%). We plotted time trends for each diagnosis. **Results:** Of the 1204 unique native kidney biopsies, cancer and diabetic glomerulosclerosis were the most frequent diagnoses (Figure 1). The majority self-identified as Hispanic or American Indian. Biopsy frequency increased with time. Patients with cancer were the oldest at the time of biopsy while those with lupus nephritis were the youngest (p <0.001). A higher frequency of cancer and diabetic glomerulosclerosis was noted with time (Figure 2).

**Conclusions:** We used natural language processing to analyze kidney biopsy registry data in a predominantly Hispanic or American Indian cohort and identified disease frequency. This registry will facilitate the study of renal parenchymal disease’s natural history and outcomes.
TH-PO593
Development of a Patient-Reported Outcome for Older Children and Adults with Nephrotic Syndrome as Part of “Preparing a Clinical Outcomes Set for Nephrotic Syndrome” (Prepare-NS)
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Background: Individuals with nephrotic syndrome (NS) experience fluid overload (FO) which can impact health-related quality of life (HRQOL). In partnership with the Food and Drug Administration (FDA), Prepare-NS aims to create and validate clinical outcome assessments (COAs) of FO in NS for use in drug development.

Methods: Context of use includes the following NS diagnoses: FSGS, minimal change disease, IgA nephropathy/vasculitis, focal segmental glomerulosclerosis, and membranous nephropathy. Linear mixed effect models were used to explore the association between HRQOL and the number of ACE (hospitalizations and emergency room visits) within the prior 3 months. HRQOL was self-reported for adults and children ≥8 years old and reported by parent proxy for children <11 using the PROMIS instrument. Models were adjusted for potential confounders, including HRQOL measures before the 3-month ACE period, comorbidities, socioeconomic factors, and medication exposure.

Results: Among 2393 patients, 1282 experienced at least one ACE with an incidence of 75 events per 100 person-years. Infection, gastrointestinal and cardiovascular events were the most common diagnoses (15, 9, and 6 events per person-years, respectively). Among adults and children ≥8, a greater number of ACE was associated with worse fatigue (p<0.001), general physical health (p<0.001), mobility (p=0.001), and global health (p<0.001).

Conclusions: Having more ACE was associated with worse HRQOL in several physical health domains among patients with GN. Our study reinforces the hypothesis that the number of acute care events (ACE) will be associated with worse HRQOL among adults and children in CureGN.

Funding: Other NIH Support - pharmacoepidemiology T32

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TH-PO595

Health-Related Quality of Life (HRQoL) in Adults with Primary Glomerular Diseases in India

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Background: There is paucity of information about the health-related quality of life (HRQoL) of patients with glomerular diseases.

Methods: We used PROMIS 29 v2.1 (Patient-Reported Outcomes Measurement Information System) tool to assess the HRQoL impact of primary glomerular diseases in adult patients, under the following domains: physical function, anxiety, fatigue, depression, sleep disturbance, ability to participate in social roles and activities, and pain interference in daily activities. A composite score representing the patient’s global HRQoL was calculated using T scores (mean=50, standard deviation=10) of individual domains. Linear regression models were evaluated for all domains and composite scores independently.

Results: 301 patients were recruited (100 minimal change disease/focal segmental glomerulosclerosis, 75 membranous nephropathy, 109 IgA nephropathy, and 17 membranoproliferative glomerulonephritis). Mean T-scores were: physical function - 48.7 (46.6-50.8), anxiety - 51.4 (50.3-52.6), sleep impairment (MCS and PCS) of 50) for the US general population. Parents of pediatric patients reported mean SF-12 physical and mental component scores (PCS, MCS) were 41.5 and 44.5, respectively. Both adult and pediatric patients with FSGS experience impaired work productivity and activity interference due to FSGS-related reasons.

Conclusions: As captured by EJI-SER, higher environmental and social burden are associated with lower eGFR and higher risk of kidney failure in the CureGN cohort. This first use of the EJI-SER in GD demonstrates the need for additional investigation into drivers of disparities in GD and policies and resources that address these structural inequities.

Figure: Impact of EJI-SER on kidney survival

TH-PO597

Humanistic Burden of Rare Kidney Diseases: Understanding the Impact of IgA Nephropathy (IgAN) and FSGS on Patients and Care Partners

Study (HONUS): Preliminary Results for FSGS in the United States (US)

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Background: FSGS is known to cause significant clinical and economic burden, however, less is known about the humanistic burden associated with the disease. HONUS is a multi-national, cross-sectional survey study to evaluate humanistic burden of rare kidney diseases, including FSGS.

Methods: The study recruited adult patients with their care-partners, and parents of youth (8-17 years) with FSGS or IgAN. The survey collects data on demographic/clinical characteristics, health-related quality of life (HRQoL), employment (Work Productivity and Activity Impairment [WPAI]), humanistic burden (PedsQL), and disease impact on employment (Work Productivity and Activity Impairment [WPAI]). This preliminary analysis uses US data collected from FSGS adult patients, their care-partners, and parents of youth with FSGS by April 2023. Data were evaluated descriptively.

Results: The analysis included 76 adult FSGS patients and their care-partners, and 29 parents of youth with FSGS (proxy for pediatric patients). Most patients were Caucasian (adults, 68%; pediatric, 69%) and female (adults, 76%; pediatric, 59%), with a mean age of 44 years (adults) and 12 years (pediatric). Most adult patients were in CKD stages 3-5 (3, 26%; 4, 4%; 5, 25%); 13% had received transplant. For adult patients, mean SF-12 physical and mental component scores (PCS, MCS) were 41.5 and 44.5, respectively, lower (reflecting worse HRQoL) than previously published mean scores (MCS and PCS of 50) for the US general population. Parents of pediatric patients reported a mean total PedsQL (parent proxy) score of 65.8, lower (reflecting worse HRQoL) than previously published scores (parent proxy range: 82-88) for healthy US pediatric populations. Adult patients reported 39% activity impairment and 28% overall work productivity loss due to FSGS-related reasons, while care-partners/parents of adult and pediatric patients reported overall work productivity loss of 15% and 31%, respectively, due to FSGS-related reasons.

Conclusions: Both adult and pediatric patients with FSGS experience impaired HRQoL compared to the US general population, impacting adult work productivity and that of care-partners and parents.
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Background: Kidney disease is a well-known extra-intestinal manifestation associated with intestinal bowel disease (IBD), with different underlying etiologies. Little is known about the overall outcomes and predictors.

Methods: Retrospective, observational, cohort study. Patients with previous diagnosis of IBD in whom a kidney biopsy was performed at Mayo Clinic between 1994-2022, were included. Kidney transplant patients were excluded. The main outcomes were kidney failure (defined as eGFR<15 ml/min/1.73m²) and kidney function recovery at last follow-up (categorized as ≤75%, 25-75%, <25% of baseline eGFR).

Results: From a total cohort of 318 patients, 111 patients with IBD and long-term follow-up available were selected (45 ulcerative colitis and 66 Crohn’s disease), with a mean age 48±17 years (40% females). Sixty-eight (61%) were under treatment with 5-ASA. IgA nephropathy, chronic interstitial nephritis and acute interstitial nephritis were the most common diagnoses (22%, 19%, 13%). Median eGFR at presentation was 30 [IQR17–54] ml/min/1.73m² and urinary protein-to-creatinine ratio 0.8 [0.3–3.4] g/g, with no differences between type of IBD. During a median follow-up of 59 (12–109) months, 29 (26%) patients progress to end-stage kidney disease (ESKD). By multivariable Cox regression analysis, the main predictors of kidney failure were age (HR: 1.04, p=0.002), baseline eGFR (HR: 0.94; p=0.003) and histologic total chronicity score (HR: 4.01; p=0.001). 26 (24%), 19 (17%), and 66 (59%) achieved complete, partial or no remission/recovery of kidney function, respectively. Global survival (ESKD+death) was significantly better in patients who achieved complete/partial recovery of kidney function.

Conclusions: One-fourth of patients with kidney disease associated with IBD progress to ESKD, and the main determinants of this outcome is age, baseline eGFR and degree of chronicity in kidney biopsy.

Kidney Survival according to Grades of Histologic Total Chronicity Score

Table 1 Frequency of various kidney diseases in patients with IBD

<table>
<thead>
<tr>
<th>Disease</th>
<th>CD</th>
<th>UC</th>
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</thead>
<tbody>
<tr>
<td>IgA</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>FSG</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Anti-Saccharomyces MRSV</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>ANCA-c+</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>16</td>
</tr>
<tr>
<td>TIN</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>CD</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>UC</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

(©IBD - 4 patients had IBD without distinctive features of CD/UC -- 1 each had IgAN, FSGS, TIN, ATN
4 patients in CD and 1 in UC had only ATN; MGRS=monoclonal gamopathy of renal significance, ANCA=Anti-neutrophil cytoplasmic antibody; Others: neoplasm, non-specific interstitial fibrosis

TH-PO599
Kidney Disease Outcomes in Patients with Inflammatory Bowel Disease
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Background: Patients with inflammatory bowel diseases (IBD), Crohn’s disease (CD) and ulcerative colitis (UC) may have extra-intestinal manifestations (EIM). The prevalence of histologic patterns of kidney disease seen in IBD patients are known, but clinical characteristics and long-term kidney outcomes remain ill-defined.

Methods: We performed a multi-center, retrospective, study of IBD patients who had a kidney biopsy across 3 centers. Inclusion criteria were: (i) IBD diagnosis based on clinical/histological characteristics and (ii) kidney biopsy with pathology report available. Baseline clinical data were analyzed for the whole cohort while outcomes were evaluated in those with available follow-up. Between groups, comparisons for continuous variables were made using Wilcoxon two-sample test and Fisher’s exact test for categorical values.

Results: The frequency of various glomerular (GN), tubulointerstitial (TIN), and vascular (VD) processes are listed in Table 1. Patients with VD were older compared to other groups. At presentation, proteinuria was higher in patients with GN compared to those with TIN [2.13 (0.84, 4.07) vs. 0.30 (0.25, 1.25); p<0.05] and kidney function was worse in those with TIN compared to GN [3.10 [1.98, 4.50] vs. 2.10 [1.20, 3.11], p=0.05]. TIN occurred in 3 treatment naïve patients. In median follow-up of >3 years, 6 of 33 (17%) GN patients, 1 of 8 (12.5%) TIN, and 2 of 4 (50%) VD patients developed ESKD.

Conclusions: Patients with IBD may have varying forms of CKD including GN, and routine monitoring of kidney function is essential for early diagnosis and treatment. TIN may occur as an EIM independent of sulfasalazine therapy. Future studies are required to understand plausible shared immunopathogenesis.

TH-PO600
Frequency of Adverse Events and Risk of Relapse Following SARS-CoV-2 Vaccination in Patients with Glomerular Diseases: A Multicentre Retrospective Study
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Background: Sars-cov2 vaccination has altered the natural course of COVID-19. We aimed to explore the frequency of adverse events of vaccination in patients with glomerular diseases (GD) including the risk of GD relapse afterwards.

Methods: Patients were included if they had biopsy-proven GD and received at least one dose of sars-cov2 vaccine. Patients who ended up in ESKD prior to vaccination or received a GD diagnosis after vaccination were excluded. We recorded demographics, histopathological diagnosis, immunosuppressive regimens, GD outcome before and after vaccination, and adverse events associated with the vaccine. Outcomes of GD included remission, relapse, treatment resistance, ESKD, and death. The rate of GD relapse post vaccination was estimated among patients who had achieved remission.

Results: 315 patients with biopsy-proven GD prior to sars-cov2 vaccination were included, with a mean age of 51(36-63) years at the time of diagnostic biopsy, of whom 142(45.1%) were males. Patients received a median of 3(3-4) vaccine doses. The median time from the diagnostic kidney biopsy to the 1st vaccine dose was 48.9(19.8-106.2) months. Among 255 patients with known GD status at vaccination, 139 (44.1%) were on immunosuppressive therapy, 224(87.8%) were on remission and 31(12.2%) were still active. 66(21.0%) patients reported systemic side effects (fever, arthralgias, myalgias) and 122(38.7%) local side effects (pain, swelling, itching, edema) associated with the vaccination. Renal function and 24-hour proteinuria remained stable after vaccination. Among patients in GD remission at vaccination, 23(9.0%) experienced a relapse during a follow up time of 18.2(15.5-20.1) months. Of those, 8 (7.8%) were on immunosuppression and 15 (18.1%) were not (p=0.058). The mean time to GD relapse following vaccination was 2.5(1.2-6.4) months.

Conclusions: According to the findings from this cohort, vaccination against sars-cov2 appears safe for patients with GD, with no significant impact in renal function or the probability of relapse.

Funding: Government Support - Non-U.S.
TH-PO601

Outcomes of COVID-19 Infection in Patients with ANCA-Associated Vasculitis Receiving Avacopan Therapy
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Background: The complement C5a-C5AR signaling axis plays a crucial role in the pathogenesis of ANCA-associated vasculitis (AAV) and COVID-19 infection. Avacopan, a C5a receptor antagonist is an adjunct treatment for remission induction in AAV. Virobelineb, a C5a antibody was granted Emergency Use Authorization by the FDA for severe COVID-19 infection. In AAV, COVID-19 infection poses an increased mortality risk. Additionally, the risk of severe COVID-19 infection is increased in patients receiving rituximab and glucocorticosteroids.

Methods: We performed an observational, retrospective study examining outcomes of patients with AAV treated with avacapan and who had COVID-19 infection. Data on ANCA type, immunosuppressive treatment, COVID-19 course, and COVID-19 vaccination status were collected from patients who were treated after a review of medical records.

Results: A total of 7 patients were included. The mean (SD) age was 65.1 ± 7.5 years old. Four patients had MPO-AAV and 3 patients had PR3-AAV. Two patients had a relapsing disease, and the rest had a new diagnosis of AAV. Six patients received at least 3 COVID-19 vaccines and a single patient received two COVID-19 vaccines. Five patients received a combination of rituximab, cyclophosphamide, glucocorticoids, and avacapan, whereas 2 patients received rituximab, glucocorticoids, and avacapan. The mean (SD) time from the date of initiation of induction immunosuppression to avacapan initiation was 20 (±2.5) days. The mean (SD) time from avacapan initiation to COVID-19 infection was 110 (±62) days. At the time of COVID-19 infection, all patients remained on rituximab therapy. The mean (SD) time between the last rituximab dose and the onset of COVID-19 infection was 63.8 (±57.1) days. Avacopan was continued in all patients. COVID-19 treatment included Paxlovid (n=3), Bebtelovimab (n=1), Remdesivir (n=1), remdesivir and dexamethasone (n=1), and no treatment (n=1). All patients had mild symptoms except one patient who was hospitalized and died from severe COVID-19 infection.

Conclusions: COVID-19 clinical course appears to be mild in the majority of AAV patients treated with avacapan, with a single patient experiencing severe COVID-19 infection and death. More studies are needed to explore the interplay between C5a blockade and infectious complications from SARS-CoV-2.

TH-PO602

Analysis of Clinical Features in ANCA-Associated Rapidly Progressive Glomerulonephritis Treated with Avacapan: A Single-Center Experience in Japan
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Background: Although avacapan (AVA) has recently become available as an induction therapy of ANCA-associated vasculitis, but the use of corticosteroids has not been established. Therefore, we conducted a retrospective analysis of the clinical database of ANCA-associated rapidly progressive glomerulonephritis (ANCA-RPGN) patients in our hospital with a reduced regimen of corticosteroids.

Methods: All patients met the CHCC classification criteria for MPA and GPA at disease onset. Seven patients [3(43%)] females] followed for at least 12 weeks since August 28, 2018, 4(57.1) mg/kg/day and then tapered off at 12 weeks.

Results: AVA was used in 12 patients with AAV, of whom 7 presented with RPGN. Of the 7 patients with renal involvement (4 MPO-MPA, 2 MPO-GPA and 1 GPA-PRA), 6 newly diagnosed and 1 relapsing disease received a remission induction. The mean age was 70.0±12.1 years, mean BMAS was 16.4±3.1, prednisolone (PSL) was 52.1±17.8 mg/day. At the start of AVA, s-Cr was 2.3±1.1 mg/dL, eGFR was 25.0±11.8 ml/min/1.73m², CRP was 1.9±3.1 mg/dL and the dose of PSL was 37.1±17.0 mg/day. At week 12 and 24, percentages of participants who could discontinue PSL were 43%, 60% and remission rates were 100%, 80%, respectively. There were no serious adverse events and no patients requiring maintenance dialysis. At week 12 and 24, doses of PSL were 3.6±4.5/1.5±2.2 mg/day, s-Cr were 2.6±4.6/1.7±4.0 mg/dL, eGFR were 34.2±14.2 /35.6±17.7 ml/min/1.73m² and CRP were 2.7±6.7/0.1±0.09 mg/dL, respectively.

Conclusions: These results showed that AVA may be effective and have acceptable safety profiles in relatively elderly AAV-RPGN patients in daily practice in Japan.

TH-PO603

Treatment, Relapse, and Complications of Myeloperoxidase (MPO) and PR3 ANCA-Associated Glomerulonephritis: Report from an Australian Centre

Background: ANCA-associated vasculitis (AAV) is managed with combination immunosuppression. Infections are the most common cause of excess morbidity and mortality. Multidisciplinary clinics have improved outcomes in several chronic diseases but have not been evaluated in AAV.

Methods: A retrospective cohort study was performed of patients diagnosed with AAV at Monash Health in Melbourne, Australia between January 1, 2000 and February 28, 2018, excluding children and those with EGPA. Hospitalization rate was calculated as number of hospitalized patients out of those at risk excluding day admissions. Survival analysis was performed, with subjects entering analysis at diagnosis.

Results: Of 165 patients, 22 were hospitalized for infection within the first 12 months of AAV diagnosis with a hospitalization rate of 15 per 100 person-years. Median length of stay was 9.4 days. Hospitalization rate for infection did not change with vasculitis clinic establishment in 2014 (18 per 100 person-years pre vs. 8 per 100 person-years post, p=0.10). After infection, kidney disease (excluding routine dialysis), cardiovascular disease, and disease relapse accounted for the greatest burden of hospital days. Hospitalization rate for any cause reduced from 70 per 100 person-years before clinic establishment to 51 per 100 person-years after (p=0.02). Those with MPA were at comparable risk of death to those with GPA (HR 1.22, 95% CI 0.53-2.80). Where known, the most common cause of death was infection, followed by kidney failure (diabetes non-remission for medical or social reasons), and malignancy within the first 12 months of AAV diagnosis.

Conclusions: Establishment of a multidisciplinary vasculitis clinic was with a significant reduction in hospitalization rate for any cause, with a trend toward a reduction in hospitalization rate for infection. Infection was the most common cause of death.

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

Underline represents presenting author.
TH-PO605

Changing Phenotypes and Clinical Outcomes over Time in Microscopic Polyangiitis
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Background: Diagnosis and management of Microscopic Polyangiitis (MPA) have evolved considerably over the last decades, but it is unknown whether clinical, histological presentation and patient and renal outcomes have changed accordingly.

Methods: We compared clinical-pathological characteristics at diagnosis, and the risk of death and of end stage kidney disease (ESKD) in patients diagnosed with MPA between 1980 and 2022, after grouping them in two periods (p): p1980–2001 and p2002–2022. We compared the mortality rate between the two periods using Kaplan-Meier estimator and Cox-regression and competing risks of ESKD and death using the Aalen-Johansen estimator, Fine-Gray multiple regression and multi-state models.

Results: Out of 187 patients, 77 were in p1980-2001, and 110 in p2002-2022. Patients in p2002-2022 were older (66.2(14.0) vs 57.7(15.8); P<0.001), had a better kidney function (eGFR 25.9(24.8) vs 21.5(24.2) mL/min/1.73m²; P=0.011) and a lower prevalence of the Berden sclerotic class (4.8 vs 18.2%; P=0.006). Despite a similar crude and adjusted patient survival, the risk of ESKD decreased during p2002-2022, compared to p1980-2001 (0.30 [95%CI 0.16-0.57; P=0.001]) (Figure). The result remained significant after accounting for death after ESKD in multistate models and after adjusting for potential confounders (0.33 [95%CI 0.18-0.63; P=0.001]).

Conclusions: Clinical presentation of MPA has become less severe over the last decade, leading to a reduced risk of ESKD, despite a comparable risk of death. Older age, changing clinical patterns and better kidney function at the time of diagnosis do not fully account for the reduction in ESKD, which may be instead related to new induction and maintenance therapies as well as to a greater awareness of the disease.

TH-PO606

Non-Lupus Full House Nephropathy: A Debatable Entity
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Background: Lupus nephritis (LN) is characterized by a variety of light microscopic findings on kidney biopsy and a full house (FH) pattern at immunofluorescence/immunohistochemistry. A FH pattern and lesions consistent with LN, in a patient without clinical and laboratory features of SLE have led to the descriptive term non-lupus full house nephropathy (NLFHN). We performed a systematic review focussing on NLFHN nomenclature, clinical findings and outcome.

Methods: In a reiterative process, all identified terms for NLFHN and other MeSH terms were searched in PubMed. 346 records were screened according to inclusion and exclusion criteria. The 58 records identified were published between 1982 and 2022 and 60.3% were case reports. The available clinical data of patients from different reports were collected and analysed.

Results: NLFHN was addressed with 22 different names: the same name used by different authors could refer to different entities (Figure 1). We identified 148 patients: 75(50.7%) were males; median age 35(23-58) years. Creatinine and proteinuria at onset were 1.4(0.8-2.5) mg/dL and 5.7(2.7-8.8) g/day. Less than 1/3 of patients achieved complete renal response (CRR). A clear causative agent was identified in 50 patients, mainly infective (50%). Secondary NLFHN were acute, non-relapsing diseases with lower renal function at onset compared to the idiopathic ones (P=0.001). Among the 57 patients with idiopathic NLFHN, CRR was comparable between patients treated with immunosuppression (IS) and supportive therapy; however, proteinuria and creatinine at onset were higher in patients treated with IS (P=0.089 and P=0.066). Only 8 patients developed SLE after a median follow-up of 5.0(1-9.0) years.

Conclusions: Despite increasing interest, the place of NLFHN among glomerular diseases is still uncertain, which complicates treatment decisions. Confusion arises by the lack of high-quality evidence and the lack of consensus on nomenclature. The description of three pathogenic categories is a step forward towards a shared framework of this rare entity.
TH-PO608
Impact of Sex in Clinical Presentation and Outcomes of Patients with ANCA-Associated Vasculitis with Severe Kidney Disease

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Background: The impact of sex in the clinical presentation and outcomes of patients with anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) with glomerulonephritis (AAV-GN) has not been studied, particularly in patients with severe kidney involvement (eGFR<15 ml/min/1.73 m²).

Methods: A retrospective cohort study on MPO- or PR3-ANCA patients with AAV (MPA or GPA) and eGFR<15 ml/min/1.73 m² or ESKD at presentation. Clinical presentation and outcomes were analyzed according with sex.

Results: We analyzed 166 patients with biopsy proven active AAV-GN and eGFR<15ml/min/1.73m² at diagnosis:78(47%) females and 88(53%) males. Arterial hypertension was more frequent in males (85.2% vs.70.5%,p=0.022). Serum creatinine (SCr) was higher in males when compared with females (5.2[QR 4.2-7.4] vs. 3.6[QR 2.8-5.1] mg/dL, p=0.001) but there were no differences in eGFR at presentation (9.9vs.12.1 ml/min/1.73m², p=0.053). There were no differences between groups in age at diagnosis, GPAVs-MPA, ANCA specificity, frequency of alveolar hemorrhage, BVAS score, chronicity score or crescentic features on kidney biopsy. Males received IV methylprednisolone more frequently (84.1% vs. 69.2%, p=0.023), however the rate of progression to ESKD at 12 months between groups was similar(p=0.186). When analyzing only the 71 patients that started dialysis within 4 weeks, infections at 12 months were more common in males(53.4% vs.30.8%, p=0.003), however the rate of progression to ESKD at 12 months between groups was similar(p=0.186). When analyzing only the 71 patients that started dialysis within 4 weeks, infections at 12 months were more common in males(53.4% vs.30.8%, p=0.003), however the rate of progression to ESKD at 12 months between groups was similar(p=0.186).

Conclusions: Males had increased frequency of infections at 12 months.

TH-PO609
A Retrospective Observational Study of the ANCA-Negative Renal Vasculitis Cohort in the National Rare Kidney Disease Registry

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Background: A recent single centre study reported that ANCA-negative pauci-immune glomerulonephritis (PIGN) presents in younger patients, with higher end-stage kidney disease (ESKD) risk, despite lacking differences in histopathology. Fewer extrarenal manifestations were observed. The aim of this study was to review ANCA negative vasculitis PIGN outcomes in the Irish Rare Kidney Disease Registry.

Methods: Of 616 patients with PIGN in the registry, 13 were ANCA-negative (defined as negative on anti-MPO and anti-PR3 immunofluorescence / ELISA), with PIGN confirmed on kidney biopsy. Data collection included demographics, biopsy results, and outcomes.

Results: The mean age was 56.8 years (SD 12.85). 4 patients had renal limited disease. Most common other symptoms/system involved included: constitutional (n=4) and ENT (n=4), muco-cutaneous/ophthalmonic (n=2), chest (n=2), neurological (n=1), abdominal (n=1). The mean estimated glomerular filtration rate (eGFR) at diagnosis was 19.4ml/min/1.73m (SD 19.9). Mean creatinine was 423µmol/L (SD 259.9). 8 patients had UPCR documented, with the mean UPCR recorded as 543.2 (SD 747.3). Applying the Berden score to 11 participants: 6 focal, 3 mixed, 1 crescentic, 1 sclerosed were observed. 10 of 13 patients received immunosuppression. Induction treatment included Myeloprednisolone (n=7), Cyclophosphamide (n=7), Rituximab (n=2), oral prednisolone (n=3), and PLEX treatment (n=1). 9 patients continued on maintenance treatment: oral prednisolone (n=6), Azathioprine (n=5), Mycophenolate Mofetil (n=3), Cyclophosphamide (n=1), Rituximab (n=1). 4 patients were on renal replacement therapy (RRT) at diagnosis, 1 patient developed end-stage kidney disease (ESKD). 10 patients achieved remission, 1 did not. 3 had documented relapse. 1 patient died within 5-years of diagnosis.

Conclusions: ANCA-negative vasculitis with renal involvement requires early detection and treatment to prevent kidney disease progression. Renal disease may occur as a single manifestation or as part of a multi-systemic presentation, underscoring the importance of organ surveillance. Further elucidation of the pathogenesis and prognostic markers of relapse in ANCA negative vasculitis, will play a key role in improving outcomes.

TH-PO610
Impact of Reclassification by the 2022 ACR/EULAR Classification Criteria on the ANCA-Associated Vasculitis Study Population


Background: In 2022 the American College of Rheumatology (ACR) and European Association of Associations for Rheumatology (EULAR) presented new classification criteria for the three subsets of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV): granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA). Our aim was to assess the impact of the new 2022 ACR/EULAR classification criteria on future GPA, MPA and EGPA studies.

Methods: An established, single center cohort of patients with a clinical AAV diagnosis in a tertiary academic hospital was used as source population. Clinical diagnosis and disease characteristics at time of diagnosis were collected by manual review and matched to the novel 2022 ACR/EULAR classification criteria for GPA, MPA and EGPA studies.

Results: We included 183 GPA, 54 MPA and 27 EGPA patients. In total 32/264 (12%) patients were reclassified. 22/183 (12%) clinical GPA patients were reclassified: 11 (6%) as MPA and 11 (6%) were unclassified. 3/94 (3%) GPA patients were reclassified: 1 (2%) as MPA and 2 (4%) were classified. 7/27 (25%) EGPA patients were reclassified: 3 (11%) as GPA and 4 (15%) patients were unclassified. One clinical GPA patient could be classified as both GPA and MPA. After reclassification, PR3+ patients remained predominantly GPA and MPA. Patients with an unspecified AAV diagnosis and patients with insufficient clinical data for the time of the diagnosis were excluded.

Conclusions: With 12% reclassification the 2022 ACR/EULAR classification criteria will impact inclusion in future studies. Reclassification is often based on ANCA serology and impacts the distribution of typical risk factors for disease relapse in MPA and GPA subgroups.

TH-PO611
Canadian Society of Nephrology Commentary on the 2021 KDIGO Glomerulonephritis Guidelines and 2023 ANCA/Lupus Updates

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Background: The Canadian Society of Nephrology (CSN) completes commentary on published Kidney Disease Improving Global Outcomes (KDIGO) Guidelines. In 2021, KDIGO published Glomerulonephritis (GN) guidelines with recent 2023 guideline updates. KDIGO guidelines includes Recommendations and practice points (PP), which are used when there is insufficient evidence for a Recommendation. In this article we describe the process and highlight findings of the CSN commentary on the KDIGO GN guidelines.

Methods: The CSN established a working group including adult and pediatric nephrologists, pharmacists, pediatricians, pathologists, and patient partners with expertise in GN across Canada. The working group aimed to review guideline’s relevance and applicability to the Canadian context when caring for patients with GN. Recommendations from the 2021 KDIGO 2021 GN guidelines and 2023 ANCA/Lupus were assessed with a standardized survey assessing whether working group members agreed or not with the Recommendation with focus on highlighting specific Canadian context that may impact the recommendation. Recommendations attaining <80% consensus or
Glomerular Diseases: Clinical and Epidemiologic Studies

Prevalence and Outcomes of Anti-Glomerular Basement Membrane Disease with and Without Secondary Glomerular Pathologies

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Background: Anti-glomerular basement membrane (Anti-GBM) disease is a rare but devastating autoimmune kidney disease. Anti-GBM disease can co-exist with several other glomerular pathologies, but little is known about the frequency of these associated pathologies and patients’ renal outcomes compared to patients who have anti-GBM disease alone.

Methods: We retrospectively evaluated Mayo Clinic Renal Pathology Database and included patients (age ≥ 18 years) with a diagnosis of anti-GBM disease on a native kidney biopsy who were treated at the Mayo Clinic from 2000 to 2021. Detailed pathological findings were collected from renal pathology reports. Clinical characteristics and therapies were collected from review of medical records.

Results: Total of 209 anti-GBM cases were identified and of these, 49 cases (23.4%) were treated at Mayo Clinic (internal), whereas 160 cases (76.6%) only had their biopsy reviewed at Mayo Clinic but were treated elsewhere (external). Of 209, 191 were typical anti-GBM (91.4%) and 18 (8.6%) were atypical anti-GBM. Of typical anti GBM cases (n=191), 119 (62.3%) had no other glomerular pathology, 53 cases (27.8%) had at least one other pathologies. 17 (8.8%) had anti-neutrophilic cytoplasmic antibody (ANCA)-associated glomerulonephritis (ANCA-GN), 10 cases (5.2%) had membranous nephropathy (MN), 6 cases (3.1%) had IgA nephropathy, 3 cases (1.6%) had thrombotic microangiopathy (TMA) and 1 case (0.5%) had fibrillary glomerulonephritis. ANCA-GN patients were significantly older than patients with anti-GBM alone and had significantly higher serum creatinine (SCr) compared to patients with associated MN. Those with MN had significantly higher urinary protein compared to those with anti-GBM disease and those with ANCA-GN patients with ANCA-GN had the highest degree of sclerosis compared to other pathologies. Of the 49 internal cases, 32 (65.3%) required dialysis upon presentation and 91.7% survived at 1 year. Of those who required dialysis, only 9.1% discontinued dialysis. There were no different in the outcomes between groups.

Conclusions: Co-existent glomerular pathology is common among patients with anti-GBM disease and can occur in up to 40% of patients. ANCA-GN accounts for over 70% of those co-existing pathologies. Clinical characteristics may potentially serve as clues to look for secondary pathologies in patients who present with anti-GBM disease.

Predictors of Major Adverse Kidney Disease Events in a Real-World Population with IgA Nephropathy


Background: IgA nephropathy (IgAN) is a glomerular disease that may progress to kidney failure. While albuminuria or proteinuria and reduced kidney function are associated with greater risk, other predictors are less clear. The study aim was to use a real-world population to assess clinical predictors of major adverse kidney disease events (MAKDE) in IgAN.

Methods: The study population was derived from electronic health records data in the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry at Providence and UCLA Health systems. Demographics, clinical characteristics, and prescriptions were obtained for adults ≥ 18 years old with a diagnosis code for IgAN in 2016-2020. Kaplan Meier survival analysis and Cox proportional hazards models evaluated MAKDE: 40% eGFR decline, eGFR <15 mL/min/1.73 m², and administrative codes for kidney failure, dialysis, or transplant.

Results: Patients with IgAN (N=1,099) were 50% women (n=554) and 55±18 years old. At baseline, mean eGFR was 77.28 ±8.24 mL/min/1.73 m² (Chronic Kidney Disease Epidemiologic equation 2021); median urine albumin/creatinine ratio (UACR) and urine protein/creatinine ratio (UPCR) were 119 (interquartile range 30-518) mg/g and 0.7 (0.3-1.9) g/g. Renin angiotensin system (RAS) inhibitors and corticosteroids were prescribed to 49% (n=538) and 25% (n=278), respectively. MAKDE occurred in 13% (n=144) by 3 years. Predictors of MAKDE were Asian race, hospitalization, diabetes, RAS inhibitor use, and lower baseline eGFR (Figure). In a sensitivity analysis model including baseline UACR or UPCR measurements (n=335), levels above versus below the median had an adjusted hazard ratio of 2.10 (95% confidence interval 1.07-4.11).

Conclusions: MAKDE were common in patients with IgAN. Asian race and illness severity reflected by hospitalization, diabetes, and RAS inhibitor use, as well as reduced kidney function and albuminuria or proteinuria, predicted these events.

Funding: Commercial Support - Travere Therapeutics

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
ESKD and CKD Progression Among a Diverse Immunoglobulin A Nephropathy (IgAN) Population

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Background: IgAN is the most common glomerulonephritis and a leading cause of ESKD but real-world data on natural history of the disease are sparse. This study evaluated kidney outcomes among a diverse IgAN population in an integrated US health system.

Methods: Longitudinal cohort study (1/1/2000-12/31/2021) was performed within Kaiser Permanente Southern California members with biopsy-proven primary IgAN. Secondary IgAN was excluded. Kidney outcome was composed of a ESKD (diagnosis or transplant) and/or CKD progression. Patients were followed from index biopsy until kidney outcome and censored for mortality, disenrollment, or end of study. Multivariable Cox regression was used to estimate hazard ratios (HR).

Results: Among 687 patients with IgAN, mean age was 45.5 (SD 14.7) yrs. with 52% males, 40% Hispanic/Latino, 30% Asian/Pacific Islander, 24% White, 3% Black, and 39% with eGFR<45. At biopsy, mean eGFR was 58 and mean urine protein creatinine ratio (UPCR) was 2.5 g/g. A total of 270 (39%) had a kidney outcome (39 ESKD, 231 CKD progression) with median time to outcome of 1.3 years (2.4 years among eGFR <30 patients). Median time to ESKD was 2.6 years (4.7 years among eGFR<30 patients). The composite kidney outcome rate was 96.8 (per 1,000 person-years) without significant difference across race/ethnic groups. Additional analysis evaluating effect of uPCR identified as predictors of ESKD and CKD progression.

Conclusions: Among a diverse IgAN population within a real-world environment, we observed a high rate of kidney outcomes in patients with lower eGFR and hypertension, but no difference across race/ethnic groups. Additional analysis evaluating effect of uPCR and treatment on kidney outcomes is ongoing.

Design and Rationale for PERFORM Patient Registry1,2

An Observational Cohort of Patients Utilizing TARPEYO® for Immunoglobulin A Nephropathy (IgAN) in the United States

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Background: Immunoglobulin A Nephropathy (IgAN) is a rare autoimmune disease characterized by the deposition of galactose-deficient IgA1 in the mesangial area of the glomeruli. Up to 50% of patients with IgAN are at risk of developing ESRD within ten to twenty years of diagnosis with poor survival outcomes. TARPEYO® (budesonide) was the first US FDA approved treatment (accelerated approval granted in December 2021) to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein:creatinine ratio (UPCR) ≥ 1.5 g/g. Given the rarity and progressiveness of IgAN, an understanding of real-world treatment patterns and patient outcomes is warranted. The PERFORM Patient Registry1,2 uses a novel direct-to-patient approach to capture electronic health data and patient-reported data in real-world patients with IgAN who are utilizing TARPEYO.

Methods: Adult participants (≥18 years) with at least one dispensed prescription of TARPEYO® in 12 months self-enrolled in the registry online via the IQVIA Integrated Health Platform application study. This approach includes participant consent to sharing of their electronic health data (electronic medical records [EMR], TARPEYO dispensing claims) and collection of electronic participant-reported data (including the participant reported outcome [PRO]) of EQ-5D-3L). Participants will be followed for a minimum of 36 months, until their withdrawal of consent or the end of the registry, whichever occurs first.

Results: This study will describe data obtained via the online study application for eligible participants. Additional exploratory analyses include characterization of the IgAN-treated participant population in terms of demographic and clinical characteristics of TARPEYO treatment utilization and clinical management of the disease over time.

Conclusions: This is the first direct to patient real-world registry of patients with IgAN utilizing TARPEYO. Patient recruitment via Version 1.0 of the registry began in December 2022 and the full registry Version 2.0 is expected to launch in May 2023.

Commercial Support - Novartis Pharmaceuticals Corporation

Levels of Socioeconomic Deprivation Are Associated with Worse Kidney Outcomes in Patients with IgA Nephropathy: Data from UK RaDaR

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Background: The UK National Registry of Rare Kidney Diseases (RaDaR) recruits adults and children with biopsy-proven primary IgA nephropathy (IgAN) and eGFR <60 mL/min/1.73 m² or proteinuria ≥0.5g/24h from 107 adult and paediatric kidney units across the UK, including retrospective and prospective data. Given the well established gradient between greater socioeconomic deprivation and worse health, in this study we aimed to determine whether socioeconomic deprivation influenced the risk of developing kidney failure in IgAN.

Methods: Deprivation quintile was derived using patient postcodes matched to Index of Multiple Deprivation (IMD) scores. Kidney survival from diagnosis was analysed using Kaplan Meier methods and Cox regression. The event was initiation of kidney replacement therapy, censored for death.

Results: The characteristics of 1,427 IgAN patients in RaDaR by IMD quintiles are shown in the Table. There was a clear association between risk of development of kidney failure and deprivation quintile (Figure) with the most deprived IgAN patient group exhibiting significantly faster progression. HR for kidney failure after adjustment for age, eGFR at diagnosis and gender for IMD >3 quintile: 1.46 (1.15-1.84), p=0.0017.

Conclusions: Outcomes in this large IgAN cohort have been published and shown to be poor with few patients expected to avoid kidney failure in their lifetime. This analysis demonstrates even worse outcomes if more socioeconomic deprivation & highlights the need to develop strategies to ensure everyone only to be exposed to the new therapies that are showing promise in preventing kidney failure in IgAN.
TH-PO619

Long-Term Renal Survival in Patients with IgA Nephropathy: A Systematic Review and Meta-Analysis
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Background: IgA nephropathy (IgAN), a primary glomerular disease named more than 50 years ago, is still one of the main causes of end-stage renal disease (ESRD) worldwide. Patients with ESRD incurred higher yearly costs and bear great financial pressure. Assessment of trends in renal survival could indicate whether changes in treatment strategies have resulted in improved long-term renal outcomes.

Methods: We searched the PubMed, Embase and Cochrane Database for cohort studies and clinical trials on renal survival with IgAN from their inception to November 2021. The outcome was defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in estimated GFR (eGFR), or end-stage renal disease (ESRD). We extracted data on 3-year, 5-year, and 10-year renal survival in IgAN. Besides, we separately analyzed studies from developed countries and developing countries. We also analyzed the effect of proteinuria on long-term renal survival.

Results: We included 146 articles that reported on 98,334 patients from 1988 to 2021. The 3-year, 5-year and 10-year renal survival were 94.12% [95% confidence interval (CI) 94.08% to 94.16%], 88.64% (95% CI: 88.58% to 88.70%) and 77.46% (95% CI: 77.34% to 77.59%), respectively. In the past few decades, there have been no significant changes in 3-year and 5-year renal survival in IgAN patients. However, the 10-year renal survival of IgAN had gradually decreased since the late 1990s. Survival in developed countries was higher than in developing countries and fluctuate less. Furthermore, when proteinuria was < 1.0 g/24h, renal survival was improved.

Conclusions: We found that long-term renal survival was not increased over the years in IgAN. And the renal survival was lower in developing countries than in developed countries. The proteinuria was crucial in long-term prognosis of IgAN. When proteinuria was <1g/24h, long-term renal survival was significantly improved. These results could be used to counsel patients on long-term renal survival and know the trend of survival in developed and developing countries.

Funding: Government Support - Non-U.S.

TH-PO620

Characteristics and Outcomes of IgA Nephropathy in the Canadian Province of Manitoba
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Background: Immunoglobulin A (IgA) nephropathy is a common primary glomerulonephritis with variable clinical presentation. The aim of the current study was to characterize the population of patients with IgA nephropathy in the Canadian province of Manitoba.

Methods: In this retrospective, population-based cohort study, we identified all patients with biopsy-proven IgA nephropathy in the province of Manitoba, Canada between July 1, 2002 and December 31, 2019. Natural-language processing software was used for data extraction from pathology reports, which was then linked to administrative data via the Manitoba Centre for Health Policy. Descriptive statistics are presented to describe the population.

Results: We identified 366 patients (mean age at biopsy 43.2 years, 39.6% females). Mean estimated glomerular filtration rate (eGFR) at biopsy was 50 mL/min/1.73m2, and mean urine albumin-to-creatinine ratio was 167.7 mg/mmol. Of the 122 patients with Oxford scores, 29 (23.8%) had M1, 46 (37.7%) had E1, 107 (87.7%) had S1, 29 (23.9%) and 43 (35.3%) had T1 and T2, respectively, while 33 (27%) had either C1 or C2. When stratifying by income quintiles, 31.7% of patients were in the lowest income quintile versus 46.6% of the highest. Comparing eras (2002-2010 versus 2011-2019), receipt of disease-modifying treatment within 6 months of biopsy remained stable for renin-angiotensin system inhibitors (69.6 vs 69.7%), anti-blood pressure medications (57.8 vs 60.6%) and glucocorticoids (23.0 vs 20.4%). Statin use increased significantly between pre-biopsy (12% vs 29.0%, p<0.001). Patients were more likely to receive glucocorticoids if they had Oxford scores M1 versus M0 (41.4% vs 18.3%, p<0.01), E1 versus E0 (37.0 vs 15.8%, p=0.0078), or C1+2 versus C0 (51.5 vs 13.5%, p<0.0001). Over a median of 5.6 years of follow-up, 163 (44.5%) patients developed kidney failure and 69 (18.9%) patients died.

Conclusions: In this cohort, IgA nephropathy was associated with substantial risk of kidney failure and mortality. This study demonstrated the feasibility of using natural language processing as a data extraction technique, and will facilitate further epidemiologic research in this cohort. The study was limited by small sample size, incomplete Oxford scoring and lack of blood pressure data.

Funding: Government Support - Non-U.S.

TH-PO621

Analysis of the Real-World Management of IgA Nephropathy (IgAN) Patients in Five European Countries
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Background: Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. Current treatment strategies focus on controlling blood pressure and minimising proteinuria. This study investigated the real-world management of IgAN in five European countries through a physician questionnaire and patient chart review.

Methods: From 21 Dec 2022 to 6 Feb 2023, physicians from France, Germany, Italy, Spain and the UK completed a questionnaire on IgAN management, and patient charts from their centres were analysed. Physicians had to have a ≥5 CKD stage 1-4 patients under their management, including ≥4 IgAN patients not on dialysis. Physicians had to be a ≥12 years, diagnosed with IgAN, not be on dialysis and have an eGFR ≥15 mL/min/1.73m2.

Results: Participating physicians (N=261) each saw a mean of 30 IgAN patients in the last year. Patients audited as part of the study (N=473) were mostly male (71%), 78% were Caucasian, mean age was 47 years and 57% were in CKD stage 3. The mean time since referral to their current physician was 4.2 years. Proteinuria was >1 g/day in 66% of patients at referral and in 50% of patients at the current assessment (N=403 with both referral and current values). This was despite 92% of patients being taking an ACE inhibitor and/or ARB, 43% taking a SGLT2 inhibitor and 16% taking a steriod. Physicians considered rate of eGFR decline to be moderate in 19% and fast in 6% of patients. However, among patients with eGFR values over 2 years (N=293), rate of eGFR decline was 3 mL/year in 12%, 4-5 mL/year in 16% and ≥6 mL/year in 19% of patients. Relapse occurred at least once in 54% of patients; steroid therapy was used to control the most recent relapse episode in 60% of patients. Most physicians (78%) agreed that they would prefer to administer therapies specifically approved for IgAN and 66% agreed that there is a lack of non-immunosuppressive treatments for IgAN.

Conclusions: Many patients with IgAN continue to have persistent proteinuria despite ACE inhibitor/ARB treatment, and progressive disease is common. Overall, this study indicates that there is a need for more effective treatment strategies to reduce proteinuria and disease progression in patients with IgAN.

Funding: Commercial Support - CSL Vifor

TH-PO622

Comparing Proteinuria and Kidney Survival in FSGS and IgA Nephropathy (IgAN): A NEPTUNE Analysis
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Background: Changes in disease activity markers are important outcomes for clinical trials in rare proteinuria kidney disease. While novel therapies had not achieved complete remission using Kaplan-Meier method.

Methods: We studied children and adults with FSGS or IgAN enrolled in Nephrotic Syndrome Study Network (NEPTUNE) at the time of clinically indicated biopsy and follow-up. We tested the association between lowest proteinuria within 12 months (mo) after biopsy and the time to composite of ESKD/40% eGFR decline using Kaplan-Meier method.

Results: A total of 211 FSGS and 58 IgAN patients were included. Compared to IgAN, FSGS patients had higher baseline eGFR, UPC and obesity rates, but similar age and blood pressure. Relative change in proteinuria was -42±8% vs -39% by 12mo and -42±6% vs -63% by 24mo in FSGS and IgAN, respectively, but a significant proportion with either diagnosis did not achieve complete remission (Fig 1). Associations of other proteinuria in 12mo and shorter kidney survival time were similar across diseases (Fig 2).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Lower proteinuria by 12mo after biopsy was associated with similar improvement in kidney survival in FSGS and IgAN. A substantial proportion of patients under usual care have high proteinuria at 24mo, highlighting unmet need for new treatments.

Funding: NIDDK Support, Other NIH Support - NCATS, Commercial Support - Travere Therapeutics

Figure 1. Forest plots showing the estimated OR with 95% CI for men with BPLN compared to women.

Table 1. Meta-regression analysis for the effect of sex differences on the composite kidney outcome.

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

TH-PO623

Sex Differences in Lupus Nephritis: A Meta-Regression Analysis

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Background: More frequent and severe lupus nephritis (LN) has been reported in men compared to women, but data are limited and inconsistent. We performed a meta-analysis to compare the histopathologic findings and outcomes between men and women with biopsy-proven LN (BPLN).

Methods: We conducted a systematic search of electronic databases through 2021 using the terms "lupus nephritis" and "sex/gender". Screening was limited to studies of adult patients with BPLN. We compared the biopsy findings and outcomes between the sexes. Pooled odds ratios (OR) with 95% confidence intervals (CI) were generated, and meta-regression performed to assess the impact of several covariates, using random-effects models.

Results: 25 studies were included (1210 men and 6635 women). 20 studies reported kidney histopathology, 11 kidney outcomes and 8 mortality rates. Men had a higher OR for class IVa-V LN (1.26, 95% CI: 1.01-1.56) and the composite kidney outcome (doubling serum creatinine, kidney replacement therapy or eGFR<15 ml/min) (2.20, 95% CI: 1.39-3.68) and a lower OR for complete remission (0.52, 95% CI: 0.39-0.68) (Fig. 1). Meta-regression did not reveal statistically significant study-level relationships between sex differences in any of the covariates and the composite kidney outcome (Table 1).

Conclusions: Our analysis confirms the association between male sex and increased LN severity as well as worse kidney outcomes. Larger prospective studies are needed to validate this association and inform treatment strategies that may hold unique value for this high-risk population.

TH-PO624

Factors Predictive of Infections over Time in Lupus Nephritis Patients: Data from a Single-Center Retrospective Cohort

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Background: Infection is a common complication among patients with lupus nephritis (LN) who started treatment. Previous studies have shown that infection has become the leading cause of death in patients with LN. Therefore, early identification of risk factors for infection in LN patients is of great significance for complication prevention and improvement of prognosis. The aim of this study was to explore the clinical predictors of infection in patients with LN.

Methods: Patients who were diagnosed with LN and treated with immunosuppressive therapy at Guangdong Provincial People’s Hospital from 2000 to 2020 were enrolled. Demographics, laboratory data, glucocorticoid dosage, antimarial usage, immunosuppressive agents and infection details were included. Cox regression model was adopted to identify risk factors of infection. Both Univariable and multivariable analyses were performed.

Results: 1. A total of 374 LN patients were enrolled, of which 85.3% (n=319) were female. The average age was 30±12 years and the age ranged from 5 to 81 years. The mean of height was 1.58±0.89m and weight was 51.62±9.87kg. 219 patients (58.6%) with LN developed infection during follow-up, of which 111 (29.7%) were severe infection. 2. In order to compare changes of variables from 3 months, 6 months and 12 months after treatment, our study conducted cox regression analysis. We also conducted ROC and showed the AUC respectively (0.78, 0.70 and 0.521). Multivariable analysis demonstrated that IgM (HR=1.288,95%CI : 1.074-1.544,p=0.006) and free light chain λ (HR=1.783,95%CI : 1.000-3.177,p=0.050) were predictive factors of infection while after 3month treatment, anti-dsDNA reduction(HR=0.728,95%CI : 0.563-0.924,p=0.016) and hemoglobin increase(HR=0.790,95%CI : 0.652-0.958,p=0.017) were protective.

Conclusions: Our study showed that the incidence of infection in LN patients during treatment was high. Changes of variables in 3months after treatment had the most significant influence on infection and severe infection. High levels of IgM and serum free light chain λ before treatment increase the risk of infection and dsDNA antibodies decreased and hemoglobin increased at the third month of treatment, were protective.

Funding: NIDDK Support
The Impact of Late Renal Biopsy on Renal Survival in Patients with Lupus Nephritis

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Background: Lupus nephritis (LN) is it possible to observe differences in incidence and even severity according to the location and characteristics of the population studied. This study aims to describe the clinical-epidemiological profile and the influence of late diagnosis among LN patients with LN at the Nephrology Service of the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo, between the period from 1999 to 2015.

Methods: Retrospective descriptive observational study of patients diagnosed with LN and biopsied before six months of the onset of LN symptoms compared those biopsied after six months or more than of the onset of symptoms.

Results: The total sample size was 398 patients. PAN was positive in 94.1% of patients, anti-DNA in 77.7% and anticoagulop in 27.1%. The full-house pattern was observed in 124 patients (33.2%). Considering the time from the onset of LN-related symptoms until the kidney biopsy, in 47.5% this time was less than 6 months (early group) and in 52.5% this time was greater than or equal to 6 months (late group). The chronicity index was lower in the group biopsyied less than 6 months, 2 (1-4) vs 3 (2-5), p=0.003, with a higher activity index in this same group (5 (3-8) vs 4 (3-6), p=0.006). The chronicity index had a positive correlation with initial, 3-month, 6-month and 5-year creatinine after renal biopsy, with r=0.56 and p=0.0001, r=0.51 and p=0.0001, r=0.51 and p=0.0001 and r=0.38 and p<0.0001, respectively. Fifty-three patients progressed on dialysis over five years follow-up and in univariate analysis late renal biopsy and chronicity index starting at 4 were independent factors for this worse outcome.

Conclusions: This study showed that renal outcomes in renal replacement therapy or chronic kidney disease were associated with delayed renal biopsy and higher chronicity index at diagnosis. Late biopsy comes from a delay in referral to a tertiary hospital nephrologist and therefore a delay in diagnosis and initiation of appropriate treatment for that patient.

Clinical Outcome of NELL1-Associated Membranous Nephropathy and Membranous Lupus Nephritis: A Prospective Multicenter Study

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Background: Primary membranous nephropathy (PMN) and membranous lupus nephritis (MLN) are autoimmune disorders characterized by immune complex deposit in the basement membrane. The optimal immunosuppressive regimen for these conditions remains undefined, and limited research exists on their renal outcomes.

Methods: This study included 108 patients with PMN and 43 patients with MLN (23 Class V only, 20 Class V + III or IV) diagnosed through renal biopsy at eight South Korean hospitals from September 2015 to April 2022. All patients received standard immunosuppressive therapy, including glucocorticoids with additional agents such as calcineurin inhibitors, mycophenolate mofetil, or cyclosporine. Renal outcome was assessed by comparing serum creatinine levels at baseline and one year, adjusted to baseline levels. The response rate was defined as CR (<0.5 g/m² reduction in proteinuria), PR (≥50% reduction in proteinuria), and TF (failure to achieve CR or PR). Median follow-up period was for 11 months in both PMN and MLN.

Results: PMN patients exhibited older age (57.3±12.9 vs 37.4±14.1, p<0.001), higher male proportion (66.1% vs 37.0%, p<0.001), higher BMI (26.0±4.6 vs 23.0±5.1, p<0.002), increased prevalence of hypertension (50% vs 16.3%, p<0.001), higher serum creatinine (0.9±0.4 vs 0.7±0.3, p=0.03), decreased albumin (2.6±0.7 vs 2.9±0.7, p=0.04), and increased urine protein creatinine ratio (6.1±3.0 vs 4.4±4.8, p=0.015) compared to MLN patients. After one year, in multivaried regression analysis, PMN patients showed that the increase rate of serum creatinine was greater than MLN patients (22.4% vs 11.7%, p=0.027), indicating worse renal function in the PMN group, while the reduction rate of proteinuria was similar in both groups (57.6% vs 61.7%, p=0.306). Response rates (CR+PR) and treatment failure rates (TF) did not significantly differ between the two groups (PMN: CR+PR=77.6%, TF=22.4%; MLN: CR+PR=76.7%, TF=23.3%, p=0.891).

Conclusions: This study showed the comparable response rate between PMN and MLN patients after treatment with immunosuppression. However, PMN patients had more deteriorated renal function compared to MLN patients during the median follow-up period of 11 months. Further evaluation with longer follow-up time is necessary to gain comprehensive insights into renal outcomes in these patient groups.

Clinical Outcome of NELL1-Associated Membranous Nephropathy

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Background: Neuronal epidermal growth factor-like 1-associated membranous nephropathy (NELL1 MN) is related to multiple secondary causes, including malignancy and intake of complementary and alternative medicines. The association of CAM intake to NELL1 MN is well-reported in India. However, the outcome of the NELL1 MN remains to be determined.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: We analysed retrospectively clinicopathologic features of NELL1 MN and compared these to non-M-type Phospholipase A2 receptor (PLA2R)/NELL1 MN from our PGIMER-primary MN registry and LTMC, Mumbai. We express the data as numbers, percentages, mean ± standard deviation (range) for normally distributed variables and median and interquartile range, otherwise.

Results: A total of 21 patients had NELL1 MN: the median age, proteinuria, creatinine and albumin were 37 (26,55)-5 years, 6,7(3,9,10.5) g/day, 1 (0.7,1.4) mg/dl and 2.4 (1.9,2.7) g/dl, respectively. 14(67%) patients received a modified Ponticelli regimen. For comparison, we included 21 consecutive patients of non-PLA2R/NELL1 MN. The median age, proteinuria, creatinine and albumin were 41 (30,54) years, 5.3 (2.7,8.7) g/day, 1 (0.7,1.3) mg/dl and 2.4 (1.9,3.0) g/dl, respectively. 14 (67%) had a history of CAM intake in the NELL1 MN group, which was higher than the non-PLA2R/NELL1 MN group (p<0.001); the malignancy work-up was negative in all the cases. The requirement for immunosuppressive therapy was higher in the NELL1 MN group compared to the non-PLA2R/NELL1 MN group (p=0.04). In the NELL1 MN group, we lost two patients to follow-up after a median follow-up of 18 (10,28) months; 15 (79%) patients achieved remission. Two patients died due to infectious complications. 78% and 65% of the patients in the NELL1 and non-PLA2R/NELL1 MN achieved remission (p=0.48).

Conclusions: The present report highlights the association of NELL1 MN with CAM intake compared to non-PLA2R/NELL1 MN. Three-fourths of the NELL1 MN responded to in-sighting drug withdrawal/ immunosuppressive therapy.

Funding: Government Support - Non-U.S.

TH-PO630 Kidney Outcomes in Self-Reported Black Patients with Primary Membranous Nephropathy in the Cure Glomerulonephropy Study (CureGN)

Background: Primary membranous nephropathy (pMN) is a common cause of nephrotic syndrome in adults. Disease progression in Black versus non-Black patients with pMN remains to be fully characterized.

Methods: CureGN is an ongoing multi-center prospective, observational cohort of children and adults with biopsy-proven pMN or 3 other primary glomerular diseases. First diagnostic biopsies were performed between 2010 and 2023. For this analysis, we report baseline clinical data at enrollment, proportion of time on immunosuppression during follow-up, and incident rates for kidney failure and 40% eGFR decline. Time to kidney outcomes was estimated using adjusted Cox proportional hazards models.

Results: As of May 2023, 608 pMN patients were enrolled (580 with available follow-up data). Of those, 93 were self-reported Black/African American race: median age 52 (IQR, 37-64); 39% female; and median follow-up time of 4.4 yrs. Among 444 pMN patients, patients' mean age was 50 (IQR, 45-55); 62.5% female; and mean follow-up time of 5.3 yrs. Median baseline eGFR was 76.7mL/min/1.73m² for Black/AA and 78.7mL/min/1.73m² for non-Black. The proportion of time on immunosuppressive therapy was similar (p=0.07). Among 444 pMN patients, 21 (4.7%) Black/AA and 77 (17.3%) non-Black reached a kidney failure event (defined as death, ESKD, or ≥50% eGFR decline). Among 608 pMN patients, 15 (2.5%) Black/AA and 145 (24.0%) non-Black reached a ≥40% eGFR decline event.

Conclusions: In patients with pMN, self-reported Black race appears to be strongly associated with worse kidney outcomes despite having similar eGFR at enrollment. Additional analyses including assessment of genetic factors are underway to gain understanding of determinants of this observed association.

Funding: NIDDK Support

TH-PO631 Membranous Nephropathy Outcomes Among Children and Adults: Cure Glomerulonephropy Study (CureGN)

Background: Membranous nephropathy (MN) is a rare entity in children, whereas it’s one of the most common causes of primary nephrotic syndrome in adults. There are limited data on disease progression in children, as well as uncertainty about differences between childhood vs adult MN.

Methods: CureGN is a multi-center prospective, observational cohort of children with biopsy-proven glomerular diseases. For this analysis, baseline clinical data and proportion of time on immunosuppression (IS) across study follow up were reported. Cox proportional hazard models were used to estimate time to kidney outcomes, and linear mixed models to assess estimated glomerular filtration rate (eGFR) trajectories. Models were adjusted for sex, age at biopsy, IS prior to biopsy, urine protein to creatinine ratio (UPCR), eGFR, and time from biopsy to enrollment.

Results: Among 608 MN participants (580 with follow-up visit), 54 (9%) had childhood-onset MN (age <18 at time of biopsy) with characteristics including: 48% female, median age 14 years (IQR, 12-17), and 15% self-identify as Black. Overall, childhood-onset MN had an increased risk of end stage kidney disease (HR, 5.1; 95% CI, 1.45-18) in comparison to adults. The eGFR decline was steeper in children (3.75 (0.87) mL/min/1.73m² per year) than adults (0.14 (0.78) mL/min/1.73m² per year) (p<0.0001).

Conclusions: Despite potential for remission, children with MN had steeper eGFR decline and faster time to kidney failure than adults. Additional data are needed to extend our understanding of determinants of disease and outcomes to guide therapies and inform practice guidelines.

Funding: NIDDK Support

TH-PO632 The Epidemiology of Primary Membranous Nephropathy: A Single-Centre Study over Two Decades

Background: Membranous nephropathy is the commonest cause of nephrotic syndrome in non-diabetic White adults over the age of 40, and can be either primary (pMN) or secondary. Management aims to induce remission spontaneously with supportive care, or with immunosuppression (IS). Here, we describe the natural history of this condition in a large tertiary centre in the UK.

Methods: 178 patients with pMN were identified over 2 decades. We collected data on demographics, baseline laboratory values, treatment received and outcomes including progression to renal replacement therapy (RRT) and mortality. Analysis was performed on the whole cohort and specific subgroups.

Results: Median age was 58.3 years with 63.5% male. Median baseline eGFR was 76.7mL/min/1.73m² and urine protein-creatinine ratio 664mg/mol. The primary endpoint of RRT was achieved in 11% (19/178) of patients over a median follow-up of 8 years (IQR, 5-14). Median eGFR at baseline, 76 (65,87) mL/min/1.73m², significantly declined (p<0.001) over time (2GFR=-0.24 (0.2,0.4) mL/min/1.73m² per year).

Conclusions: We provide a comprehensive epidemiologic analysis of pMN at a large tertiary UK centre. Only 10.1% progressed to RRT (much lower than classically reported). For novelty, the KDIGO risk classification was linked to outcomes, highlighting its utility for identifying patients most likely to progress. The Salford glomerulonephritis research group was supported by an unrestricted project grant from CSL Vifor.

Funding: Commercial Support - CSL Vifor

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

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Table 1. Baseline characteristics of the studied MN patients with and without an ATE or VTE at presentation.

<table>
<thead>
<tr>
<th>Variable</th>
<th>With ATE/VTE (n=21)</th>
<th>Without ATE/VTE (n=106)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male, n [%])</td>
<td>14 (67)</td>
<td>48 (45)</td>
<td>0.375</td>
</tr>
<tr>
<td>Age (years)</td>
<td>55 ± 9</td>
<td>55 ± 5</td>
<td>0.999</td>
</tr>
<tr>
<td>PLA2R-related M. %</td>
<td>20 (95)</td>
<td>11 (11)</td>
<td>0.013</td>
</tr>
<tr>
<td>C4d (measure) (u/L)</td>
<td>152 (70-144)</td>
<td>18 (14-34)</td>
<td>0.187</td>
</tr>
<tr>
<td>α2Macroglobulin (g/L)</td>
<td>91 (77-113)</td>
<td>91 (77-113)</td>
<td>0.283</td>
</tr>
<tr>
<td>UPE (g/m2 renal)</td>
<td>6.0 (5.0-9.3)</td>
<td>5.9 (5.0-10.5)</td>
<td>0.350</td>
</tr>
<tr>
<td>PLA2R antibody (RU/ml)</td>
<td>90 (29-175)</td>
<td>99 (22-218)</td>
<td>0.604</td>
</tr>
</tbody>
</table>

*aPLA2R titers at presentation were available for 16 and 360 patients in the cases and control groups respectively.

**TH-PO634**

A Nomogram Prediction Model for Treatment Failure in Primary Membranous Nephropathy

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**Background:** The natural course of primary membranous nephropathy (PMN) is heterogeneous. Immunosuppressive therapy is recommended to PMN patients at risk for renal function deterioration. Prediction model for treatment failure of PMN has been rarely reported.

**Methods:** This study retrospectively included PMN patients diagnosed by renal biopsy in Sichuan Provincial People’s Hospital from January 2017 to December 2020. Information of clinical characteristics, laboratory test, pathological examination, and treatment was collected. The outcome was treatment failure at the end of twelve months. Simple logistic regression was used to identify candidate predictive variables. Forced-entry stepwise multivariable logistic regression was used to develop the prediction model, of which the performance was evaluated using AUC, calibration plot, and DCA analysis. Internal validation was performed using bootstrapping method.

**Results:** A total of 310 patients were enrolled in this study. The comorbidity rates of hypertension and diabetes were 37% (112/310) and 11% (33/310), respectively. At renal biopsy, the medium levels of eGFR, serum creatinine, serum albumin, proteinuria and PLA2R antibody were 102.3 m/min/1.73m², 70.1 µmol/L, 24.3 g/L, 5.9 g, and 35.48 RU/ml. 116 patients achieved the outcome. Forced-entry stepwise multivariable logistic regression indicated that PLA2R antibody (OR=1.002, 95%CI: 1.001-1.003, P=0.002), renal interstitial inflammatory cells infiltration (OR=1.935, 95%CI: 1.393-2.478, P=0.017), and C3 deposition on immunofluorescence (OR=0.294, 95%CI: 0.186-0.469, P<0.049) were the three independent risk factors for treatment failure of PMN. The final prediction model has an AUC (95% CI of 0.653-0.717) and a net benefit in the range of 23%-77%.

**Conclusions:** PLA2R antibody, renal interstitial inflammatory cells infiltration, and C3 deposition on immunofluorescence were the three independent risk factors for treatment failure at 12 months in PMN. Our prediction model may help to identify patients with risk of treatment failure thus avoid unnecessary drug exposure and side effects.

**TH-PO635**

Interim Analysis of Dapagliflozin in Inactive Lupus Nephritis Cross-Over Randomized Trial


**Background:** Clinical trials with sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated to slow the progression of CKD but excluded Lupus Nephritis (LN) patients. This study will assess efficacy and safety of dapagliflozin in inactive LN with residual proteinuria.

**Methods:** The present cross-over RCT(RBR-3vcg568) is including adults with chronic LN class III or IV (+/-V), proteinuria >500mg/24h and eGFR ≥50m/min/1.73m² in maintenance therapy. RAAAS should be stable ≥4w. We exclude patients with recurrent urinary infections; biopsy with active LN (AI>2) and use of induction therapy in the last 12mo, including CNI; and prednisone ≥20mg/d. Patients are randomized to receive dapagliflozin 10mg on top of standard of care (SoC) therapy or not. After 24w the groups are switched off. Primary endpoint is reduction of proteinuria compared to baseline at 6 and 12mo. Secondary endpoints are changes in weight and blood pressure and number of infections. The sample size was calculated for 28 patients enrolled for 80% power to detect a 25% relative risk reduction in proteinuria (α=0.05).

**Results:** From 87 screened class III or IV (+/-V) LN patients in maintenance therapy, we excluded 67 due to active LN, low proteinuria or low eGFR. We have included 20 patients that were randomized 1:1. There were 18 (90%) women, mean age was 39.5y (±11.1), 1 (5%) had diabetes, median eGFR was 49.5ml/min (40.8-113.8), median proteinuria was 1333mg/24h (833.8-1749), 1 (5%) had low C or C4, all patients had SLEDAI ≤6 and used MMSF≥2/day. We analysed 6 and 7 patients from initial dapa and 6 and 4 patients from initial SoC after 3 and 6mo, respectively. Although the sample was not powered to compare the groups, initial results showed lower proteinuria in both groups at 3 and 6mo compared to baseline but did not show differences between them. Dapagliflozin was well tolerated, there were no infection episodes during the follow-up.
no weight and blood pressure changes, but 5 (45.4%) patients had symptom of hematuria.

Conclusions: We expect that the complete results of this trial will help to evaluate whether the SGLT2 inhibitor, added to LN maintenance therapy, could safely reduce the residual proteinuria of inactive LN patients.

Funding: Government Support - Non-U.S.

TH-PO636
Current Status of Treatments for IgA Nephropathy in Japan: A Descriptive Study Using Claims Database
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Background: Several questionnaire-based studies have clarified the current status of treatment for IgA nephropathy (IgAN) in Japan. However, there have been few studies based on the medical claims records. The aim of this study is to clarify the current status for IgAN using the medical claims database in Japan.

Methods: Medical claims data were retrieved from JMDC (Tokyo, Japan). To interpret the medical claims data, we used the International Classification of Diseases, Tenth Revision codes (ICD-10) for disease, Anatomical Therapeutic Chemical (ATC) codes for drugs, names of the medical practice for treatment procedure, respectively. First, we extracted the claims who had disease code of IgAN from April 2014 to October 2020 (31,282 patients, 469,173 receipts). Then, we included the patients aged between 18 and 80 years at the index date with confirmed IgAN diagnosis at least 6 months of continuous insurance coverage/enrollment after the index date. We defined the newly diagnosed IgAN patients as those who underwent renal biopsy and confirmed IgAN diagnosis twice (main disease). Treatment patterns were categorized by ATC codes and names of the medical practice. Patient who occurred in severe infectious disease was defined as recorded the sequential organ failure assessment score in hospital record.

Results: Among the 4,542 included patients, 2,205 patients (48.3%) received the corticosteroids. Of those, severe infectious disease occurred in only 8 patients (0.17%). Renin-angiotensin system inhibitors (RAS-I) were used in 2,682 patients (59.9%). Women aged 18-29 years had a lower prescription rate of RAS-I (30.2%) than other groups. Of the 856 patients who were newly diagnosed IgAN (49.6% men; mean age 44.9), 396 patients (49.2%) underwent the tonsillectomy and 684 patients (85.0%) underwent the treatment procedure (358 patients: 44.5%).

Conclusions: The tonsillectomy with corticosteroid pulse therapy was the standard treatment in Japan.

Funding: Government Support - Non-U.S.

TH-PO637
Clinical Manifestation and Prognosis of Membranous Nephropathy in Patients with Primary Sjögren Syndrome
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Background: Glomerulonephropathy (GN) in primary Sjögren’s syndrome (pSS) was rare. We aimed to compare the clinical features and prognosis between patients with membranous nephropathy and pSS (pSS-MN) and idiopathic MN (iMN) patients.

Methods: From January 1993 to September 2022, at Peking Union Medical College Hospital, we enrolled 96 pSS-MN patients diagnosed with renal pathology and the revised version of the American-European Consensus Group. The control group was 150 iMN patients diagnosed with renal pathology and positive serum anti-M-type phospholipase A2 receptor (PLA2R) antibody.

Results: Compared to the iMN patients, the pSS-MN patients were older, predominantly females (80.2% vs. 44.7%, P < 0.05), with lower 24 h urine proteins, higher serum IgG levels, more anemia, and hypoalbuminemia. pSS-MN patients had lower ratios of positive serum anti-PLA2R antibody (34.0% vs. 59.1%) and positive tissue PLA2R antigen (65% vs. 87.3%) (both P < 0.05). During the median time of 22 months, treated with a combination of glucocorticoids, immunosuppressive agents (cyclophosphamide, calcineurin inhibitors, tripterygium glycosides), or rituximab, the patient’s eGFR remained normal. Moreover, the 24 h urine proteins decreased from 3.1 g/d to 0.8 g/d.

Conclusions: We reported the largest cohort of pSS-MN patients displayed more pronounced immunological anomalies, with a lower prevalence of positive serum anti-PLA2R antibody and tissue PLA2R antigen than the iMN patients, and responded well to the treatments with various immune modulators.

Funding: Government Support - Non-U.S.

TH-PO638
Membranous Nephropathy: A Retrospective Observational Study in a Single Renal Unit
Mei Y. Tan, Elsheaera Mohammed, Richard J. Fluck, Kahi Ping Ng. Royal Derby Hospital, Derby, United Kingdom.

Background: Membranous Nephropathy (MN) is a common cause of nephritic syndrome in adults. The diagnosis and treatment paradigms for MN have evolved with the identification of PLA2R autoantibodies and evidence for the use of Rituximab. We aim to retrospectively examine the treatments and outcomes of all adults diagnosed with MN in a single renal centre, March 2013 to March 2023.

Methods: Patients’ demographics, clinical presentation, treatments, full remission (FR), partial remission (PR), relapse, renal outcome and complications were collected via electronic health records.

Results: In total, 75 patients were identified with 13 diagnosed as secondary MN. Of the 58 patients with primary MN, their mean age was 57 (SD=14) years with 72% male and 35% positive serum anti-PLA2R. At diagnosis, their mean eGFR was 68 (SD=27) ml/min, uPCR 781 (SD=357) mg/mmol, serum albumin 20 (SD=6) g/l. 98% received RAAS inhibitor. Ten patients (17%) achieved FR or PR without further need of immunosuppressive therapy (IS). Of the 48 patients, the median time from diagnosis to start of IS was 2 (IQR 4) months. The majority (63%) received oral cyclophosphamide and prednisolone (CYP) as first line IS, whilst 19%, 15% and 4% received calcineurin inhibitor (CNI), prednisolone only and Rituximab, respectively. After first IS, 26% and 24% achieved FR and PR. 23 patients (47%) required second course of IS whilst 11 and 5 patients required third and fourth courses of IS, respectively. Relapses occurred in 29% of the patients. Overall, the mean eGFR at 6 months, 12 months, 2 years and 5 years was 64, 61, 62, 56 ml/min, two progressed to kidney failure and five died. The FR and PR rates were 41%, 37% following CYP, 47%, 11% following CNI and 27%, 64% following Rituximab. Pancytopenia (n=1), deranged liver function test (n=2), recurrent or opportunistic infections (n=3) and malignancies (n=4) were reported amongst those who received CYP. No significant complications were reported with Rituximab since its first use in October 2020.

Conclusions: In this cohort of MN, their overall long-term renal outcome was favorable. Although the FR rate was < 50%, progression to kidney failure was rare. Relapses remain a challenge. IS is complicated by infection and neoplasia. Biologies and diagnostics may refine therapy options in the future.
Incidence Rates of Primary Focal Segmental Glomerulosclerosis (FSGS) Within a Diverse Adult Southern California Population, 2010-2021

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Background: FSGS is a leading cause of end-stage kidney disease. However, little epidemiologic data exist exploring the specific FSGS subtypes that increase the importance of understanding this rare disease and subsequent management strategies. The goal of this study was to estimate the incidence of FSGS and primary FSGS among a large diverse population in the United States.

Methods: A retrospective cohort study within Kaiser Permanente Southern California, from 2010 to 2021. Descriptive analysis was performed on clinical characteristics, treatment, and outcomes. Chi-squared test was performed to analyze the difference between children and adult groups.

Results: 470,000 patients with chronic kidney disease (CKD) were enrolled, of which 182 patients were C3G confirmed by renal biopsy. Among them, 9 were diagnosed with dense deposit disease and 91 were diagnosed with C3 glomerulonephritis. At the time of diagnosis, 46.2% of C3G patients had an eGFR<60 ml/min/1.73m², 47.1% had low serum complement C3, 48.8% had low serum C4, 22.5% had abnormal blood/urine protein electrophoresis, and 3% had elevated serum globulin. Besides C3 deposition, 4.9% and 12.7% of patients combined IgA and IgG deposition in pathological immunofluorescence, respectively. Compared to children, adult patients tended to present severe symptoms at diagnosis (Table 1). 55 patients (53.9%) received treatment with RASI, while 24 patients (23.1%) received glucocorticoids and 24 patients combined glucocorticoids with other immunosuppressants (cyclosporine, etc.). 16 patients were followed up for more than one year. Among them, 2 patients showed a 40% decrease in eGFR from baseline, and 3 patients developed end stage renal disease (ESRD) within one year.

Conclusions: C3G has heterogeneous clinical characteristics, and adult patients presented more serious symptoms at diagnosis. Gaps are identified for C3G patients standardized treatment in China, and targeted therapy is urgently needed.

Funding: Commercial Support - Beijing Novartis Pharma Co. Ltd.
TH-P0642
Characteristics of Patients with Complement 3 Glomerulopathy (C3G) in a US Multi-Center Assessment
Briana C. Ndife,1 Carolina A. Aldworth,1 Kathleen Murphy,1 Jennifer Nguyen,1 Irina Pivneva,2 Marie Louise Edwards,2 Annika Anderson,2 James Signorovitch,2 Pietro A. Canetta,3 Novartis Pharmaceuticals Corporation, East Hanover, NJ; 1Analysis Group Inc Boston, Boston, MA; 2Columbia University Irving Medical Center, New York, NY.

Background: C3G is characterized by C3 deposition in the glomeruli caused by abnormal activation of the alternative complement pathway. There are no approved therapies for C3G. Despite supportive care, C3G remains a progressive form of kidney disease, with novel treatments needed to improve outcomes. Contemporary datasets on the clinical burden of patients with C3G are limited. Using real-world evidence from electronic medical records, this study describes the characteristics of patients diagnosed with C3G in the US.

Methods: This was a retrospective cohort study of patients included in the US Optum Life Science clinical electronic health record database who were aged ≥12 years at C3G diagnosis (per ICD-10 or SNOMED; index date) between 01/2015 and 06/2022. Patients had continuous clinical activity ≥12 months before (baseline) and ≥6 months after (follow-up) index date, and were followed until death or data end. Patient and clinical characteristics at index date were evaluated using descriptive statistics.

Results: Of 284 patients in the final sample, 78% were White, 11% African American, 2% Asian, and 10% other/unknown. Mean age ± SD was 49 ± 21 years, 50% were male, and 136/228 (60%) had stage ≥3 CKD at index. At baseline, mean Charlson Comorbidity Index (CCI) score ± SD was 2.3 ± 2.7. Of comorbidities included in the CCI, the most common were chronic pulmonary disease (25%) and diabetes without chronic complication (20%). At baseline, hypertension (65%) was the most common C3G-related comorbidity; 10% of patients had undergone dialysis and 12% kidney transplant. Obesity (BMI ≥30) was recorded in 100/249 patients (40%). Common C3G-related treatments at baseline included corticosteroids (54%), ACE inhibitors (41%), ARBs (26%) and immunosuppressants (21%). At baseline, proteinuria was assessed in 126 patients (44%); mean protein/creatinine ratio ± SD was 2.9 ± 3.9 g/g. Of 100 patients (35%) with available data, 34% had complement C3 level <77 mg/dl.

Conclusions: This contemporary assessment of patients with C3G from a national US cohort identified a population that presented with multiple comorbidities and advanced kidney disease around the time of diagnosis.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

TH-P0643
CKD Progression in Patients with Complement 3 Glomerulopathy (C3G) in a US Multi-Center Assessment
Briana C. Ndife,1 Carolina A. Aldworth,1 Kathleen Murphy,1 Jennifer Nguyen,1 Irina Pivneva,2 Marie Louise Edwards,2 Annika Anderson,2 James Signorovitch,2 Pietro A. Canetta,3 Novartis Pharmaceuticals Corporation, East Hanover, NJ; 1Analysis Group Inc Boston, Boston, MA; 2Columbia University Irving Medical Center, New York, NY.

Background: Patients with C3G have high rates of progression despite treatment. Using electronic medical record data, this study characterized disease progression in a US cohort of patients with C3G.

Methods: This was a retrospective cohort study of de-identified patients within the US Optum Life Science clinical electronic health record database, aged ≥12 years at C3G diagnosis (per ICD-10 or SNOMED) between Jan-2015–Jun 2022. Index date was the date of diagnosis. Patients had continuous clinical activity ≥12 months before (baseline) and ≥6 months after (follow-up) index. Patients were followed until death or data end. Patient and clinical characteristics were assessed using descriptive statistics, and time to CKD progression using Kaplan–Meier analyses.

Results: Of 284 patients in the final sample, mean age ± SD was 49 ± 21 years; 136/228 (60%) had stage ≥3 CKD at index. During follow-up, 115/188 patients (61%) progressed to ≥4 CKD stage at index, and/or to kidney failure; median time to progression was 12.6 months (95% CI: 9.4, 17.7). At 6 and 12 months, 38% and 48% of patients, respectively, had a progression of CKD stage. In progressors (n=115), mean age was 54 years and mean Charlson Comorbidity Index (CCI) score was 2.8; in non-progressors (n=73), mean age was 48 years and mean CCI score was 1.8. Among progressors and non-progressors, 14% and 6% of patients, respectively, were African American, had hypertension (79% and 55%), and had prior kidney transplant (10% and 3%) at baseline. At index, 68/115 (59%) of progressors and 28/73 (38%) of non-progressors had CKD stage ≥3. Within 90 days of index, a higher proportion of progressors relative to non-progressors were treated with corticosteroids (54% vs 41%), ACE inhibitors (23% vs 14%) and ARBs (26% vs 20%). Up to 90 days after index, mean SD protein/creatinine ratio was 2.3 ± 2.6 g/g in 21 assessed non-progressors and 3.7 ± 5.0 g/g in assessed progressors. The proportion of patients with complement C3 level <77 mg/dl at baseline was 15/47 (32%) among progressors and 29/34 (85%) among non-progressors.

Conclusions: Patients with C3G progress rapidly despite supportive care. Noted differences between progressors and non-progressors warrant further investigation.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

TH-P0644
Qualitative Analysis Reveals Insights to Meet the Needs of Patients with C3 Glomerulopathy (C3G)

Background: C3 glomerulopathy (C3G), a rare condition characterized by abnormal regulation of the alternative complement pathway, results in kidney function impairment that can progress to end-stage renal disease. Published evidence of the patient experience in managing this rare condition is scarce. Therefore, the American Kidney Fund (AKF) sought to gain insight into the unique needs and challenges of people affected by C3G by convening a focus group of patients and caregivers.

Methods: Through convenience sampling via a C3G social media page, 8 participants were recruited for a virtual, 60-minute focus group. Six participants were adults diagnosed with C3G and two were caregivers of children with C3G. The focus group was recorded and transcribed, then analyzed for key themes using thematic analyses.

Results: Findings revealed 3 overarching themes: limited C3G awareness among health care providers, a lack of patient-friendly C3G education material, and a need to stay connected to the community. Participants faced challenges identifying health care providers knowledgeable about C3G and with experience treating patients with C3G leading several to travel far for their care. Many also discussed their struggle with finding accessible, educational information in the national literature to learn more about their condition and treatment options. Social support needs were also identified including connecting with others with this rare condition and seeing progress being made with advancements in treatments and ongoing trials.

Conclusions: C3G educational resources written in plain language, especially targeted at newly-diagnosed patients, are needed. Additionally, increased HCP education and better avenues for identifying HCPs well-versed in C3G will help patients feel more confident in their care and management plans. Lastly, finding avenues to connect patients with rare disease experts from clinical trials and ongoing advancements will help to relieve the emotional burden felt by patients and caregivers. As part of this effort, AKF is developing a C3G education campaign centered around tackling these barriers. Gathering patient input is imperative to ensure educational resources are meaningfully tailored to patient needs and values to improve health outcomes.

Funding: Commercial Support - Novartis Pharmaceuticals

TH-P0645
Patient Characteristics and Renal Outcomes of C3 Glomerulopathy (C3G) and Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN) in the UK: A Retrospective Analysis of 287 Patients in the UK National Registry of Rare Kidney Diseases (RaDaR)
Lewis Downward,1 Katie Wong,1 Claire Proudfoot,1 Nicholas Webb,2 Edwin K. Wong,2 Daniel P. Gale,2 1Rare Renal Disease Registry, Bristol, United Kingdom; 2University College London Research Department of Renal Medicine, London, United Kingdom; 3National Renal Complementary Therapies Centre, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, United Kingdom; 4Novartis AG, Basel, Switzerland.

Background: Membranoproliferative glomerulonephritis (MPGN) is a rare, chronic kidney condition that encompasses immune-complex MPGN (IC-MPGN) and C3 glomerulopathy (C3G). There is limited literature on treatments and outcomes in MPGN.

Methods: This is a descriptive, retrospective study of patients recruited to RaDaR with MPGN confirmed by biopsy or clinical diagnosis and renal function. Baseline patient characteristics and logrank statistic were used to investigate time to kidney failure and linear mixed effects models to investigate annual estimated glomerular filtration rate (eGFR) slope by disease subtype.

Results: Of 287 patients included in these analyses: 135 (47%) had confirmed C3G and 152 (53%) IC-MPGN. Median age at diagnosis was 14 years for C3G patients and 23 years for IC-MPGN patients. The majority of patients in the C3G and IC-MPGN cohorts were white (74% and 79% respectively). 53% of the IC-MPGN cohort and 45% of the C3G cohort were female. C3G patients had a three-year eGFR decline compared to IC-MPGN patients (5.1 vs 3.4 mL/min/1.73m2/year), although no significant difference was found in the time from diagnosis to kidney failure (median time to kidney failure 8.3 vs 11.1 years for C3G and IC-MPGN respectively, p-value 0.14, Figure 1). Of 141 patients with medication data, 51 (36%) were adult and 90 (64%) were paediatric at diagnosis. 59% of these patients were given RAS blockade (ACE-I/ARBs), and 46% were given corticosteroids as their initial treatment (Figure 2).

Conclusions: RaDaR is a large and robust data source allowing investigation into C3G/IC-MPGN natural history. We found heterogeneity of current treatment approaches in this cohort and rapid progression to kidney failure despite current treatments.

Funding: Commercial Support - Novartis
TH-PO646

Persistence of Signs and Symptoms in Treated Patients with C3 Glomerulopathy (C3G): Evidence from Real-World Data

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Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease, with an estimated incidence of 1-2/million/year. C3G is associated with a high risk of disease progression, approximately 50% of patients reach kidney failure within 10 years of diagnosis. This analysis aimed to describe C3G signs and symptoms (S&S) in treated patients.

Methods: Data were drawn from the Adelphi C3G Disease Specific Programme, a cross-sectional survey of C3G-treating nephrologists in US, France, Germany, Italy, Spain, UK (EU5), China and Japan between August 2022 and April 2023. Nephrologists completed structured forms for consecutive patients presenting with C3G. The forms included demographics, clinical information and reasons for diagnostic delay.

Results: 111 nephrologists completed records for 385 C3G patients (189, 60, 36). Of the 288 receiving treatment at time of survey, median patient age at time of Dx was 38.8, and 59% were male. Median time from symptom onset to the patient’s first physician consultation was reported for 78% of patients. In the EU5 (n=150) this was 4.1 weeks (IQR: 0.3-8.7), in the US (n=63) and China (n=59) this was 4.4 weeks (IQR US: 1.3-6.4, IQR CN: 1.3-12.4), and Japan (n=30) 6.8 weeks (IQR: 4.1-17.6). Median time from first physician consultation to confirmed C3G Dx was reported for 85% of patients. Half of the patients received DxD within 4.6 weeks, 10% experienced a much longer period (Table 1). Reasons for a delay >4 weeks between first consultation and Dx were reported for 54% of patients (n=206). Waiting to conduct biopsy (39% EU5, 38% US, 27% China and 45% Japan) and delay >4 weeks between first consultation and Dx were reported for 54% of patients (n=206). Waiting to conduct biopsy (39% EU5, 38% US, 27% China and 45% Japan) and waiting for biopsy results (33% EU5, 20% US, 38% China and 32% Japan) were the most common causes. When (e)GFR was recorded at DxD (84%), 43% of patients were at CKD stages 3b-5 (GFR <45 mL/min/1.73 m2).

Conclusions: While half of patients with C3G receive a diagnosis within 4-6 weeks of presentation, 1 in 10 wait over 21 weeks. During this time patients may progress to later stages of CKD. Accelerating DxD may improve prognosis for some patients.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Table 1: C3G Dx delay and (e)GFR

<table>
<thead>
<tr>
<th>Time from 1st consultation to C3G Dx (weeks)</th>
<th>All patients (n=206)</th>
<th>Patients with initial consultation date and DxD date (n=122)</th>
<th>EU5 (n=60)</th>
<th>US (n=77)</th>
<th>CN (n=30)</th>
<th>IP (n=39)</th>
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</thead>
<tbody>
<tr>
<td>25% percentile</td>
<td>2.9</td>
<td>5.0</td>
<td>2.1</td>
<td>3.2</td>
<td>3.9</td>
<td>4.4</td>
</tr>
<tr>
<td>Median</td>
<td>4.6</td>
<td>10.6</td>
<td>4.1</td>
<td>3.9</td>
<td>3.4</td>
<td>3.9</td>
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<tr>
<td>75% percentile</td>
<td>10.4</td>
<td>14.0</td>
<td>10.4</td>
<td>10.8</td>
<td>10.8</td>
<td>10.8</td>
</tr>
<tr>
<td>90% percentile</td>
<td>15.1</td>
<td>21.0</td>
<td>15.1</td>
<td>14.1</td>
<td>14.1</td>
<td>14.1</td>
</tr>
<tr>
<td>eGFR at Dx</td>
<td>34.0</td>
<td>45.0</td>
<td>34.0</td>
<td>35.0</td>
<td>34.0</td>
<td>35.0</td>
</tr>
<tr>
<td>CKD stage 3b-5</td>
<td>43%</td>
<td>51%</td>
<td>43%</td>
<td>52%</td>
<td>43%</td>
<td>52%</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.
TH-PO648

The Idiopathic Hypocryoglobulinemia as an Emerging Membranoproliferative Glomerulonephritis

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Background: A considerable number of patients with high clinical suspicion for cryoglobulinemia either show negative results for the detection of cryoglobulins or show only trace amounts which cannot be characterized for composition. We aimed at establishing whether the failure to detect or the detection of trace amounts of cryoglobulin with conventional methods either identifies a peculiar subset of low level cryoglobulinemia (from now on hypocryoglobulinemia) or represents a separate entity.

Methods: Using a modified precipitation technique in hypo-ionic medium, we prospectively identified between 2008 and 2021 237 patients (median age 60.8 years [22-97], 137 females) having <0.5% cryocrit and clinical suspicion of autoimmune disorder.

Results: 54 out of 237 patients (22.7%) had a history of HCV infection. 169 out of 237 patients (71%) had an established underlying disease, while 68 patients (28.6%) (median age 62.9 years [29-93], 35 females) did not show either laboratory markers or clinical symptoms consonant with an underlying etiology. These 68 cases with only trace amounts of cryoglobulins were defined as having a putatively idiopathic hypocryoglobulinemia. Nineteen of these 68 patients (27.9%) had a history of HCV infection. Twenty-four patients out of 68 (35.3%) were positive for rheumatoid factor (RF), while 25 (36.7%) patients had signs of complement consumption, and 36 (52.9%) had increased inflammatory indexes. Seven patients only had arthralgia and constitutional symptoms while 61 out of 68 (89.7%) presented with at least one of the three cardinal signs of cryoglobulinemic vasculitis including skin lesions, peripheral nerve involvement, and glomerulonephritis. Seventy-five percent of the subjects had type III hypocryoglobulins. In patients with hypocryoglobulinemia the histologic features of glomerulonephritis (also examined by electron microscopy) resembled those of mixed cryoglobulinemia-associated glomerulonephritis.

Conclusions: In conclusion, hypocryoglobulins are often polyclonal and are mainly unrelated to HCV infection. Patients who present high clinical suspicion for vasculitis, especially glomerulonephritis and yet test negative for cryoglobulinemia detected by standard techniques, could require deeper investigation even in the absence of HCV infection, RF activity or signs of complement consumption.

TH-PO649

Prognostic Factors and Outcomes of a Large Brazilian Retrospective Cohort of Renal Amyloidosis

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Background: To date, no large studies have characterized the epidemiology and outcomes of the main types of renal amyloidosis in Brazil or Latin America.

Methods: This retrospective cohort study evaluated 81 patients with biopsy-proven renal amyloidosis prospectively identified between 2008 and 2021. Follow-up started at kidney disease presentation and ended at death or December 2022. Clinical presentation, including age, serum creatinine, proteinuria and amyloid type, as well as survival and etiologic type was classified as confirmed in 43.1% and probable in 56.9%. AL was the etiologic type, followed by endocapillary hypercellularity (6.7%) were the most common patterns of glomerulonephritis followed by endocapillary hypercellularity (6.7%) were the most common patterns of glomerulonephritis (EGRF) decline was 8.45±6.41 mL/min/1.73m²/year. Multivariate analysis showed that eGFR<60 mL/min/1.73m² at diagnosis was an independent risk factor for progression to ESKD (HR 5.45 [95% CI, 1.04-28.60]), 11.5% of the patients underwent chemotherapy treatment, even without evidence of plasma cell disorder. Only 9 (60%) of the unrelated probands had a family history of CKD or amyloidosis. Differences in penetrance rate were observed according to the age of the patients (77.4%≤50 years) vs 22.6% (<50 years), p=0.028.

Conclusions: ALFibE545V amyloidosis showed significantly variable penetrance according to age range. In patients with hypertension, proteinuria, and progressive renal impairment, one should consider this diagnosis to carry out targeted genetic testing for AFib, particularly for the p.E545V variant, especially in family members of identified cases. This procedure would avoid inappropriate treatment.

Funding: Government Support - Non-U.S.

TH-PO651

The Clinico-Pathologic Characteristics of Patients with Fibrillar Glomerulonephritis

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Background: Fibrillar glomerulonephritis (FGN) is a rare glomerular disease with lack of sufficient understanding of the disease pathogenesis. As a result, there is a lack of good evidence to guide therapy for patients with FGN.

Methods: We identified patients with FGN from the Cleveland Clinic Kidney Biopsy Epidemiology Project from January 2015 to March 2023. Retrospective chart review was performed to obtain demographic and clinical characteristics.

Results: From 45 patients with FGN, 30 patients had sufficient data. 70% were female and 86% self-reported as white. The median age was 64 years. Clinical features at kidney biopsy were: hypertension (100%), acute or chronic kidney disease (100%), hematuria (76%), proteinuria (60%), nephrotic syndrome (48%). Hypocomplementemia was identified in one case. Work up for secondary associations revealed, M protein (20%), Hepatitis C virus infection (16%), autoimmune conditions (23%) and solid tumor malignancy (10%). Mean serum creatinine and proteinuria at biopsy were 2.7mg/dl (0.7-10) and 3.6 gm/dl (0.1-8.7) respectively. Regarding pathology, pure mesangial (90%) followed by endocapillary hypercellularity (6.7%) were the most common patterns of injury. The majority of patients (76%) had moderate to severe interstitial fibrosis and tubular atrophy and 13% had crescents. DNAB9F was tested on 2 samples, both were positive. 86% of patients had positive IF staining for IgG/C3/K/L with the majority of IgG staining being described as a smudgy pattern. EM showed mesangial pattern deposition and GBM thickening in more than 80% of patients. Regarding treatment and outcomes, most patients were treated with non-immuno-modulatory antiproteinuric agents. Of 7 patients treated with immunosuppressive therapy, 5 patients received Rituximab. During an average of 24 months (0-76) follow up for 13 patients with data, 23% had partial resolution, 2 patients progressed to ESKD, and 53% (7) progressed to ESKD. Aside from a positive correlation between biopsy and ESRD, no predictive variables were identified on univariate and multivariate analysis.

Conclusions: FGN is a rare glomerular disease with poor renal outcomes. Treatment strategies vary. Prospective, multicenter studies are necessary to better understand the disease pathogenesis and identify appropriate therapy.

Funding: Private Foundation Support

TH-PO652

Post-Transplant Recurrence of Glomerular Diseases: Analysis of the CureGN Database

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Background: Post-transplant recurrence of glomerular diseases is one of the leading causes of graft failure. Identification of risk factors and predictive biomarkers are needed to guide management.

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

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Methods: CureGN is a prospective multicenter international consortium of patients with biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), IgA nephropathy/vasculitis (IgAN), and membranoproliferative glomerulonephritis (MPGN). We included pediatric and adult patients from CureGN who underwent deceased or living kidney transplantation. The primary outcome was the risk of post-transplant recurrence. Recurrence was defined as a log-rank test. For secondary outcomes, clinical characteristics of recurrent and non-recurrent patients were compared by t-test, Mann-Whitney, or Fisher’s exact test. Risk factors of post-transplant recurrence were analyzed by Cox regression.

Results: A total of 144 patients were enrolled, including 19 MCD, 68 FSGS, 51 IgAN, and 6 MN. Overall, the mean age was 29.7±18.8, 46 (32%) were pediatric, 87 (60%) were male, and 88 (61%) were White. During a mean follow-up of 31.9±20.7 months, post-transplant recurrence occurred in 32%, 15%, and 12% of MCD, FSGS, and IgAN patients, respectively. In case of the MCD patients, a recurrence in MCD and FSGS, the mean time to recurrence was 7.8±13.5 and 14.7±16.8 months, respectively (Fig.1A). In the combined analysis of MCD and FSGS, none of the variables were associated with increased risk of recurrence (Fig.1B). All of the recurrent patients had dialysis pre-transplant, while 64% in the non-recurrent group (P = 0.002). For IgAN, the mean time to recurrence was 10.9±12.6 months and there was a tendency toward less White and more pre-transplant dialysis in the recurrent group. Overall, having a recurrence was associated with decreased post-transplantation eGFR in FSGS (HR 15.1, CI 95% 3.7–63.2) and IgAN (HR 27, CI 2.4-3.7) in linear regression after adjusting for time.

Conclusions: In the diverse CureGN cohort, post-transplantation graft recurrence was most common in MCD, followed by FSGS and IgAN. The recurrence of FSGS and IgAN was associated with reduced kidney graft function.

TH-PO665
Clinical Characteristics and Risk Factors Analysis on a Cluster of Patients with Acquired Solitary Kidney
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Background: Patients with acquired solitary kidney (ASK), including those who underwent unilateral nephrectomy and those presented with non-functional unilateral kidney atrophy due to acquired causes. While the long term outcome of ASK patients remains an issue of debate. The aim of this study was to observe the clinical characteristics of ASK patients and identify the risk factors for poor prognosis.

Methods: We performed a retrospective analysis on a case series of ASK patients once hospitalized in Renmin Hospital of Wuhan University, China, from January, 2011 to November, 2022. Preoperative and postoperative clinical and demographic data were collected until last admission. Univariate and multivariate Logistic regression models were used to analyze the risk factors for patients with postoperative eGFR <60 mL/min.

Kaplan–Meier cumulative prevalence curves were used to compare the incidence of ESRD in different groups of ASK patients.

Results: A total of 144 patients were enrolled in this study. Among them, 220 (65.5%) cases underwent unilateral nephrectomy due to hydropnephrosis126 (37.5%) or renal cancer 94 (28.0%), the rest 116 (34.5%) patients were treated conservatively. The median age at diagnosis was 51.5 years old (IQR: 42.02, 62.02), and after the median follow-up time of 6 years (IQR: 3.12,75), the prevalence of hypertension, diabetes, anemia, hyperuricemia, hematuria and proteinuria were 43.8%, 15.7%, 40.8%, 37.8%, 71.1% and 44.3%, respectively. K-M survival curve showed that ASK patients with hypertension, hyperuricemia, anemia, age at diagnosis ≥60 years, UT-TP<2g/d were more likely to progress to ESRD. 3. Multivariable logistic regression analysis showed the risk factors which independently associated with the decreased eGFR including the age at diagnosis ≥60 years, follow-up time >10 years, hypertension, anemia, hyperuricemia, UT-TP<2g/d, contra lateral kidney operation history.

Conclusions: In conclusion, the ASK patients with underlying comorbidities, appeared to have a more severe disease in the long-term. It is particularly significant to strict and routine follow-up for ASK patients in high-risk.

TH-PO664
Belimumab for Recurrent Lupus Nephritis After Kidney Transplant
Mark D. Kilpatrick,1,2 Gaurav Gupta,1 Jason M. Kidd.1,2 1Virginia Commonwealth University, Richmond, VA; 2Thomas Jefferson University Hospital, Philadelphia, PA.

Introduction: A 31-year-old woman with a history of end stage kidney disease (ESKD) due to systemic lupus erythematosus (SLE) glomerulonephritis (Class IV/V) underwent deceased donor pediatric on bicep kidney transplant. Nine months after transplant, she developed proteinuria with 2.2 g on spot protein to creatinine ratio. Serum creatinine was stable at 1.3 mg/dl and she was maintained on tacrolimus 0.4 mg daily, mycophenolate mofetil 360 mg twice daily and prednisone 5 mg daily. She had no prior history of rejection.

Case Description: Renal biopsy was performed and showed focal, active nephritis with mesangial hypercellularity, capillary wall thickening, and chronic changes. Serum belimumab levels were checked and were within the therapeutic range. At 12 months post transplant, prednisone dose was reduced to 5 mg daily. The patient was continued on belimumab without any adverse effects. At 24 months, she continued to take prior immunosuppressive therapy.


TH-PO655
Belimumab-Induced Delirium and Behavioral Changes in a Patient with Lupus Nephritis: A Case Report
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Introduction: Belimumab is a monoclonal antibody against B-lymphocyte stimulator, approved by the United States Food and Drug Administration in 2011 for patients with active systemic lupus erythematosus or active lupus nephritis who are receiving standard therapy. Here, we describe a rare case of a patient developing delirium and behavioral changes after subcutaneous (SC) belimumab initiation.

Case Description: A 65-year-old female with lupus nephritis Class IIIIC was started on SC belimumab due to progressive proteinuria while taking prednisone 40 mg daily, mycophenolic acid 180 mg twice daily and hydroxychloroquine 200 mg twice daily. After starting SC belimumab, the patient developed intermittent confusion, forgetfulness and aggressive behavior e.g., inability to recognize her daughter, yelling at others without reason, refusal to go to church despite being an active and regular member previously, and inability to recognize and use common household items. After she threatened to jump out of a moving car when her demands were not met, her husband took her to the emergency room. In the ER, initial laboratory workup and intracranial imaging were unremarkable. Patient was advised to discontinue belimumab and was discharged home. The symptoms resolved completely one to two days after discontinuing SC belimumab. The patient continues to take prior immunosuppressive therapy.

Discussion: Based on the timing of symptom onset, negative head imaging, unremarkable laboratory workup and immediate resolution after discontinuing belimumab, the symptoms were most likely caused by SC belimumab. She has tolerated belimumab intravenously so far without any adverse effects, thus ruling out steroids as a possible cause. Literature review showed that intravenous belimumab has been associated with depression, anxiety and suicidality, however, SC belimumab resulted in less psychiatric events than placebo (1). We believe this is the first case of SC belimumab induced delirium and behavioral changes in lupus nephritis patient after SC belimumab initiation. It is important to educate patients and caregivers about such symptoms. This should be verified in post-marketing surveillance of belimumab as well as specific surveillance during clinical trial follow up.

TH-PO656
The Effect of Voclosporin as Monotherapy in Treating Lupus Nephritis
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Introduction: The current standard of care for lupus nephritis typically involves the use of combination therapy with immunosuppressive medications, such as mycophenolate mofetil (MMF) or cyclophosphamide, along with low-dose corticosteroids. While these medications can be effective in treating lupus nephritis, they are also associated with a range of potential side effects. We present a case of a young female patient who had multiple recurrent infections while on MMF which prompted conversion to voclosporin monotherapy with success in maintaining complete remission.

Case Description: We present a case of a 21-year-old African American female with a past medical history of systemic lupus erythematosus (SLE), diagnosed at the age of 18, complicated by lupus nephritis (LN) class III. The patient was initially treated with a combination of mycophenolate mofetil (MMF), low-dose corticosteroids and hydroxychloroquine. Despite achieving partial remission with this treatment, the dose of MMF had to be reduced due to recurrent infections and persistent leukopenia. Voclosporin was eventually added to the regimen with the aim of achieving complete remission. However, MMF was eventually discontinued as the patient continued to have clinical flares. The patient was continued on voclosporin monotherapy for the next 12 months, during which she achieved complete remission of her LN, with a stable serum creatinine and undetectable proteinuria.
Discussion: Lupus nephritis is a serious complication of SLE, and its treatment often requires the use of immunosuppressive medications, such as MMF and cyclophosphamide which bring with them a wide range of side effects including infections and myelosuppression. Vosclopin is a novel calcineurin inhibitor that has shown promise as a potential treatment for LN. It has been shown to be effective and well-tolerated in combination with MMF and low-dose corticosteroids in the AURA-LV and Aurora 1 trials. This case report demonstrates that vosclopin monotherapy may be an effective and safe treatment option for LN along with low-dose prednisone for LN in patients who are unable to tolerate or have contraindications to other immunosuppressive medications.

TH-PO657
A Rare Complication of Prolonged Immunosuppression in Lupus Nephritis
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Introduction: Epstein-Barr virus (EBV) is a well-recognized virus associated with lymphoproliferative disease (LD). Immunodeficiency and immunosuppression can lead to the reactivation and replication of the virus, increasing the likelihood of malignancy. We present a case of a patient with Lupus nephritis (LN) patient on long-term immunosuppression presenting with non-transplant-associated central nervous system (CNS) LD.  

Case Description: A 35-year-old woman with frequently relapsing LN Class IV on mycophenolate mofetil (MMF), Plaquenil and prednisone for 15 years presented with numbness and weakness in the left side of her face and arm. MRI head showed bilateral supratentorial enhancing lesions (Fig 1). Positive dsDNA Ab, reduced C3, normal C4, EBV positive in cerebrospinal fluid, blood viral load >750 units/mL. CNS lesion biopsy confirmed iatrogenic EBV-associated LD (Fig 2). MMF was discontinued. Rituximab was started for the management of LD with resolution of the symptomatology. To date, lupus nephritis has remained quiescent on Rituximab.

Discussion: EBV-associated LD is influenced by the level of immune suppression and reduced surveillance by T cells. Certain medications can impede the proliferation of lymphoblastoid cell lines, and others affect T-cell function. In vitro and animal model studies have shown that prolonged use of MMF was associated with diminished recovery of V62+ T cells and increased occurrence of EBV reactivation. MMF, commonly used in autoimmune diseases, may unmask an inherent susceptibility of the CNS for immunosuppression-related LD. While LD is frequently considered after organ transplantation, it is less often considered in non-transplant immunosuppressed patients. A high index of suspicion is needed when caring for non-transplant immunosuppressed patients presenting with primary CNS symptoms. Prompt evaluation is necessary to distinguish between lupus cerebritis and LD to individualize care and improve patient outcomes.

TH-PO658
Combined Diagnosis of Proliferative Lupus Nephritis and Tubulointerstitial Infection: A Treatment Dilemma
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Introduction: The treatment of tuberculosis (TB) infection (previously termed latent TB) during the induction phase of treatment for proliferative lupus nephritis (LN) is challenging. The use of high dose immunosuppression (IS) can cause TB disease. Rifampycin-based treatment for TB infection can also lead to major drug-drug interaction as rifampin can reduce the serum levels of mycophenolate mofetil (MMF), hence the level of IS.  

Case Description: A 38-years-old Mexican male who presented with lower limb edema. Initial labs showed leukocytosis and acute kidney injury with nephrotic syndrome. Blood cultures grew Streptococcus pyogenes. Workup for glomerulonephritis (GN) revealed a positive ANA and hypocomplementemia, consistent with immune complex mediated GN. He received antibiotics for a total of 14 days. The urine protein/creatinine ratio (UPCR) one week later increased to 36.9 g/g from 3.2 g/g. Kidney biopsy demonstrated class III++ V LN with 5/22 globally sclerosed glomeruli, 4 with segmental endocapillary hypercellularity with 2 cellular crescents on light microscopy and full house staining on immunofluorescence. Electron microscopy demonstrated mesangial, intramembranous, and sup-epithelial electron dense deposits and extensively effaced foot processes. The patient was discharged on conservative anti proteinuric therapy, as well as MMF. Routine TB screening with Quantiferon was positive, so he started on rifampin and isoniazid. Follow-up 1 month later demonstrated UPCR of 1.76 g/g with no signs of TB disease.  

Discussion: The term latent TB was changed to TB infection because these patients are infected with viable mycobacteria in various stages of containment by the host immune system. Therefore, during the induction phase of treatment of LN, with use of high dose IS, the presence of TB infection presents a high risk of progression to TB disease. We found no case reports of simultaneous diagnosis of proliferative LN and TB infection. Treatment literature is obtained from transplant patients diagnosed with TB infection, where rifampin was found to lower the level of MMF. Therefore, we suggest close follow-up of these patients to rule out TB disease and non-responsiveness to LN treatment during each visit.

TH-PO659
A 35-Year History of Lupus Nephritis Without Renal Fibrosis or Scarring: How Is This Possible? Extosome 2
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Introduction: Recently, Exostosin 1/Exostosin 2 (EXT1/2) was identified as a novel antigen in membranous nephropathy associated with autoimmune disease, particularly lupus nephritis (LN). These patients have distinct clinical features, notably favorable outcomes despite high proteinuria. Current guidelines provide treatment recommendations for patients with LN. However, whether these represent the best approach to the subgroup of patients with EXT1/2+ LN remains elusive.

Case Description: A 54-year-old female with a 35-year history of class IV & V LN presented with proteinuria/hematuria along with hair loss and rash. The patient was not on any immunosuppressive drugs and was taken off hydroxychloroquine 2 years prior for retinal toxicity. History was significant for HTN, osteoporosis, hypovitaminosis D, AVN of hips and knees, nephrolithiasis, HLD, glaucoma, and hysterecetomy for uterine fibroids. Serology showed negative ANA (previously positive), positive anti-dsDNA, low C3, and low C4. Kidney biopsy revealed membranous LN Class V with EXT2+, PLA2R+, THBD7A+, NELL1- staining. Notably, a near total lack of fibrosis or glomerulosclerosis was observed. Treatment was reinitiated with mycophenolate mofetil and tacrolimus for nephrotic syndrome, and losartan for HTN.  

Discussion: Our patient has a long history of recurrent LN, with a notable lack of renal fibrosis or sclerosis. Further investigations revealed EXT2 positivity. Despite evidence demonstrating a favorable renal prognosis associated with EXT1/2+ LN, it is unclear whether these patients remain susceptible to other diseases, as persistent proteinuria can affect other clinical outcomes. Our patient had a recurrence of disease in the context of no immunosuppressive therapy. Without further evidence, we favor a standard approach to immunosuppressive therapy (as in EXT1/2 negative counterparts). We believe EXT1/2 immunohistochemical phenotyping of patients with LN should be performed to aid in our understanding of this subgroup. There are many outstanding questions regarding EXT1/2 and this case underscores the need for more research to help guide treatment practices.

TH-PO660
DNAJB9-Associated Fibrillary Glomerulonephritis with Systemic Lupus Erythematosus: A Case Series
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Introduction: Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease with DNAJB9 positivity. We report 2 cases with lupus nephritis and FGN.

Case Description: Case 1: A 53-year-old woman with history of systemic lupus erythematosus (SLE), hypertension and depression presented severe proteinuria. The patient was diagnosed with SLE 20 years ago, her last lupus flare was 5 years ago. Over the course, her proteinuria worsened with spot urine protein-creatinine ratio (UPCR) was elevated at 3.54 with serum creatinine stable at 0.47mg/dl. Hep B and C, HIV, ANCA and PLA2R antibodies are negative. SLE serologies were not active. Serum c-ANCA (148mg/dl) and C4 (42mg/dl) were in range. The serum light chain kappa lambda ratio was 1.05. She was on MMF and hydroxychloroquine. A kidney biopsy confirmed lupus
nephritis membranous type/ class V and glomerular dense fibrocellular deposits suggestive of mesangioproliferative glomerulonephritis (MNGN). DNAJB9 was positively amplified by PCR: received rituximab infusion therapy (1gm X 2 doses). Two months of follow up showed improvement in UPCR (0.9) with stable serum creatinine at 0.41mg/dl. One year out, the patient remains in remission. Case 2: A 65-year-old female with SLE (diagnosed 40+ years ago), hypertension and arthritis who presented with rising serum creatinine at 2.4 mg/dl. Her UPCR was stable at 0.3. Serologic work up was negative. Serum C3 complement levels were mildly low (74mg/dl) and serum C4 complement levels were in range (18mg/dl). The Serum light chain kappa/ lambda ratio was 1.86. The patient was intolerant to BP lowering agent, and low dose aspirin. Kidney biopsy showed glomerular membranonephritis with mesangio proliferative pattern and abundant electron dense material with fibri lary substructure inflicting mesangium and glomerular basement membranes. Immunohistochemical staining of DNAJB9 was positive in mesangial and glomerular basement membrane. Complement. ANCA and ANA were negative. Seropositive lupus nephritis is a rare cause of nephrotic syndrome, and the limitations of Complement. TH-PO663 A Rare Case of “Lupus-Like” Glomerulonephritis Presenting as Pulmonary Renal Syndrome (PRS) Mingyu He,1 Sheetal Koul,2 Iris J. Lee,3 1Teaching Hospital University, Philadelphia, PA; 2Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Introduction: PRS is a life-threatening condition characterized by rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH). The main causes of PRS include ANCA associated vasculitis (AAV), anti-GM2 disease, or immune complex mediated glomerulonephritis (GN). Herein, we present a rare case of PRS with positive P-ANCA, but a “full house” crescentic GN on renal biopsy, with a negative ANA panel.

Case Description: A 59-year-old female with history of osteoarthritis presented with productive cough and dyspnea for two days. CT chest showed bilateral ground glass opacities. Extensive infectious workup was negative. On the third day, she developed fever, hemoptysis, and rapidly progressive dyspnea necessitating intubation. Bronchoscopy revealed DAH. Her creatinine increased from 2.2 mg/dl on admission (baseline Cr 3.4mg/dl) to 9.2 mg/dl within one week. Urinalysis revealed significant proteinuria (300 mg/dl) and RBC 40-60/HPF. Serologic workup revealed a high P-ANCA titer (> 1.640) and an elevated myeloperoxidase (MPO) antibody of 13. Anti-GM2, ANA, and anti-dsDNA were negative. Complements were normal. Kidney biopsy showed fibrillary glomerulonephritis with cellular/endothelial crescent formation. Immunoflavohorhesis (IF) revealed an intense “full house” staining. She was treated with plasmapheresis, steroid, and cyclophosphamide, resulting in the resolution of respiratory failure and improvement in Cr to 2.7 mg/dl upon discharge.

Discussion: Our patient’s clinical picture supports a diagnosis of AAV with renal involvement, which typically presents as a pauci-immune crescentic GN with negative IF on biopsy. The presence of a “full house” IF pattern, suggestive of Lupus nephritis, was unexpected in this case. While P-ANCA can be found in 10% of patients with SLE, the absence of ANA excludes the patient from meeting the new EULAR/ACR criteria for SLE diagnosis. SLE/AAV overlap syndrome has been reported as a rare entity, with biopsy features of both diseases. In such cases, the presence of ANCA antibody is often associated with more active lupus disease, higher ds DNA antibody levels, and worse renal function. Our case suggests the potential for AAV to overlap with other autoimmune syndromes, highlighting the importance of further studies to validate this association and develop a treatment strategy.

TH-PO664 Diagnosing Challenges in Lupus: Systemic Lupus Erythematosus Initially Presenting as Unicentric Castleman Disease Allison Miller, Vanderlage L. Kung, Ruchi Thanawala, Rupali S. Avassar. Oregon Health and Science University, Portland, OR.

Introduction: Multiple conditions mimic Castleman Disease (CD), a group of lymphoproliferative disorders, including infection, neoplasms and autoimmune disease. There is well-described clinical overlap between systemic lupus erythematosus (SLE) and CD as both can manifest with lymphadenopathy, proteinuria and positive anti-nuclear antibody (ANA) serology. Distinguishing between these two entities can be a vexing process and requires a multidisciplinary approach to care.

Case Description: A 23 year-old woman presented with dyspnea. Chest imaging revealed a mediastinal mass and pleural effusion (Figure 1). The mass was resected and the patient was diagnosed with HHV-8 and EBV-negative CD. A clinician noted persistent hyperproteinemia and discovered 8.2 grams per day of proteinuria despite surgical management. Work up included a kidney biopsy that showed a “full house” immune complex mediated glomerulonephritis with focal activity, endocapillary hypercellularity and large subendothelial deposits. Serologic testing revealed positive ANA, anti-doube-stranded DNA antibody and hypocomplementemia. The patient’s final diagnosis was revised to SLE and she achieved remission with immunosuppressive therapy.

Discussion: To our knowledge, this is the first reported case of unicentric CD mimicking SLE in a patient with nephrotic syndrome. Because unicentric CD is managed with surgery alone, this report highlights the need for a broad diagnostic workup to rule out underlying conditions mimicking lupus nephritis. In this patient, workup for nephrotic syndrome prompted kidney biopsy and serologic testing that was essential for establishing the correct diagnosis and management.

TH-PO665 Not All Lupus Nephritis Is “Complement”-ary William M. Parkinson,1 Ryan Rayman,1 Andy Guan,1 Thomas S. Denapoli,2 Jesse M. Wickham,3 Brooke Army Medical Center, Fort Sam Houston, TX; 1Pathology Reference Laboratory, San Antonio, TX.

Introduction: Lupus nephritis (LN) is a common but serious manifestation of Systemic Lupus Erythematosus (SLE) that can lead to high morbidity and mortality, ulceration and loss of function in patients with SLE. Typically, LN presents early in the clinical course of SLE, often within the first 3 years after diagnosis. Although the clinical manifestations of LN vary greatly, from nearly asymptomatic to rapidly progressive glomerulonephritis (RPGN), the typical presentation of LN includes edema, hypertension, proteinuria, and cytopenia. In this case, we present a patient with a classical presentation of lupus nephritis that did not follow the typical serologic findings.

Case Description: A 19-year-old white female with no significant past medical history presented to her primary care with 6-month history of intermittent bilateral iliococcygeal leg pain and a 20lb weight gain. She initially attributed her leg pain to a high level of physical activity. Pain was worse between her knees and ankles and only temporarily alleviated with rest, massage, and ice. Over the past month, she developed new bilateral swelling in her legs. She denied history of recent illness, chest pain, SOB, congestion, malaise, rash, photosensitivity, oral ulcers, joint pains, or any history of kidney disease. Initial labs were significant for elevated lipid panel, ESR, and TSH with hypothyroidism. Urine analysis showed >3 proteinuria with micro positive for >50% dysmorphic RBC and acanthocytes. Complement levels were normal suggesting against lupus nephritis. However, subsequent ANA was positive in glomeruli. Patient received rituximab infusion therapy. 9 months follow up showed stable UPCR (0.2) with elevated but stable serum creatinine at 1.86mg/dl. Her BP improved without any medications and clinically lower extremity edema disappeared. There was no progression of disease.

Discussion: The association between SLE and DNAJB9 associated FGN is unclear. Rituximab may serve as a potential treatment strategy. TH-PO666 Is It Rhabdomyolysis or Is It Lupus? A Case of Dual Presentation of Neurological Nephropathy Tina Zhang, Farah Daccueil, Stony Brook University Hospital, Stony Brook, NY.

Introduction: Acute kidney injury in unconscious patients has a wide range of differential diagnoses; rhabdomyolysis is a common cause. However, acute rhabdomyolysis is rarely the most common presentation of an unconscious patient. Here we report diagnosis of lupus nephritis with severe rhabdomyolysis.

Case Description: A 40-year-old male with no medical history presents after being found unresponsive. Per a friend, for past few weeks, patient had been feeling ill with several Urgent Care visits for fever, prescribed multiple rounds of antibiotics with no improvement. On admission his speech was slurred, and he had bruising over his arms, dry mouth and lips, with blue extremities. Social history was noted for smoking 20 pack years, occasional marijuana use and micro-dosing mushrooms. Physical exam was significant for bilateral lower extremity reticulon and severe cyanosis of fingers and toes. Admissions lab had severe electrolyte abnormalities: Na 116 mmol/L, K 6.2 mmol/L, Cl 79 mmol/L, HCO3 16 mmol/L, BUN 105 mg/dl, and Cr 3.26 mg/dl, calcium 6.8 mg/dl, albumin 1.9 g/dl, PO4 10.0 mg/dl, CKP 653 U/L, uric acid 12.3 mg/dl, urinalysis with large blood, 1 RBC, 100 protein, trace LE, negative nitrites and 1 WBC, urine PtCr 0.41 g/dl, and negative urine culture. Urine drug screen was positive for cannabinoids only. Blood gas showed pH 7.17, pCO2 41.6 mmHg, pO2 33 mmHg and HCO3 16 mEq/L. US showed bilateral DVT was grossly unremarkable. Due to worsening electrolytes and creatinine, renal replacement therapy was started. Additional labs including C3, C4, ANA, anti-dsDNA, SM/RNP Ab and chromatin Ab were consistent with Lupus. Pulse dose steroids were initiated, and renal biopsy results revealed acute tubular injury with myoglobin casts and class II lupus nephritis. After pulse dose steroids and 2 weeks of intermittent hemodialysis, kidney function improved substantially. Due to severe Nephritis is known to occur in unconscious patients with severe AKI (1). Few case reports diagnose new-onset lupus with concomitant rhabdomyolysis without renal failure requiring dialysis. Additionally, the widespread skin involvement and digit amputation diagnosis made management and diagnosis for this case difficult and thought provoking.
Glomerular Diseases: Epidemiology and Case Reports

TH-PO665
Guillain-Barre Syndrome Presenting Alongside Lupus Nephritis: Case and Management
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Introduction: Systemic lupus erythematosus (SLE) can affect any organ system including the nervous system. However, peripheral nervous system involvement occurs in less than 10% of cases. We present here a case of Guillain-Barre syndrome (GBS) occurring in a patient with undiagnosed new onset lupus nephritis.

Case Description: The patient is a 21-year-old female with past medical history of well controlled skin-limited SLE treated with hydroxychloroquine who presented with two weeks of ascending bilateral muscle weakness and the inability to ambulate in the setting of a recent gastrointestinal infection. Due to high suspicion for Guillain-Barre syndrome (GBS), she was started on plasmapheresis (PLEX) and pulse dace steroids. Despite completing 5 sessions of PLEX, her condition worsened and required mechanical ventilation due to respiratory muscle involvement. She further developed locked-in-syndrome. She, then completed 5 days of IVIG without any improvement. On day 13, she was noted to have acute kidney injury (AKI) with nephrotic range proteinuria, along with rare dysmorphic RBCs on urine sediment. Serology was positive for an SLE flare with lupus nephritis, class V. Despite treatment with steroids, she quickly developed non-oliguric AKI, requiring hemodialysis. She was started on mycophenolate mofetil along with prednisone, resulting in recovery of kidney function within one month of initiating immunosuppression. However, she had much slower recovery in GBS symptoms, resolving 6 months after initial presentation.

Discussion: It is difficult to speculate which came first: GBS or lupus nephritis, since we know GBS can be initial presentation for lupus nephritis, however, GBS can trigger lupus nephritis as well through aberrant immune activation. However, when GBS coexists with lupus nephritis, its treatment is controversial, with standard treatment (PLEX +/- IVIG) being less effective. Currently no specific guidelines exist to treat GBS in such setting. The coexistence of atypical HUS with mutations in complement regulatory proteins and lupus nephritis is rare. Our patient had a successful outcome with regulatory proteins and lupus nephritis is rare. Our patient had a successful outcome with TH-PO666
Cardiac Failure in Fibrillary Glomerulonephritis Associated with Systemic Lupus Erythematosus
Carina S. Zapata Beltran,1 Elisa M. Guerrero Gonzalez,1 Giovanna Y. Arteaga Muller,2 Mara C. Olivo Gutierrez,2 Ricardo A. Garza Treviño,1 Daniela C. Elvir,1 Joary Vargas Santana,1 Virginia Soto,1 Hospit&al Universitario José Eleuterio González, UANL, Monterrey, Mexico; 1Instituto Nacional de Cardiología Ignacio Chavez, Mexico, Mexico.

Introduction: SLE involves the kidneys in a large percentage of cases, and less frequently, there is the presence of myocardial damage with a prevalence of 8-25%. Case Description: This is a 42-year-old male with a past medical history of pleural tuberculosis diagnosed three years ago, presenting with refractory exudative left pleural effusion, dyspnea, and pleuritic pain. He also has a three-year history of type 2 diabetes mellitus. His current symptoms as the same previously additional bilateral pleural effusion (transudative), intolerance to lying down, no peripheral edema, no retinopathy on fundoscopy. Laboratory findings included Hb of 11.7 g/dL, normo-normo anemia, eGFR by CKD-EPI of 28 mL/min/1.73m², proteinuria of 8.9 g/24hrs with an inverted albumin/ globulin ratio. Echocardiogram showed an ejection fraction of 23%. Only ANAs (1:640) and anti-U1-RNP (>200) antibodies were positive. C3 and C4 were normal. Renal biopsy showed negative staining with Congo red, indicating glomerulonephritis due to immune complexes with a membranoproliferative and nodular pattern. Immunofluorescence revealed a diffuse, global, and granular full house pattern, electron microscopy revealed fibrillary deposits measuring 10-20 nm.

Discussion: The presence of antibodies anti-U1-RNP and the occurrence of myocarditis are related to autoimmune activity against striated muscle. Myocarditis occurs in 5% to 10% of patients with SLE and most cases are asymptomatic and it can potentially result in heart failure. Atypical serology, unusual clinical presentation, and nodular biopsy make the diagnosis challenging, requiring electron microscopy for the diagnosis. The mesangium shows diffuse expansion of the matrix with predominantly global proliferation, which gives some glomeruli a hiperlobulated appearance with the presence of acellular nodules. There are subendothelial and mesangial deposits of fibrils measuring 10-20 nm.

TH-PO667
Lupus Nephritis Complicated by Atypical Hemolytic Uremic Syndrome and Heterozygous Deletion in CFHRI1-CFHR3 Successfully Treated with Ravulizumab
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Introduction: Atypical hemolytic uremic syndrome (aHUS) involves unchecked activation of the alternative pathway leading to deleterious action of complement on the endothelium. Failure to control complement activation is often due to inherited or acquired deficiencies of complement regulatory proteins, including Factor I, Factor H, Membrane Cofactor Protein, and CD46.

Case Description: 21 year old female with history of SLE presented with acute kidney injury (AKI) with an active urine sediment. Kidney biopsy showed diffuse lupus nephritis class IV and thrombotic microangiopathy (TMA). She was started on mycophenolate (MMF) 1g bid which she received for 2 wk, but was off for 4 wk, as she was not able to fill her medications, leading to admission for worsening AKI. Laboratory: hemoglobin 6.1g/dl, platelet 185,000/ul, serum creatinine 7.25 mg/dl, UPCR 3.5 g/l, low C3 (57mg/ dl), LDH 472 IU/l, haptoglobin 36 mg/dl, 2-3 schistocytes noted on blood smear. She was Induced with soludemol and Mytologic 720 mg BID. Five sessions of plasmapheresis (PLEX) were done due to TMA biopsy findings. She developed microangiopathic hemolytic anemia (MAHA), severe thrombocytopenia, tonic-clonic seizures, and required hemodialysis. ADAMTS 13 level was normal and anti-phospholipid studies were negative. Given the high suspicion of atypical HUS, ravulizumab was added to her regimen. Hemoglobin and platelet count normalized after 2 weeks. She remained dialysis dependent for 6 weeks. Renal function improved and serum creatinine has remained stable at 3.6 mg/dl off dialysis. Genetic testing revealed compound heterozygosity for exon 2-6 deletion in CFHRI and exon 1-6 deletion on CFHR3.

Discussion: The coexistence of atypical HUS with mutations in complement regulatory proteins and lupus nephritis is rare. Our patient had a successful outcome with addition of ravulizumab. Initial treatment with plasma exchange and conventional therapy with MMF and glucocorticoids did not improve MAHA, thrombocytopenia, or kidney function.

TH-PO668
A Do-Not-Miss Diagnosis: Thrombotic Thrombocytopenic Purpura in Systemic Lupus Erythematosus
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Introduction: Thrombotic thrombocytopenic purpura (TTP) is a rare complication of systemic lupus erythematosus (SLE) associated with high mortality. We report the case of a patient with SLE complicated by the development of fatal TTP.

Case Description: A 42-year-old male with history of SLE presented to an outside hospital endorsing three days of hematuria, hematemesis, dysarthria, malaise, and cutaneous changes for one week. His objective data there was pertinent for platelets (PLT) of 2 k/ul, creatinine of 2.38 mg/dl (baseline 0.8), and CT evidence of peripheric stranding. On arrival to our hospital, he was tachycardic, tachypneic, afibrile, and normotensive. Examination revealed jaundice with diffuse ecchymoses, and a normal neurological status. Laboratory studies on arrival were pertinent for undetectably low PLT count, hemoglobin 8.4 g/dl, creatinine 2.55 mg/dl, total bilirubin 3.6 mg/dl (direct 1.0), haptoglobin 20 mg/dl (ref 30-200), schistocytes on blood smear, LDH 3,433 U/L, D-dimer 38.5 ug/mL, fibrinogen 603 mg/dL, PT of 15.2 s, PTT of 34 s, and a normal vitamin B12. The patient’s mental status rapidly worsened in the ensuing hours, and he developed hypoxic respiratory failure with a serum lactate of 12 mmol/L. He was referred to the intensive care unit to start empiric therapeutic plasma exchange (TPE). His ADAMTS13 activity level resulted at <5% (ref >61%) and notably the ADAMTS13 inhibitor activity was elevated. Prior to initiation of TPE, however, the patient was found unresponsive and in cardiac arrest. After forty minutes of advanced cardiovascular life support, it was determined that the patient would not recover.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
support effort, the patient was pronounced deceased just twelve hours after admission. Autopsy showed platelet-rich microthrombi in multiple organs, severe thrombocytopenia, and no deep vein thrombi most consistent with TTP. 

Discussion: Thrombotic microangiopathies (TMA) are rare clinical syndromes characterized by thrombocytopenia, microangiopathic hemolytic anemia, and microvascular thrombus formation leading to end-organ damage. TTP is a rare and often lethal complication of sLE (sTTP) and its diagnosis is challenging due to the significant overlap in signs and symptoms. As illustrated by this case, severe thrombocytopenia in a patient with sLE should raise concern for sTTP as any delay in its diagnosis can be fatal. Early diagnosis and prompt initiation of treatment including therapeutic plasma exchange is crucial.

**TH-PO669**

Effective Treatment of Renal Thrombotic Angiopathy due to Idiopathic Multicentric Castleman Disease with Rituximab

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Introduction: Idiopathic multicentric Castleman disease (iMCD) is a rare, benign lymphoproliferative disorder. Renal involvement in iMCD is uncommon but is usually associated with thrombotic microangiopathy, and effective therapies have not been rigorously studied. First-line therapy includes steroids and monoclonal antibodies targeting IL-6. We present a case of iMCD with renal involvement unresponsive to siltuximab but responsive to rituximab.

Case Description: A 36-year-old gentleman presented with shortness of breath, edema, lymphenadopathy, and fevers and was found to have a serum creatinine (sCr) of 2.5 mg/dL. Urine sediment showed muddy brown casts and he had subnephrotic range proteinuria. A renal biopsy showed acute microangiopathy with diffuse glomerular endotheliosis and minimal fibrosis. A subsequent inguinal lymph node biopsy showed reactive lymphoid hyperplasia with some changes suggestive of Castleman disease. He was initiated on steroids and sCr improved to 0.94 mg/dL. One year after the initial presentation, he was re-admitted with dyspnea and acute kidney injury (AKI). A repeat renal biopsy showed chronic angioptic changes accompanied by scattered endotheliosis and mild fibrosis, and he was placed on a prednisone taper with improvement in his renal function. Given his recurrent disease, he was started on siltuximab and received 3 doses. He failed to respond to this and was transitioned to rituximab with subsequent resolution of his AKI, proteinuria, and lymphenadopathy.

Discussion: Renal involvement in severe cases of iMCD is rare but is usually associated with microangiopathy and endothelial injury; however, little is known about the most effective treatment. Siltuximab is often the first-line therapy, but there is limited data for patients who do not respond. Second-line therapies include chemotherapy, immunomodulators, and immunosuppressants. Our case demonstrates improvement in renal function and resolution of proteinuria with rituximab.

**TH-PO670**

Atypical Hemolytic Uremic Syndrome with Normal Complement Studies in a Patient with Complement Factor I Deficiency

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Introduction: Atypical hemolytic uremic syndrome (AHUS) is a type of thrombotic microangiopathy (TMA) that presents with organ dysfunction, particularly involving the kidney. AHUS occurs due to dysfunction in the alternative complement pathway and occurs sporadically, secondary to malignancy, drugs, or autoimmune diseases, or can be inherited. We present a rare case of AHUS due to a genetic mutation in complement factor (CFI) and normal complement studies.

Case Description: A 27-year-old female with uncontrolled hypertension (HTN) was admitted for hypertensive emergency (blood pressure 211/119) and acute kidney injury (Cr 15.4 mg/dL, baseline 3 mg/dL). Further workup showed hemoglobin 8.2 g/dL (ref. 11.2-15.7 g/dL), platelets 78 K/uL (ref. 182-369 K/uL), low haptoglobin, and elevated LDH. Infectious and autoimmune processes were ruled out. Complement levels C3 and C4 were normal. While awaiting an AHUS complement panel, she required dialysis and subsequent kidney biopsy which showed TMA with 40% interstitial fibrosis and 60% acute tubular injury. Eculizumab therapy was initiated for suspicion of AHUS based on biopsies findings. A few days later, AHUS panel came back showing no abnormalities in the alternative complement pathway, except elevated CSb-9. After discharge, she was found to have a heterozygous mutation of the CFI gene which has been associated with atypical dominant AHUS. Eculizumab therapy was continued and the patient was monitored closely outpatient.

Discussion: In the setting of normal complement studies, one cannot rule out AHUS as the primary cause of TMA. If the index of suspicion is high, it is recommended to start empirical Eculizumab and send off genetic studies to rule out a genetic cause of the AHUS, which may prevent unnecessary cessation or delay in Eculizumab therapy, and hence improve outcomes.

**TH-PO671**

Unusual Presentation of ANCA-Associated Vasculitis with Full-House Pattern Immunostaining

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Introduction: Pauci-immune glomerulonephritis is the most common cause of rapidly progressive glomerulonephritis (RPGN) mainly secondary to antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV). Typically, renal involvement lacks the presence of immune deposits. Here we present a case of AAV-induced RPGN with a full-house pattern immunofluorescence (IF).

Case Description: A 35-year-old male with a history of uncorrected congenital heart disease presented to the hospital with lower extremity edema. Evaluation revealed AKI with creatinine 5.43 mg/dL, urine analysis with >100 RBCs /µL, +50 proteinuria, and anti-DNAds. PLASMIC score was five. Due to moderate suspicion of Thrombotic Thrombocytopenic Purpura (TTP), the patient was treated with Methylprednisolone 1g/d every 6 hours, followed by Prednisone 1mg/kg/day and Rituximab (500mg/wk - 4 weeks), in addition to plasmapheresis. On the 4th day of hospitalization, she developed refractory hypervolemia and worsening of renal function, requiring hemodialysis during this time. She passed away.

Discussion: Renal involvement by AAV typically has no or few immune deposits. Full-house immunofluorescence has been rarely reported in the setting of ANCA vasculitis and it is unusual. Although histopathology in our patient is suggestive of AAV, the presence of full house pattern on IF with positive serum ANA is concerning for possible overlap syndrome where lupus and ANCA vasculitis accompany. Despite the absence of anti-dsDNA and anti-sm, still, lupus cannot be ruled out. This case is one of a few reported cases having AAV with RPGN presentation and concomitant full-house pattern in kidney biopsy, possibly representing lupus/AAV overlap.
Thrombotic Microangiopathy Secondary to Acute Pancreatitis: A Rare Association
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Introduction: Thrombotic microangiopathy (TMA) due to acute pancreatitis is rare with only 35 cases reported since 1978. The diagnosis requires a high index of suspicion and if not managed timely, can lead to severe morbidity and mortality. Here we report a case of TMA due to acute pancreatitis that was promptly recognized and successfully treated with Eculizumab.

Case Description: A 58-year-old woman presented with one-day history of abdominal pain, nausea and vomiting after ingesting seafood. She was Jehovah’s witness. Labs on admission showed an elevated lipase, 1900 U/L (13-60 U/L). Serum creatinine was at baseline (1.7 mg/dl) and treatment for acute pancreatitis was initiated. Two days later, serum creatinine increased to 8 mg/dl. Labs also showed features of microangiopathic hemolytic anemia and thrombocytopenia (Hgb 4 g/dl, platelet 46 K/ul, haptoglobin < 10 mg/dl, lactate dehydrogenase 2424 U/L). Schistocytes (>100/bhp) were present on peripheral smear. ADAMS 13 activity was normal. C3 was low normal at 99 mg/dl (normal range 90-180 mg/dl) and C4 was normal. TMA was suspected and eculizumab was initiated on day 7. Two days after starting eculizumab, platelet count improved to 128 K/ul, hemoglobin to 7 g/dl, LDH was 800 U/L and haptoglobin normalized. She remained dialysis dependent on discharge but 4 weeks later renal function recovered and she came off dialysis. Serum creatinine 6 weeks later is 3.6mg/dl. She remains on eculizumab. Genetic testing did not show any pathogenic mutations.

Discussion: Pancreatitis can occur in 2% of cases due to TMA, but pancreatitis causing TMA is exceptionally rare. In cases where TMA causes acute pancreatitis, it precedes the onset of pancreatitis, whereas, when acute pancreatitis causes TMA, it manifests typically 2-3 days after the pancreatitis (as in our case). The etiology of TMA after pancreatitis is speculated to be due to inflammatory mediators causing vascular endothelial injury, transient complement activation and ADAMS 13 inhibition. Eculizumab has been shown to shorten renal and hematological recovery but only reported in 3 of 35 cases. Most patients can stop the drug after 3-6 months. Importantly, in our case, we treated with eculizumab since she was Jehovah’s witness and refused plasma exchange. AKI in acute pancreatitis can have a broad differential but early recognition of TMA-induced AKI can be lifesaving.

TH-PO674
A Rare Presentation of Genetic Complement-Mediated Thrombotic Microangiopathy
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Introduction: Complement genetics has recently gained prominence in understanding the pathogenesis of complement mediated thrombotic microangiopathy (CM-TMA) and the development of a specific therapy that is potentially lifesaving. We present a rare case of ischemic cortical infarcts concurrently with CM-TMA, successfully treated with eculizumab.

Case Description: A 46-year-old male with a history of hypertension and chronic type B aortic dissection presented to the hospital for evaluation of presyncope and paraparesis. Labs showed profound renal failure with serum creatinine (sCr) of 14 mg/dl (baseline 1.14 mg/dl about 4 years before his presentation). A urinalysis showed >3000 mg of protein, traces of blood and perinuclear basement membranes (BBM). The patient was started on hemodialysis for worsening uremia, and shortly he developed ischemic stroke symptoms. MRI of the brain showed acute multifocal ischemic infarcts. Additional testing showed anemia, thrombocytopenia, elevated lactate dehydrogenase, low haptoglobin, and schistocytes in the peripheral smear. ADAMS 13 was normal. Further workup and serologies for possible infectious or autoimmune diseases were negative. SPEP was normal. A kidney biopsy showed acute on chronic thrombotic microangiopathy. Although TTP associated with Avelumab is reported, HUS associated with Avelumab has not been reported so far. Possible mechanisms of kidney injury that have been proposed include: excessive inflammatory cytokine production, and enhancing complement-mediated inflammation. Prompt discontinuation of the offending agent along with initiation of complement inhibitory therapy is key to the successful management.

TH-PO675
ANCA Glomerulonephritis: Uncommon Presentation as Renal Masses
Suhaib A. Al-Sawaiheen, Brian Monk, Mohamed Hassanin, Bushra Syed, Neville R. Dossabhoy, Yoshitsugu Obi. The University of Mississippi Medical Center, Jackson, MS

Introduction: Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) can manifest with diverse systemic symptoms and commonly affects the kidneys, causing necrotizing glomerulonephritis (GN). Here, we report a rare case of AAV presenting as renal cortical masses.

Case Description: A 70-year-old male presented with fatigue, loss of appetite, and a 50-lb weight loss over six months. Initial laboratory workup was unremarkable including normal serum creatinine and urinalysis. CT scan showed non-specific bilateral pulmonary nodules and a ‘rind’ of abnormal soft tissue surrounding the abdominal aorta. Three months later, follow-up CT scan revealed worsening peri-soft tissue thickening (max 3 cm) and the development of bilateral renal cortical masses (largest measuring 2.5 cm). Further workup showed positive p-ANCA with elevated MPO levels (>8.0 U; ref. >0.4 U), CRP (72 mg/dl; ref. <0.5 mg/dl), and mildly elevated IgG4 (137 mg/dl; ref. 2.4-121 mg/dl). Two kidney biopsies were obtained. The standard core biopsy showed plasma cell-rich infiltrates without IgG4 positivity, while the fine needle aspiration (FNA) to a renal mass showed focal necrotizing and crescentic GN with granulomatous vasculitis. Induction therapy with high-dose steroids and rituximab was initiated. Steroid dosage was tapered over a year, and maintenance rituximab doses were adjusted based on CD19+CD20+ cell counts and MPO-ANCA tiers. The patient has remained in clinical remission, without hematuria, proteinuria, or elevated serum creatinine over 4 years.

Discussion: AAV can form inflammatory masses in various organs, including kidneys, pancreas, orbit, and peri-aortic soft tissue, akin to IgG4-related disease. In a recent case series, patients with ANCA-associated renal masses often had elevated serum IgG4 levels or increased tissue IgG4+ plasma cells. Few cases had normal urinanalysis and serum creatinine despite biopsy findings of crescentic GN, as in our case. Our case is particularly unique: (1) repeated CT scans confirmed rapid development and progression of renal cortical masses; (2) routine urinalysis and serum creatinine were normal, and IgG4 was detected in FNA of the renal mass but not in the core biopsy. In patients with suspected AAV and renal masses, kidney biopsy is essential to establish the diagnosis and rule out cancer and infection before starting immunosuppression.

TH-PO676
ANCA-Ag Associated Chronic Renal Failure Due To Avelumab-Induced Thrombotic Microangiopathy: A Case Report
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Background: Avelumab is a humanized anti-PD-L1 monoclonal antibody, is effective in treating advanced solid tumors. However, immune-related adverse events (irAEs) have been reported. We report the first case of Avelumab-induced thrombotic microangiopathy (TMA).

Case Description: A 58-year-old female, with a medical history of stage 3 ovarian cancer and hypertension was referred by her oncologist due to worsening kidney function. Avelumab was initiated. A rise in creatinine was noted two months after starting Avelumab. A renal biopsy showed acute on chronic thrombotic microangiopathy. Although there was no hemolysis or thrombocytopenia noted. Supplemental work up including ADAMS 13, APLA, and autoimmune workup were normal. In the setting of possible atypical HUS secondary to PD1 inhibitor exposure, eculizumab was initiated. In the most recent follow-up, kidney function has been steadily improving reaching a range between 1.7-2.0 mg/dl.

Discussion: Although TTP associated with Avelumab is reported, HUS associated with Avelumab has not been reported so far. Possible mechanisms of kidney injury that have been proposed include: excessive inflammatory cytokine production, and enhancing complement-mediated inflammation. Prompt discontinuation of the offending agent along with initiation of complement inhibitory therapy is key to the successful management.
PMH except a recently completed antibiotic course 3 weeks ago for a URI. She was afebrile, HR 116/min, BP 158/110mmHg, SpO2 97% on RA. Lab workup WBC 8.4, Hgb 7.0, platelets 207, Na 136, K 4.4, HCO3 17, BUN 76, Cr 9.4 mg/dl (no baseline), and albumin 2.6 g/dl. UA: microscopic hematuria, 3+ protein. UPCR 6.3 g/g. UDS negative. Autoimmune workup was all negative including PR3/MPO. Trans-abdominal US showed fetal demise for which she underwent emergent vaginal delivery. From a kidney standpoint, the patient required hemodialysis on admission for volume overload. Given her severe anuric AKI, she underwent a kidney biopsy that showed: Diffuse necrotizing and crescentic glomerulonephritis, pauci immune, 23/24 glomeruli with cellular crescents and fibrinoid necrosis. The patient was treated with pulse steroids, rituximab 1 gram x 2, and plasmapheresis every other day for total of 7 sessions. She became non-oliguric; however, remained dialysis-dependent at the time of transfer to a pediatric hospital.

Discussion: We present a challenging case of ANCA-negative vasculitis complicating pregnancy leading to fetal demise. Our patient was managed similarly to an ANCA-positive vasculitis. We wonder if adding aserum creatinine to the routine urinalysis as part of first-trimester screening would have led to earlier diagnosis and changed this unfortunate outcome.

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

TH-PO679
Avcapacan and ANCA
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Introduction: ANCA-negative vasculitis, although rare, is associated with increased morbidity and mortality. In this case report, we present a patient with ANCA-negative vasculitis and highlight the use of the novel agent Avcapacan.

Case Description: A seventy-four-year-old male with a medical history of hypertension, insulin-dependent diabetes, and coronary arterial disease presented to urgent care with symptoms of shortness of breath, cough, lower extremity swelling, and hypoxia. He was thought to have multifocal pneumonia and heart failure. Despite initial treatment, his edema worsened, and subsequent laboratory tests showed an increase in serum creatinine from 1.7 mg/dl to 3.75 mg/dl. Urinalysis revealed microscopic hematuria and proteinuria quantified at 8.89 g/day. Concerns arose regarding rapidly progressive glomerulonephritis, and a secondary serological workup yielded largely negative results, including ANCA. A kidney biopsy was performed, revealing pauci-immune crescentic glomerulonephritis of the focal necrotizing type with moderate activity and minimal chronicity. The patient underwent Rituximab induction therapy along with steroids for maintenance. However, due to worsening edema, hypertension, hyperglycemia, and weight gain, a decision was made to switch the patient to Avcapacan. At six months follow up, the patient’s serum creatinine reduced to 1.89 mg/dl, and proteinuria decreased to 0.81 g.


TH-PO680
ANCA Vasculitis in a Patient with Significant Silica Exposure
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Introduction: Exposure to free crystalline silica (silicon dioxide) is classically associated with an array of lung diseases. It has also been associated with ANCA vasculitis. Here we describe a case of ANCA vasculitis attributed to silicosis, a diagnosis that occurred through a multidisciplinary involvement.

Case Description: A 77-year-old male with a past medical history presents with a one-year cough and hemoptysis. For the past 20 years, he has worked as a granite cutter, installing counter tops; he smokes 2-3 cigarettes per day. He was found to have a creatinine of 2.5 mg/dl (0.8 mg/dl eight months ago). Labs were notable for nephrotic range proteinuria of 5 g/day creatinine and 3+ hemoglobinuria with 13 RBCs/HPF but normal complement and negative rheumatoid factor, HIV, and anti-HCV. He had positive MPO-ANCA, dsDNA, and ANA. CT chest without contrast showed numerous nodules. After discussion between nephrology, rheumatology, infectious disease, and pulmonology, he was admitted for expedited kidney biopsy and bronchoscopy. Kidney biopsy revealed glomerulonephritis with 30% active crescents and both IgG and C3 deposition, not entirely typical for lupus or ANCA vasculitis but concerning for drug-induced or infection-associated ANCA. Bronchoscopy showed hemosiderin laden-macrophages but BAL was consistent with diffuse alveolar hemorrhage and negative for tuberculosis through AFB stain and culture. Since his quantiferon was positive and he had immigrated from a TB-endemic region, concern for miliary tuberculosis was high, so he underwent VATS lung biopsy which was consistent with silicosis based on pathology of dysthene incarcierated nodular aggregates of dust-laden macrophages, fibrosis, and birefringent particles. A diagnosis of ANCA vasculitis associated with silicosis was made. He received...
rituximab but experienced a severe infusion reaction so treatment was changed to cyclophosphamide and steroids with improvement in his creatinine although without return to baseline. He is also receiving treatment for latent tuberculosis.

**Discussion:** Silica exposure has been described in the literature to cause a variety of autoimmune conditions including ANCA vasculitis and lupus although the mechanism is unclear. Our patient’s occupational exposure and biopsies support this diagnosis. This case highlights the importance of a thorough exposure history and multi-disciplinary engagement to arrive at a diagnosis.

**TH-PO681**

**Obinutuzumab in Combination with Avcopan in Rituximab-Resistant ANCA-Associated Vasculitis (AAV)**

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**Introduction:** Rituximab (RTX) is now considered the standard for induction (along with glucocorticoid) and maintenance therapy of patients with AAV. We report 2 patients with AAV who had active disease despite RTX therapy and were successfully treated with combination of Obinutuzumab (OZB) (a type II anti-CD20) and Avcopan (C5aR antagonist).

**Case Description:** Patient 1: 80 year-old female with a 10-year history of microscopic polyangiitis treated with mycophenolate MPA (60 mg/kg) and prednisone (PRED). She relapsed after being off immunosuppression for 2 years and was re-initiated on MPA therapy. Due to lack of response, she was switched to RTX induction 1g x 2 doses 2 weeks apart with PRED. At the time of RTX induction, serum creatinine (Scr) was 1.5 with MPO-ANCA titers > 8.0 U and hematuria (3-10 RBC/HPF). She was continued on RTX maintenance therapy every 6-months. However, despite RTX therapy (18 months) and CD20 B cell of zero, she had rising Scr 2.1 mg/dL with persistent hematuria and MPO titers > 8.0. Repeat biopsy showed active necrotizing glomerulonephritis (GN). Therefore, she received OZB 1g x 2 doses 2 weeks apart with Avcopan 30 mg twice daily. At last follow up (9 months after OZB), her Scr is stable at 2.0 mg/dL, hematuria completely resolved and MPO is down to 1.1 U. She has not experienced any adverse events. Patient 2: 47-year-old female was diagnosed with AAV after presenting with dyspnea on exertion, cough, nausea and fatigue for 3 months. CT chest showed bronchial opacification, airspace disease, and mild fibrosis. The patient had a history of hypertension and atrial fibrillation. BP 149/110, HR 100 beats/min, RR 18 respiration/min, T 97.7 Fahrenheit, O2 96% on room air. Blood work showed macrocytic anemia of 8.1k with MCV 97.3, platelets: 256k, sodium: 139 mg/dL, potassium: 5.1 mg/dL, bicarbonate: 16, serum creatinine: 2.8 mg/dL, albumin: 1.9, BNP: 092k. UA ~500 protein, moderate blood and RBCs 9, total protein creatinine ratio 3.88 g. Urine toxicology positive for cocaine and marijuana. C4 low 3, C3 low 68, ANA negative, RF negative, DiDiNA: ~1, P-ANCA 1-640, Myeloperoxidase ab elevated. Patient was admitted due to HF exacerbation and started on intravenous furosemide. Kidney biopsy showed Membranous, focal necrotizing crescentic and subendothelial and subepithelial deposits comprised of various combinations of IgM, IgG, IgA and C3. However, approximately 20%-10% of these patients may be ANCA negative, and here, we present two cases of IRGN, which were ANCA-negative, and demonstrated a pauci-immune crescentic pattern of injury.

**Case Description:** Table 1 describes the clinical characteristics, histologic features and outcomes for two patients who initially presented with acute kidney injury, were subsequently diagnosed with ANCA-negative pauci-immune crescentic GN on kidney biopsy and after further evaluation for secondary causes of pauci-immune GN, were found to have glomerulonephritis associated with bacterial aortic/mitral valve endocarditis.

**Discussion:** This case series depicts two patients who developed ANCA-negative pauci-immune GN in association with bacterial endocarditis. The largest case series of RTX patients with pauci-immune GN included 9 cases that were infected related. 54% of these patients had extra-renal involvement and 23% of them required dialysis at diagnosis. The diverse glomerular presentations in association with infections have significant clinical implications since the prompt recognition of an underlying systemic infection is crucial to avoid inadvertent immunosuppressive therapy. It is imperative for clinicians to screen for occult infections not only when an immune-complex GN is seen, but also when a pauci-immune process is identified on a kidney biopsy.

**TH-PO683**

**An Unusual Case of ANCA Vasculitis Coexisting with Membranous Nephropathy due to Cocaine Use**

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**Introduction:** Membranous nephropathy (MN) is one of the leading entities causing nephrotic syndrome. Cocaine is associated with leukocytoclastic vasculitis, rhabdomyolysis, and ANCA-associated vasculitis (AAV) with pauci-immune necrotizing glomerulonephritis. We are reporting a rare case of a patient with rapidly progressive focal necrotizing & crescentic and sclerosing glomerulonephritis coexisting with MN in the setting of cocaine use.

**Case Description:** 51 yo male with Heart Failure reduced EF 30%, ANCA-associated MPA with focal segmental paucimmune glomerulonephritis, Rheumatoid arthritis, polysubstance use (cocaine, alcohol), all presents with dyspnea and lower extremity edema. BP 149/110, HR 100 beats/min, RR 18 respirations/min, T 97.7 Fahrenheit, O2 96% on room air. Blood work showed macrocytic anemia of 8.1k with MCV 97.3, platelets: 256k, sodium: 139 mg/dL, potassium: 5.1 mg/dL, bicarbonate: 16, serum creatinine: 2.8 mg/dL, albumin: 1.9, BNP: 092k. UA ~500 protein, moderate blood and RBCs 9, total protein creatinine ratio 3.88 g. Urine toxicology positive for cocaine and marijuana. C4 low 3, C3 low 68, ANA negative, RF negative, DiDiNA: ~1, P-ANCA 1-640, Myeloperoxidase ab elevated. Patient was admitted due to HF exacerbation and started on intravenous furosemide. Kidney biopsy showed Membranous, focal necrotizing crescentic and subendothelial and subepithelial deposits comprised of various combinations of IgM, IgG, IgA and C3. However, approximately 20%-10% of these patients may be ANCA negative, and here, we present two cases of IRGN, which were ANCA-negative, and demonstrated a pauci-immune crescentic pattern of injury.

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**TH-PO684**

**Infection-Related ANCA-Negative Pauci-Immune Glomerulonephritis**

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**Introduction:** Infection-related glomerulonephritis (IRGN) is typically an immune-complex mediated disease characterized by a diffuse proliferative process with mesangial, subendothelial and subepithelial deposits comprised of various combinations of IgM, IgG, IgA and C3. However, several IRGN have also been reported, including those with a pauci-immune crescentic pattern of injury. The overwhelming majority of pauci-immune GN cases are associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA). However, approximately 2-10% of these patients may be ANCA negative, and here, we present two cases of IRGN, which were ANCA-negative, and demonstrated a pauci-immune crescentic pattern of injury.

**Case Description:** Table 1 describes the clinical characteristics, histologic features and outcomes for two patients who initially presented with acute kidney injury, were subsequently diagnosed with ANCA-negative pauci-immune crescentic GN on kidney biopsy and after further evaluation for secondary causes of pauci-immune GN, were found to have glomerulonephritis associated with bacterial aortic/mitral valve endocarditis.

**Discussion:** This case series depicts two patients who developed ANCA-negative pauci-immune GN in association with bacterial endocarditis. The largest case series of RTX patients with pauci-immune GN included 9 cases that were infected related. 54% of these patients had extra-renal involvement and 23% of them required dialysis at diagnosis. The diverse glomerular presentations in association with infections have significant clinical implications since the prompt recognition of an underlying systemic infection is crucial to avoid inadvertent immunosuppressive therapy. It is imperative for clinicians to screen for occult infections not only when an immune-complex GN is seen, but also when a pauci-immune process is identified on a kidney biopsy.

**TH-PO685**

**Late-Onset Hyaluradine-Associated Immune-Complex Glomerulonephritis with Overlap ANCA and Lupus Nephritis Features**

Liana Srisawitri, Indiana University School of Medicine, Indianapolis, IN.

**Introduction:** Hyaluronidase is one medication that has been long associated with drug-induced lupus and also anti-immune complex antibodies (ANCA) vasculitis. We present an unusual case of an 83-year-old patient with hyaluronidase-associated glomerulonephritis (GN) with overlap features of ANCA vasculitis and lupus nephritis.

**Case Description:** The patient presented with hemoptysis with blood clot and estimated half a cup of red blood. She has history of hypertension and atrial fibrillation. Patient has had dyspnea on exertion, cough, nausea, and fatigue for 3 months. CT chest showed bronchial opacification, airspace disease, and mild fibrosis. Patient had remote 20-pack-year history of smoking. Her medications include hyaluradine 50 mg 3 times a day for a more than 10 years. Hemoglobin (Hgb) was 6.4 g/dL (down from 9.3 g/dL, 1 month prior). SMA one month prior showed alanine transaminase (ALT) 3.2 g/dL, up from 1.4 one month prior. C3 and C4 were 0.67 six months prior. C3 and C4 were 0.7 mg/dL. Urinalysis showed 6-10 WBC and 50-100 red blood cells per high power field.

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RBC/hpf with dysmorphic RBCs and RBC casts. Urine protein/creatinine ratio was 0.62 g/g. ANA 1:640, anti-dsDNA antibody titer <40, γ-AMA 1:640, MPO-ANCA titer <7, PSSA (Ab) ≥ 8.9 IU, anti-GBM Ab 4.8 IU. Kidney biopsy showed mild mesangial hypercellularity on light microscopy and mild mesangial deposits on electron microscopy. Immunofluorescence showed 1+ IgA, IgM, C3 diffuse granular deposits. Patient was given pulse IV methylprednisolone for 3 days, followed by slow taper prednisone. Cr peaked at 3.3 mg/dl and improved to 2.1 mg/dl upon discharge.

Discussion: Patient’s presentation of pulmonary renal syndrome is common in ANCA vasculitis, supported by the high p-ANCA, MPO Ab, and PR-3 Ab. However, the classical finding of a vasculitis with purely pauci-immune necrotizing and crescentic GN were not found. Instead, glomeruli showed mild IgA predominat deposits. Low complement levels and elevated ANA and anti-hist Ab suggest hyalurane-induced GN.

Ten years of hyalurane use confers a high mortality risk, in contrast to a review of 12 cases of hyalurane-associated ANCA vasculitis showed median drug duration of 22 months. In a review of 7 cases of drug-induced lupus nephritis, the duration was >12 months for most patients. In summary, this case may be atypical hyalurane-induced GN with overlapping lupus and ANCA serology but with dominant IgA deposits.

TH-PO685

“Atypical” Atypical Anti-Glomerular Basement Disease

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Introduction: Anti-glomerular basement membrane (anti-GBM) disease frequently presents as rapidly progressive glomerulonephritis due to autoantibodies directed toward the basement membrane. The IV collagen IV alpha 3 NC 1 domain of type IV collagen presents in the glomerular and alveolar basement membrane. In atypical anti-GBM disease, serum antibodies are negative, but the biopsy shows linear IgG staining. Clinically, it presents with an indolent renal limited course and good prognosis.

Case Description: A 64-year-old woman with a history of HIV, hypertension, diabetes mellitus type 2, asthma, obesity, and fatty liver presented with elevated creatinine, hematuria, and proteinuria. She developed foamy and dark urine six months before referral. IV was stable with an undetectable viral load, CD 4 count 190 cells/mm3 on dolutegravir-ritravirine. Physical examination was unremarkable. Presentation labs were normal. Anti-GBM Ab was negative, negative ANCA, MPO, PR3, and anti-GBM. Kidney biopsy showed moderate necrotizing and crescentic glomerulonephritis involving 36% of the sampled glomeruli, as well as older fibrous crescents in 27% of the glomeruli. There was patchy interstitial nephritis and mild to moderate interstitial fibrosis and tubular atrophy. Direct immunofluorescence demonstrated linear staining of the GBMs for IgG (3+) and kappa (2+) and lambda (3+) light chains. There were no electron-dense deposits by electron microscopy. The patient was started on treatment with solumedrol and cyclophosphamide. After the development of diffuse alveolar hemmorhage, 6 sessions of plasmapheresis were performed. Cr peaked at 3.6 with improvement to 2.2 since. ESPr/CRPR were used as surrogates of disease activity, owing to the lack of ability to monitor antibody titers.

Discussion: Atypical GBM was thought to have an indolent disease course without renal crescent formation on light microscopy, but more recent literature has shown crescents in pathology and progression to ESKD. Diffuse alveolar hemorrhage has not been reported to our knowledge. Management of atypical anti-GBM is complicated, owing to the lack of anti-GBM Ab. This case highlights the importance of tailoring treatment and being aware of the evolving landscape of this entity and of the difficulties in treatment including decisions regarding plasmapheresis and methods to monitor disease activity.

TH-PO686

Pulmonary Renal Syndrome Caused by Seronegative Anti-Glomerular Basement Membrane (GBM) Disease

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Introduction: Anti-GBM disease is a common cause of crescentic RPGN with or without pulmonary hemorrhage. We present an unusual case of pulmonary renal syndrome caused by seronegative anti-glomerular basement membrane (GBM) disease without pulmonary involvement.

Case Description: A 50 YO F with history of asthma and suspected PE on apixaban presented with dyspnea and found to have hypoxia with bilateral lung opacities and AKI (Scr 1.7, baseline 0.6) Urinalysis showed hematuria and nephrotic-range proteinuria of 3.8 g/mg. Initial serologic workup for infectious and autoimmunity diologies was negative, particularly ANCA <1:20 and anti-GBM Ab 0.5 units (normal range: 0.0-0.9). A renal biopsy showed diffuse necrotizing crescentic GN involving 50% of glomeruli with linear IgG deposits along the GBM. Prompt treatment with high dose steroids, cyclophosphamide and plasmapheresis was initiated along with supportive care. Clinical course was complicated by severe hemoptysis leading to hypoxia and cardiac arrest that necessitated VV ECMO support and CRRT after ROSC. Bronchoscopy showed blood in the airway but no active hemorrhage and repeated anti-GBM Ab remained within reference range. Liooptena pneumo, 13 additional TPE sessions were done along with CYC and steroids. Later on, pulmonary function improved significantly allowing for ECMO decannulation. However, RRT-requiring AKI persisted without renal recovery.

Discussion: We present a rare case of pulmonary renal syndrome caused by seronegative anti-GBM disease occurring in only 2-3% of cases. The diagnosis relies on the detection of anti-GBM Ab along with biopsy-proven crescentic necrotizing GN and/or alveolitis but serum Ab can be negative in rare cases due to low test sensitivity, antibodies to atypical GBM epitopes, or non-IgG anti-GBM Ab. The absence of alveolar hemorrhage on initial presentation along with negative serology makes the diagnosis challenging, thus kidney biopsy becomes critical for early diagnosis and salvage treatment. Given the rarity of seronegative anti-GBM disease, there is no data on management and prognosis and the renal outcome of this case is undetermined.

Background: LN is a severe manifestation of SLE, impacting outcomes directly and indirectly through therapy. LN varies across populations. Registries are crucial for understanding LN and assessing therapies. This study evaluates LN in RENELUP to assess its status in the Colombian Caribbean.

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Underline represents presenting author.
Methods: A multicenter cohort of 579 LN patients enrolled from 2008 to 2023. REDUCE, a JAVA-based web app, recorded demographic data, severity, outcomes, treatments, and mortality. Patients were grouped into Proliferative (Class III-IV) and Non-Proliferative (Class I-II-V) LN using ISN/RPS criteria. Chi-square/Mann-Whitney U tests evaluated renal survival using Kaplan-Meier estimator.

Results: Most patients were female (87%). Mean age was 41.1±13.1 years. Proliferative LN class IV was the main profile (62%). Proliferative LN had higher serum creatinine, proteinuria, activity index compared to Non-Proliferative LN (p<0.005). Hematuria, chronicity, low C3/C4, and clinical response were similar between LN classes. Overall, LEDAI-2K was 15.4±2.5. MMF (64%) was used as main induction therapy. Renal survival comparable based on serum creatinine at first presentation (p>0.05).

Conclusions: Our study provides insights into LN in the Colombian Caribbean. Predominant proliferative LN Class IV with significant renal involvement was observed. Moderate disease activity and MMF as main induction therapy highlight clinical management in this population, emphasizing the importance of patient registries for monitoring disease and treatment outcomes.

TH-PO689
Vitamin D Levels on Lupus Nephritis: Profile of a Large Brazilian Academic Center

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Background: Lupus nephritis is present in most patients with lupus. It is believed that the imbalance between pro-inflammatory and anti-inflammatory factors is responsible for its manifestation. Vitamin D is known for its anti-inflammatory activity and plays a regulatory role in cytokine production. Therefore, we tested the association between the level of 25-OH-Vitamin D, histological class, activity index and degree of proteinuria in patients from a large Brazilian academic center.

Methods: Patients diagnosed with lupus nephritis between January 2012 and December 2018 were included. Variables evaluated were age, gender, creatinine, estimated glomerular filtration rate (eGFR) by CKD-EPI, proteinuria, histological class and serum level of 25-OH-Vitamin D at the time of kidney biopsies.

Results: 253 kidney biopsies were performed during this period, 86% in women. The mean age was 31 years (13-70), creatinine 1.3 mg/dl (0.32-8.04), eGFR of 57.9 mL/min (6.2-165.3), proteinuria of 2.7g (0.07-10.7) and level of 25-OH-Vitamin D 17 ng/mL (6.2-165.3), proteinuria of 2.7g (0.07-10.7) and level of 25-OH-Vitamin D 17 ng/mL (6.2-165.3). Spearman’s correlation between Vitamin D levels and proteinuria was -0.338 (p<0.001). The association between levels of vitamin D, histological class of lupus nephritis and activity index > 9 was significant (p= 0.007 and p 0.003, respectively), with p<0.001. The association between levels of Vitamin D, histological class of lupus nephritis and activity index > 9 was significant (p= 0.007 and p 0.003, respectively), with p<0.001. The association between levels of vitamin D, histological class of lupus nephritis and activity index > 9 was significant (p= 0.007 and p 0.003, respectively), with p<0.001. The association between levels of vitamin D, histological class of lupus nephritis and activity index > 9 was significant (p= 0.007 and p 0.003, respectively), with p<0.001.

Conclusions: Low levels of vitamin D were found in patients with more severe histological class, higher activity index and higher proteinuria, which may be involved as a risk factor for the inflammatory imbalance present in lupus and disease activity.

TH-PO690
Incidence of Primary Immunoglobulin A Nephropathy (IgAN) Among a Diverse Population in the United States

John J. Sim,1,2 Qiaoing Chen,1 John M. Chang,3 Nancy Cannizzaro,1 Dilip Mahija,1 Ancilla Fernandez,1 Sandipan Bhattacharjee,2 Cibele S. Pinto,3 Asher D. Schachter,4 Mohit Mathur,1 Kaiser Permanente Southern California, Irvine, CA; 1Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, CA; 1Otsuka America Pharmaceutical Inc, Rockville, MD; 3Visterra Inc, Waltham, MA.

Background: IgAN is a leading cause of primary glomerular disease and end stage kidney disease (ESKD) with a 10-year risk of chronic kidney disease (CKD) progression of up to 40%. Global incidence is estimated at 2-5 cases per 100,000 people. US data suggest lower rates but varies by race/ethnicity. We examined incidence of primary IgAN, leveraging a diverse, contemporary cohort from a single integrated health system in California.

Methods: A retrospective cohort was studied (1/1/2010-12/31/2021) of Kaiser Permanente members with biopsy proven IgAN, excluding secondary IgAN. Annual IgAN incidence rates were standardized by age, sex, and race/ethnicity according to the 2020 US Census using the American Community Survey (ACS). Primary IgAN rate was calculated for 2010-2021 and stratified by race/ethnicity. We estimated IgAN prevalence by using mean annual incidence x estimated disease duration.

Results: A total of 606 primary IgAN patients were identified with mean age (SD) of 46 years (15.0) with males (51.2%), Hispanic/Latinos (38.6%), Asian/Pacific Islanders (30.4%), Whites (25.6%), and Blacks (3.1%). The average annual incidence rate (per 100,000 person-years) of primary IgAN was 4.5, 1.7, 1.2, and 0.6 among Asian/Pacific Islanders, Hispanic/Latino, Whites, and Blacks, respectively. The mean annual IgAN incidence of 1.4 per 100,000 person-years equates to an adjusted IgAN prevalence estimate of 40 per 100,000 persons (incidence x estimated disease duration of 28.5 years for IgAN patients).

Conclusions: Our findings show a mean annual IgAN incidence of 1.4 per 100,000 person-years. Asian/Pacific Islander and Hispanic/Latino had the highest incidence rate of IgAN. Whether the clinical course and response to treatment for IgAN patients varies by race/ethnicity warrants further investigation.

Funding: Commercial Support - Otsuka Pharmaceuticals

TH-PO691
The Epidemiology of ANCA-Associated Vasculitides over Two Decades at a Large Tertiary Centre

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Background: ANCA-associated vasculitis (AAV) is a systemic condition affecting small blood vessels and commonly causes kidney disease. It has a reported incidence of around 20-25 per million per year. Here we aimed to describe its epidemiology at our renal centre over a 23-year period and to compare granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA).

Methods: We identified all patients with AAV between January 2000 and December 2022 through our biopsy database and electronic patient record (EPR). The cohort after exclusions totalled 278. We collected baseline demographic data, baseline laboratory values, treatment received and outcomes including progression to renal replacement therapy (RRT), relapse rates and mortality.

Funding: Commercial Support - Otsuka Pharmaceuticals
TH-PO693

Obinutuzumab with Tacrolimus as a Bridge for Membranous Nephropathy
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Introduction: Treatment of Membranous Nephropathy (MN) has been improving over the past several years. Obinutuzumab, a monoclonal antibody that targets CD20 on B-cells, is another potential therapeutic approach under investigation. Currently, Obinutuzumab is approved for the treatment of specific tumors such chronic lymphocytic leukemia.

Case Description: We describe a 64-year-old male with a history of benign essential hypertension, stage 3a chronic kidney disease presenting with worsening proteinuria. Eight years prior to presentation, he was diagnosed with MN, and at that time, he was anti-Phospholipase A2 Receptor (PLA2R) antibody negative with 4g of proteinuria. He was started on tacrolimus and got 1 year of treatment leading to remission. He relapsed months after stopping tacrolimus and his PLA2R antibody titers rose to 11 RU/mL with other low-grade proteinuria. He was continued on cyclosporine and continued for over 7 years and was discontinued a year before presentation. At the time of presentation, he had 3gm of proteinuria and was started on dapagliflozin and two infusions of rituximab with 1gm each two weeks apart with some initial allergic reaction but then completed the infusions without complications. A year later, he relapsed and PLA2R antibodies rose to 23.5 RU/mL and proteinuria of 11gm. He was given two infusions of Obinutuzumab with 1gm each two weeks apart given his anti-optimal prior response to rituximab and allergic reaction to the drug along with a tacrolimus bridge. His proteinuria improved to 2gm with serum creatinine of 1.2mg/dl. He was taken off tacrolimus few months post Obinutuzumab treatment. He continues SGLT2i and ARB therapy as well.

Discussion: Obinutuzumab is a more potent anti B cell agent that may be a promising therapy for MN. Using Obinutuzumab along with tacrolimus as a bridge to get the response of MN may serve as a potential long-term therapy for MN.

TH-PO694

EXT-1 Membranous Glomerulonephropathy
Elizabeth Pabon-Vazquez, Vatsalya Kosuru. Augusta University Medical College of Georgia, Augusta, GA.

Introduction: Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults. The most common etiology is autoimmune condition and identification of pertinent antigens could help in the management of the disease.

Case Description: This is the case of a 33yo male with past medical history of chronic inflammatory demyelinating polyneuropathy and recurrent pulmonary embolism on apixaban. Patient presented to emergency department complaining of worsening pleuritic chest pain and shortness of breath of one day of evolution. He was also tachycardic, tachypneic and had bilateral lower extremity edema. Laboratory evaluation was remarkable for >600protein and 0-3RBs on urine dipstick. Renal panel showed creatinine of 1.2mg/dl and albumin of 1.7g/dl. The patient was admitted for recurrent unprovoked pulmonary embolism despite being on anticoagulation therapy and nephrotic syndrome. Initial workup for nephrotic syndrome reported 24-hour urine protein of 20,570mg. Further work up was negative for diabetic disease, hepatitis panel, HIV panel, complements, PLA2R antibodies and lupus nephritis. However, serologic markers ANA, RNP/70kda and IgG RNP Ab were positive consistent with mixed connective tissue disease. During hospitalization, the patient developed an acute kidney injury with creatinine elevated to 2.65mg/dl, and renal biopsy was performed. Kidney biopsy showed acute tubular injury and exostosin-1 associated membranous glomerulopathy. The patient was treated with two doses of 1g rituximab, prednisone, and losartan. At subsequent clinic follow up, patient’s spot urine protein-creatinine ratio was improved to 3.4g. Renal function is stable with creatinine of 1.13mg/dl and albumin improved to 2.3g/dl.

Discussion: Exostosin 1 and 2 are novel proteins seen in secondary membranous nephropathy associated with autoimmune diseases, especially lupus nephritis. Our patient’s case is unique as his serology is positive for mixed connective tissue disease with no extra-renal manifestations and this is the first case reported of the association of MN with mixed connective tissue disease. Due to rarity of disease and lack of standard therapy we have opted for rituximab treatment based on literature review. After the initial course of rituximab treatment, our patient showed significant improvement in proteinuria to sub-nephrotic range. He is currently on medical management with losartan.

TH-PO695

Membranous Nephropathy in Kimura Disease: A Case Report and Literature Review
Motoki Muneta, Kenichi Koga, Kensei Yahata. Department of Nephrology, Osaka Red Cross Hospital, Osaka, Japan.

Introduction: Kimura disease (KD) is a chronic benign granulomatous disease characterized by the formation of indistinct masses in the subcutaneous soft tissues and lymph nodes of the head and neck region. Approximately 20% of patients with KD present with nephrotic syndrome, with 60-80%, reportedly having nephrotic syndrome. Membranous nephropathy (MN) is one of the major pathologies of renal diseases in KD; however, the underlying mechanism remains unknown.

Case Description: We herein present a 28-year-old male diagnosed with KD after biopsy of a left lower eyelid mass 11 years earlier. Two months before his presentation, proteinuria was noted for the first time. He visited our hospital with edema in the lower legs and scrotum. A blood test showed a serum creatinine level of 0.95 mg/dL and serum
albumin level of 0.9 g/dL. Urinalysis showed heavy proteinuria (7.22 g/gCr) without hematuria. Renal biopsy revealed spike formation by PAM staining and granular deposits of IgG and C3 in the glomerular basement membrane by direct immunofluorescence microscopy (IF). Electron microscopy showed subepithelial electron dense deposits (EDD). The serum anti-phospholipase A2 receptor (PLA2R) antibody was negative, while IF staining for PLA2R was positive in the glomerular basement membrane. The patient was diagnosed with PLA2R-associated MN.

**Discussion:** Target antigens in MN, such as PLA2R, were recently identified in both primary and secondary MN. Our literature review on MN in KD including 14 cases revealed that most cases showed subepithelial EDD without subendothelial EDD (Table). This result strongly suggests the involvement of autoantibodies on the surface of podocytes in its pathogenesis. In the present case, PLA2R staining was positive on the glomerular basement membrane. A literature review revealed that PLA2R staining was only performed in 8 of 12 cases investigated, and was positive in 2. Further studies on the antigens responsible are needed to elucidate the underlying pathogenesis.

**TH-PO696**

An Interesting case of Membranous Nephropathy in a Patient with Diffuse Alveolar Hemorrhage and Cocaine Use: A Case Report

Kalandabari Janga,1,2 Nanga S. Srihavu1,3 UPMC McKeesport, McKeesport, PA; 2UPMC East, Monroeville, PA.

**Introduction:** Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. 70-80% of the cases are primary. We present a case of primary membranous nephropathy in a patient with cocaine use disorder presenting with diffuse alveolar hemorrhage and acute renal injury.

**Case Description:** A 38-year-old woman with a medical history of HTN, asthma, and cocaine use presented with left-sided chest pain after a mechanical fall following a bicycle accident. She had a past medical history of asthma, severe angina, and poorly controlled hypertension. She denied any chest pain, shortness of breath, or hemoptysis. On examination, she was in severe respiratory distress. Her heart rate was 130 beats per minute, blood pressure was 120/69 mm Hg,氧饱和率为87%, respiratory rate was 30 breaths per minute, and oxygen saturation was 94% on 3 L/min of oxygen by face mask. Abdominal exam was significant for left upper quadrant tenderness. Initial work-up included a complete blood count (CBC), electrolytes, liver function tests, renal function tests, coagulation profile, and total protein. Chest X-ray showed diffuse alveolar hemorrhage, and a CT scan of the chest, abdomen, and pelvis revealed bilateral pleural effusions. Renal ultrasound showed a left kidney length of 12 cm and a right kidney length of 11 cm. A renal cortical thickness of 3 cm was noted on the left side. Renal function tests showed a serum creatinine of 1.7 mg/dL and an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m². Urinalysis showed 4+ blood and 4+ protein, with a urine protein/creatinine ratio of 4,000. Serum albumin was 3.0 g/dL. An emergency nephrology consult was obtained, and the patient was started on low molecular weight heparin (LMWH) and prednisone for management of DM.

**Discussion:** The patient was initially treated with high-dose corticosteroids and apheresis. However, her condition exacerbated, and she developed severe acute respiratory distress syndrome (ARDS). A renal biopsy was performed, and immunofluorescence microscopy revealed granular deposits of IgG and C3 in the glomerular basement membrane. The serum anti-phospholipase A2 receptor (PLA2R) antibody was negative, while IF staining for PLA2R was positive in the glomerular basement membrane. The patient was diagnosed with PLA2R-associated MN. Despite risk factors, the patient improved with treatment, and her renal function returned to baseline.

**TH-PO697**

THSD7A-Related Membranous Nephropathy (MN) in a Patient with Prostate Adenocarcinoma

Harpress Kaur,1 Amaneda Health System, Oakland, CA.

**Introduction:** Thrombopodin type-1 domain- containing 7A (THSD7A) is a transmembrane protein expressed on the podocytes that serves as an auto-antigen in patients with membranous nephropathy. We report a case of kidney biopsy proven THSD7A associated MN in a 69-year-old Vietnamese male with history of metastatic prostate adenocarcinoma and chronic Hepatitis B.

**Case Description:** A 69-year-old male admitted for weight loss was found to have chronic active hepatitis, proteinuria, diffuse mixed sclerotic and lymphic lesion, and enlarged prostate. He underwent EUS with FNA of retroperitoneal adenopathy which showed metastatic prostate cancer. Then two months later, patient presented with marked anasarca for two weeks. He was afebrile, normotensove and saturating well on RA. Labs notable for hyponatremia, 1.6, UA with proteinuria, 4+ by PAM staining and granular deposits of IgG and C3 in glomerular basement membrane. The patient was diagnosed with PLA2R-associated MN.

**Discussion:** Target antigens in MN, such as PLA2R, were recently identified in both primary and secondary MN. A literature review revealed that PLA2R staining suggested primary membranous nephropathy (Table). This result strongly suggests the involvement of autoantibodies on the surface of podocytes in its pathogenesis. In the present case, PLA2R staining was positive in the glomerular basement membrane. A literature review revealed that PLA2R staining was only performed in 8 of 12 cases investigated, and was positive in 2. Further studies on the antigens responsible are needed to elucidate the underlying pathogenesis.

**TH-PO698**

A Case of Coexisting Primary Membranous Nephropathy and Dermatomyositis

Kavita Mistry. Stewart H. Lecker. Beth Israel Deaconess Medical Center, Boston, MA.

**Introduction:** Dermatomyositis (DM) is an inflammatory disorder of the skin and skeletal muscle characterized by cutaneous eruptions and myositis. DM is associated with malignancy, interstitial lung disease, esophageal dysmotility and cardiac complications. Unlike other connective tissue diseases, DM does not classically feature renal involvement, although several small case series and retrospective analyses have described a small minority of patients with DM who develop renal pathologies, including ATN in the setting of rhabdomyolysis as well as various glomerular diseases.

**Case Description:** A 56-year-old African American woman presented with one week of leg swelling. Vital signs were remarkable for hypertension to systolic BP of 170s, and exam was remarkable for prominent facial edema and 3+ bilateral lower extremity edema, with skin hyperpigmentation on the face, neck, chest and upper arms. Physical exam at her baseline of 0.7 kg/dL. UA revealed 4+ blood and 4+ protein, quantified at 10.2 g/urine. Microscopy revealed lipid casts and <1 isomorphic RBC/hpf. Nephropathy and rheumatology were consulted and recommended workup as follows: C3 and C4 normal, SPECT negative, serum anti-PLA2R IgG negative, HIV and hepatitis B/C serologies negative, ANA positive 1:1280 nuclear fine speckled pattern. She had negative dsDNA, anti-Sm, centromere B, RNP, anti-SCL 70, anti-SS-A, anti-SS-B, anti-cardiolipin and anti-b2 glycoprotein antibodies. CK was sent on account of 4+ blood on UA with relative paucity of RBC on microscopy and was elevated at 1249 u/L. Myositis panel was sent which returned positive for anti-M2 alpha and beta antibodies, consistent with DM. A renal biopsy was performed and revealed membranous nephropathy (MN). Although serum anti-PLA2R IgG was negative, the biopsy stained positive for anti-PLA2R IgG, suggesting primary MN. Comprehensive malignancy evaluation was performed given the coexistence of both membranous nephropathy and dermatomyositis with cancers and was negative. The patient was started on rituximab for management of MN and prednisone for management of DM.

**Discussion:** To our knowledge, this is the third case report describing coexisting primary MN and DM in the absence of underlying malignancy. The biological basis for the coexistence of these two pathologies in a single patient remains to be elucidated, although it can be presumed to result from a breakdown of immune tolerance.

**TH-PO90**

Not So “Golden”: A Case of Mercury-Associated NELL-1-Positive Membranous Nephropathy

Nazli Atefi,1 Amanda M. Tuchler,1 Hassan Syed,2 Taylor Douglas,2 Cinthia Drachenberg,2 Joshua D. King.1,2 University of Maryland School of Medicine, Baltimore, MD; 1Maryland Poisson Center, Baltimore, MD.

**Introduction:** Mercury is a heavy metal that exists in various forms and can be encountered through multiple pathways of exposure. Inorganic mercury is associated with glomerular disease—particularly membranous nephropathy (MN)—as well as peripheral neuropathy. In recent years, inorganic mercury in skin lightening creams has been associated with neural epidermal growth factor-like 1 protein (NELL-1) positive MN; very few cases are reported from the United States. We report a case of skin lightening cream associated mercury toxicity and NELL-1 positive MN.

**Case Description:** A 41-year-old female with type 2 diabetes who emigrated from Afghanistan 2 years prior presented with 6 months of progressive leg edema, worsening proteinuria, and long-standing peripheral neuropathy. Four months before presentation, glomerular filtration rate (GFR) was 66 mL/min/1.73 m². Serum creatinine was 1.74 mg/dL. Subsequent 24-hour urine protein was measured at 37.1 grams. Serum creatinine was 0.6 mg/dL. On initial presentation, skin lightening cream use was queried;
Glomerular Diseases: Case Reports

TH-PO700

An Unusual Presentation of a Common Disease: Primary Membranous Glomerulopathy with Light-Chain Deposits: Case Report

Rodolfo A. Morenon,1,12 Guillermo Navarro Blackaller,1 Werner De León,4 David A. Armas,1,2 Centro Medico Militar, Guatemala, Guatemala; 3Universidad Mariano Galvez de Guatemala Facultad de Ciencias Medicas y de la Salud, Guatemala, Guatemala; 4Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Guadalajara, Mexico; 5SERPAT, Guatemala, Guatemala.

Introduction: Membranous glomerulopathy (MG) is a common cause of nephrotic syndrome (NS) caused by the formation of immune complexes along the subepithelial slope of the glomerular basement membrane (GBM) and considered as the main cause of idiopathic NS in adults. Deposits of light chain iso type are rarely seen.

Case Description: A 56-year-old Guatemalan male patient with a 3-month history of lower-limbs edema. No previous medical history. On first evaluation presented AKI with creatinine (1.04mg/dl) controls after 1-month but still with nephrotic range proteinuria.

Discussion: The pathophysiology of MG results from the formation of immune complexes, predominantly by polytypic deposits along the subepithelial slope of the GBM. Usually, these immune complexes are against PLA2R and HTSD7A but about 10% of patients with typical PMN are negative for both antibodies making it probable that more autoantibodies to podocyte antigens will be found such as light-chain deposits. Though, positive serum antiPLA2R suggest a primary etiology, the rarely seen deposition of single IgG subclass should prompt a clinical workup to exclude the presence of an underlying etiology.

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Table 1: Clinical characteristics of NELL1 membranous nephropathy

<table>
<thead>
<tr>
<th>Age range and duration</th>
<th>Creatinine (mg/dl)</th>
<th>Albumin (g/dl)</th>
<th>Serum-PLA2R (RU/ml)</th>
<th>Renal biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1 50-year-old Guatemalan male</td>
<td>0.9</td>
<td>5.6</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Case 2 60-year-old Guatemalan male</td>
<td>1.2</td>
<td>3.2</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Case 3 30-year-old Guatemalan male</td>
<td>1.0</td>
<td>2.7</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Case 4 71-year-old Guatemalan male</td>
<td>0.8</td>
<td>2.9</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

TH-PO702

I Am the Lucky Third: Spontaneous Resolution of High-Risk Membranous Nephropathy

Wadhah M. Bin Homam,1 Fatimah Ayub,1 Ahmed Elkalashy,1 Md R. Hasan,2 Joseph H. Holthoff.1 UAMS Internal Medicine/Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR; 2Arkansas College of Osteopathic Medicine, Fort Smith, AR.

Introduction: The 2021 KDIGO guidelines for the treatment of high-risk and very high-risk membranous nephropathy (MN) involve angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers, and intense immunosuppression with rituximab or combination of cyclophosphamide and steroids. Typically, these immunosuppression regimens are initiated immediately in high-risk and very high-risk MN. Here we present a case of very high-risk MN nephropathy who achieved spontaneous with only conservative management.

Case Description: A 28-year-old male with no significant past medical history presented with acute onset of left flank pain and lower limb swelling for 3 weeks. Pertinent lab workup showed proteinuria of 28g/day, serum albumin of 1.1g/dl, and normal serum creatinine. CT angiogram showed bilateral renal veins thrombosis extending to the inferior vena cava. The serological workup for glomerulonephritis came back positive for anti-PLA2R antibodies, hence diagnosing him with primary MN. Renal biopsy further confirmed MN and PLA2R stain was diffusely positive The patient underwent an interventional radiology-guided thrombectomy. Given the severity of his clinical picture and following a detailed discussion of the risks versus benefits of different protocols of immunosuppressants, a pulsed dose of methylprednisolone was administered followed by oral prednisone for modified Ponticelli regimen, but the patient later refused cyclophosphamide due to the risk of infertility and agreed with initiating of rituximab. However, the prior authorization for rituximab was unsuccessful, and the patient was discharged on a tapered course of prednisone, lisinopril, and apixaban. At six-month follow-up, proteinuria was reduced to 1.6 g/dl and renal function remained stable.

Discussion: Here we present a case of very high-risk MN in which the patient achieved spontaneous remission and remained in partial remission at the 6-month follow-up visit. Cases such as this highlight the fact that risk stratification in MN is based on criteria at the time of initial diagnosis, when in fact the disease may follow a dynamic and changing course over time. Just as low and moderate risk MN in which the primary biopsy was positive for NELL1 associated MN. Infectious work up including hepatitis panel, human immunodeficiency virus (HIV) and rapid plasma regain (RPR) were negative. Screening for underlying malignancy including computed tomography (CT) of chest, abdomen and pelvis, pap smear, mammogram and colonoscopy was unremarkable. Careful review of home medications list showed no indigenous medications except for one who was on lipase for a duration of 1 year which was stopped after the diagnosis of NELL1 MN. Supportive care such as renin-angiotensin blockade (RAAS) and diuretics were initiated with periodic monitoring of renal functions and proteinuria (Table 1). All 4 patients went into remission within 3 – 6 months.

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TH-PO701

“Finding the Bright Side”: A Case Series of Spontaneous Remission in NELL1 Membranous Nephropathy

Jon D. Buela,1 Lakshma Sankar, Kartik Kalra, Geisinger Health, Danville, PA.

Introduction: Neural tissue encoding protein with EGF-like repeats (NELL1) has been identified as a target antigen in membranous nephropathy (MN). It can be primary or associated with malignancies, stem cell transplant, de novo in kidney transplant, drugs, autoimmune diseases and infections.

Case Description: Four patients of Caucasian origin with age ranging from 50 - 71 years presented with nephrotic syndrome (Table 1). At presentation, all had urine protein creatinine ratios above 5 g/g creatinine. Immunological work up was negative. Kidney biopsy was positive for NELL1 associated MN. Infectious work up including hepatitis panel, human immunodeficiency virus (HIV) and rapid plasma regain (RPR) were negative. Screening for underlying malignancy including computed tomography (CT) of chest, abdomen and pelvis, pap smear, mammogram and colonoscopy was unremarkable.

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TH-PO703
An Unlikely Culprit: A Case of Membranous Nephropathy with Celiac Disease

Sneha M. Vaddadi, Katherine D. Wick, Kuang-Yu Jen, Niti Madan. UC Davis Health, Sacramento, CA.

Introduction: Membranous nephropathy is a cause of nephrotic syndrome, categorized as primary (e.g. anti-PLA2R-associated) or secondary (due to autoimmune conditions, malignancy). There are a few case reports demonstrating an association between membranous nephropathy and celiac disease, an autoimmune disorder affecting the small intestine with the ingestion of gluten, however, this association has not been well established. We present a case of secondary membranous nephropathy with celiac disease and subsequent complete remission with the treatment of the underlying disease.

Case Description: A 46-year-old female initially presented for evaluation of the nephrotic syndrome with a urine protein to creatinine ratio 8.6 g/g and serum albumin of 1.8 g/dL. Workup for viral, autoimmune and malignant etiology significant only for evidence of prior Hepatitis B infection and positive surface antibodies. A kidney biopsy demonstrated evidence of early-stage membranous nephropathy without secondary features. Tissue PLA2R staining and Anti-PLA2 antibody testing were negative. The patient was diagnosed with primary membranous nephropathy due to negative secondary workup. Cyclosporine and low-dose prednisone treatment for 1 year resulted in partial remission. The patient then got diagnosed with Celiac Disease. She transitioned to a gluten-free diet with continued conservative management with an angiotensin-converting enzyme (ACE) inhibitor resulting in complete remission of her disease.

Discussion: Celiac disease has been associated with IgA nephropathy; its presentation with IgG membranous nephropathy is not well-established. With an otherwise negative workup and despite biopsy results without secondary features, the etiology of the glomerular disease in this case was likely celiac disease given the complete remission only after dietary modification. This case demonstrates a potential novel association between the autoimmune condition celiac disease and secondary membranous nephropathy.

Figure 1: A. Immunofluorescence demonstrating IgG deposition along capillary loops. B. Subepithelial immune deposits on electron microscopy.

TH-PO704
Unveiling a Novel Link: A Case of Secondary FSGS with Anti-MDA5 Amyopathic Dermatomyositis

Sneha M. Vaddadi, Shubha Ananthakrishnan, Niti Madan, Kuang-Yu Jen, Nasim Wiegley. UC Davis Health, Sacramento, CA.

Introduction: Amyopathic dermatomyositis is a cutaneous predominant form of dermatomyositis, characterized by the biomarker anti-MDA5 antibody. Extra-dermatologic involvement has been shown within the pulmonary, vascular, or articular systems. No known reports demonstrate an association between this rarer form of dermatomyositis and glomerular disease. We report a case of anti-MDA5 dermatomyositis associated focal and segmental glomerulosclerosis (FSGS), treated with immunosuppressive therapy targeting the underlying autoimmune condition.

Case Description: A 56-year-old Black man with confirmed anti-MDA5 positive amyopathic dermatomyositis diagnosed via skin biopsy and otherwise negative myositis panel presented for nephrotic syndrome and acute kidney injury evaluation. Labs showed serum creatinine of 2.04 mg/dL (baseline 0.8), urine protein to creatinine ratio >7 g/g, serum albumin of 2.6 g/dL, and urinalysis without cellular sediment. A native kidney biopsy was performed, showing features of FSGS on light microscopy (LM), negative immunofluorescence (IF), with segmental foot process effacement and the presence of tubuloreticular inclusions on electron microscopy (EM). Malignancy workup was negative. The patient was treated with high-dose prednisone and mycophenolate mofetil (MMF) for targeted treatment of both dermatomyositis and FSGS, with subsequent improvement to partial remission in the first 6 months.

Discussion: To our knowledge, this is the first reported case of kidney involvement with amyopathic dermatomyositis. With an otherwise negative workup for other viral or malignant causes, the likely etiology of secondary FSGS was this autoimmune condition. MMF, a common treatment for dermatomyositis, was utilized in this case for targeted treatment of both dermatomyositis and FSGS and resulted in improved proteinuria and partial remission of nephrotic syndrome.

Figure 1: A. Periodic Acid Schiff stain showing segmental glomerulosclerosis. B. Tubuloreticular inclusion on Electron Microscopy.

TH-PO705
Compressed and Concomitant Cyclophosphamide with Prednisone for Membranous Nephropathy: Low Doses for Very-High-Risk Patients

Benjamin Silverberg, Corey J. Cavanaugh. University of Virginia, Charlottesville, VA.

Introduction: Immunosuppressive therapy for primary membranous nephropathy (MN) has undergone significant change in the last 5 years. The “modified Ponticelli” regimen for MN is the recommended therapy for very high-risk MN according to KDIGO guidelines. The regimen consists of alternating cycles of cyclophosphamide and corticosteroids for a total of 6 months and comes with dose-dependent side effects such as cytopenias, infections, and malignancy. Here, we describe our experience with compressed and concomitant CYC/GC in very-high-risk patients.

Case Description: We retrospectively analyzed 4 cases of PL2R-positive membranous nephropathy with very high-risk features treated with concomitant prednisone 0.5mg/ kg tapered with oral cyclophosphamide 1.5-2mg/kg daily over 3-4 months. All patients were male between the ages 36-62. Clinical data, including serum PLA2R-AB levels and UPCR, were collected over the treatment period and 6 months after completion (Images 1 and 2). All patients had complete or partial remission at 9-12 months follow-up. No cytopenias or infections were observed. One patient developed steroid-related diabetes.

Discussion: Compared to the 24-week modified Ponticelli regimen, our doses of GC were lower, with a shorter duration of therapy and without any loss in efficacy (Table). A compressed and concomitant CYC/GC regimen in very high-risk patients with PL2R membranous nephropathy is safe and effective in this limited case series.

<table>
<thead>
<tr>
<th>Average total CYC dose</th>
<th>Modified Ponticelli (for a 50kg patient)</th>
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<tbody>
<tr>
<td>11.25g</td>
<td>10.6-13.7g</td>
</tr>
<tr>
<td>Average total GC dose</td>
<td>60mg</td>
</tr>
<tr>
<td>11g</td>
<td></td>
</tr>
<tr>
<td>Total duration of therapy</td>
<td>13.75 weeks</td>
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TH-PO706

FAT1 as an Antigen in Antibody-Mediated Rejection-Associated Membranous Nephropathy
Latha Ali-Rehadi,1 Tiffany Caza,2 Christopher P. Larsen,2 Laurence H. Beck.3
1University of Utah Health, Salt Lake City, UT; 2Arkana Laboratories, Little Rock, AR; 3Boston Medical Center, Boston, MA.

Introduction: Membranous nephropathy can be a manifestation of antibody mediated rejection (ABMR). While recurrent membranous nephropathy has been mostly attributed to PLA2R, the targeted antigen in ABMR-associated membranous remains unknown. FAT1 has been recently found to be an antigen in post hematopoietic stem cell transplant but not in de novo membranous nephropathy related to ABMR.

Case Description: Patient has evidence of ABMR evidenced by presence of peritubular capillaritis, glomerulitis, and positive donor specific antibody (HDL A2Q) 11,000). In addition to microcirculation inflammation, membranous nephropathy was identified on kidney biopsy. Serum from the patient with De novo membranous MN recognizes HGE at a high molecular weight band (higher than THSD7A and PLA2R). We sought to investigate whether FAT1 can be the targeted antigen given the high molecular weight on western blotting. Immunostaining revealed a granular pattern of FAT1 along the capillary wall.

Discussion: FAT1 can be the antigen implicated in membranous nephropathy related to ABMR. We are currently screening a larger cohort to validate our findings.

TH-PO707

Disseminated Nocardiosis in an Immunosuppressed Patient with Membranous Nephropathy
Samia Ait Faqih, Krishnamoorthy Sundara Raman, Aalaedin Shurrab. Hamad Medical Corporation, Doha, Qatar.

Introduction: Nocardiosis is a rare life-threatening opportunistic infection which has been reported in association with immunosuppressed patients. The diagnosis is challenging because of the insidious onset of symptoms with a subacute course that progresses over several weeks. Misdiagnosis and late treatment can lead to fatal consequences. We report a new case of disseminated nocardiosis (lungs, brain, eyes and joints) in a patient diagnosed with membranous nephropathy. We also review the literature and analyze the clinical characteristics and modalities of treatment of nocardiosis.

Case Description: A 49-year-old Eritrean man diagnosed with nephritic syndrome secondary to primary membranous nephropathy with high risk progression factors. He was started on immunosuppression along with general supportive measures. He presented to the Accidents & Emergency department with fever, fatigue, productive cough, red eyes and right knee swelling since the preceding week. He had evidence of pneumonia, bilateral uveitis and right septic arthritis. He had arthroscopic drainage and washout of the knee. Cultures of sputum, blood and joint came back positive growing Nocardia otitiscavarium. CT brain imaging revealed left occipital ring enhancing lesions with surrounding edema without mass effect suggesting brain abscess. Patient was started on Trimethoprim/Sulfamethoxazole based on sensitivity testing and this was continued for 12 months. Immunosuppression was also stopped once the diagnosis was made and he had shown signs of remission around the same time. Patient responded very well to antibiotics and fully recovered.

Discussion: Immunosuppression is the most important predisposing factor for systemic nocardiosis. Poor outcome is mostly found in immunocompromised patients which can be improved by early detection and administration of the correct antibiotic regimen. More studies on nocardiosis are required to better identify risk factors associated with morbidity/mortality and to develop effective methods of prevention of the disease.

TH-PO708

Primary Sjögren Syndrome (pSS) with PLA2R-Associated Membranous Nephropathy (MN)
Mingyue He.1 Iris J. Lee.2 Temple University Hospital, Philadelphia, PA; 2Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

Introduction: pSS is an autoimmune disorder characterized by lymphocytic infiltration of exocrine glands. Renal involvement occurs in 5% of pSS cases. The prevalent renal pathology associated with pSS is tubulo-interstitial nephritis, with less frequent glomerular manifestations, mainly membranoproliferative glomerulonephritis. pSS is also a recognized cause of secondary MN. Herein, we present a rare case of co-occurrence of pSS and primary MN with negative serum PLA2R antibody (Ab) but positive tissue PLA2R Ab.

Case Description: A 27-year-old female with a history of pSS on plaquenil was referred to a Nephrology clinic for subnephritic proteinuria of 1.5 gm. Urinalysis revealed no microscopic hematuria. Her creatinine was 0.54 mg/dL with no evidence of renal tubular acidosis or nephrolithiasis. Immunological markers including ANA, dsDNA, and serum PLA2R Ab were negative. Complements were normal. HIV, HBV, and HCV tests were negative. Kidney biopsy showed MN with positive immunofluorescence for IgG, C3, and PLA2R. One year later, her proteinuria decreased to 0.47 gm with preserved renal function without treatment. Her serum PLA2R Ab remained negative.

Discussion: This case poses a diagnostic challenge as to whether the observed MN is primary or secondary to pSS. Serum PLA2R Ab is associated with MN development and has high sensitivity (78%) and specificity (99%) for primary MN. Although PLA2R Ab detection has been reported in secondary MN cases such as sarcoidosis (55%), it is largely absent in rheumatic disease-associated MN, especially lupus MN (<5%). The absence of serum PLA2R Ab in this case aligns with the “kidney as sink” hypothesis, proposing that early-stage disease may show negative serum levels due to high Ab affinity for tissue antigens. Despite having persistent negative serum PLA2R Ab levels, our patient demonstrated positive tissue PLA2R Ab staining. Moreover, PLA2R Ab levels are also indicative of disease progression. In our case, the patient, with persistently negative serum PLA2R Ab, exhibited a significant spontaneous reduction in proteinuria. Her remission occurred in the absence of any pSS therapy, suggesting a coincidental occurrence of MN and pSS. Our case highlights that primary MN can coexist with other autoimmune diseases, emphasizing the need to distinguish primary from secondary MN due to potential differences in management strategies, where PLA2R Ab detection can be insightful.

TH-PO709

A Case of Rapidly Progressive Glomerulonephritis due to Superimposed IgA Nephropathy on Collagenoibrotic Glomerulopathy
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Introduction: Collagenoibrotic glomerulopathy (CFG) is a rare disease characterized by the accumulation of type III collagen in the glomerulus. CFG and IgA nephropathy (IgAN) may coexist coincidentally, but there have been no reports presenting rapidly progressive glomerulonephritis (RPGN). Here, we report the case that developed in RPGN and was diagnosed with active IgAN accompanied by CFG.

Case Description: A 69-year-old Japanese woman complained of new-onset fatigue and generalized edema lasting one month. She had a history of rheumatoid arthritis for about 20 years and had been administered etanercept, a TNFα inhibitor, for eight years. Her serum creatinine (SCR) level used to be around 1.5 mg/dL. On admission, she exhibited gross hematuria, an elevated Scr (5.8 mg/dL), a decreased serum albumin (2.63 g/dL), a weight gain (+10 kg), and was clinically diagnosed with RPGN and nephrotic syndrome. Histological examination revealed active IgAN with positive KM55(galactose deficient)IgA1 and superimposed CFG. She temporarily needed hemodialysis, but with steroid pulse therapy and cyclophosphamide, her Scr improved to 2.66 mg/dL, and hematuria was also resolved.

Discussion: This is the first report of RPGN caused by IgAN superimposed on CFG. In IgAN, IgA deposition in the capillary wall have been reported to have a poor renal prognosis. In this case, the presence of type III collagen in the mesangial region promoted IgA deposition in the capillary wall and induced RPGN. Furthermore, this is the first case in which etanercept induced IgA nephropathy with Gd-IgA1. The mechanism of action of TNFα inhibitor-induced IgAN may be the generation of anti-drug antibodies to the glycans structures of the TNFα inhibitors. This cross-reacts with Gd-IgA1 and forms a large antigen-antibody complex, and then may have caused IgAN. Despite the rare and complex diseases, we believe the appropriate interpretation of renal biopsy findings contributed to effective treatment and favorable renal outcomes.
TH-PO710
A Novel Case of IgA Nephropathy Relapse Secondary to Adalimumab
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Introduction: IgA nephropathy is the most diagnosed glomerulonephritis worldwide. Biologic agents including tumor necrosis factor alpha (TNFα) inhibitors have been identified as a potential cause for IgAN and on our patient, recurrence.

Case Description: The patient is a 35 year old male with biopsy proven IgA nephropathy diagnosed 4 years prior to current presentation. Initially, the patient was found to have microscopic hematuria and proteinuria on routine urinalysis. Kidney biopsy was performed at that time and demonstrated focal fibrocellular and fibrous crescentic disease. He was treated with glucocorticoid therapy and RAAS blockade, leading to full remission. He had underlying uveitis managed with Rituximab and Methotrexate, then Adalimumab. On the current presentation, the patient reported an isolated episode of hematuria 2 months prior. Creatinine increased to 1.6 mg/dL from 1.1 mg/dL 4 months prior. A urinalysis demonstrated > 500 mg of albuminuria and 57 RBC/hpf. Spot urine protein to creatinine ratio was 526 mg/g. A second kidney biopsy showed light microscopy demonstrated mesangial hypercellularity. Electron microscopy revealed patchy effacement of podocyte foot processes.

Discussion: We report a case of IgA nephropathy, which was initially treated with glucocorticoid therapy, leading to a sustained remission. Later, the patient was started on Adalimumab due to uveitis. IgAN relapsed after taking Adalimumab for 6 months. On diagnosis, the patient was started on Mycophenolate Mofetil as a steroid sparing strategy. The patient deferred repeat treatment with glucocorticoid therapy. The patient was treated supportively with RAAS blockade and SGLT2i, with good anti-proteinuric response. This is a novel case of recurrence of IgA nephropathy, as there is scant literature available that studies IgA Nephropathy related to Adalimumab. Furthermore, physicians must be aware of this potential side effect when prescribing Adalimumab, particularly in patients with underlying IgA nephropathy.

TH-PO711
IgA Nephropathy and IgA Vasculitis, Two Sides of the Same Coin: A Rare Case of Rapidly Progressive IgA Nephropathy with IgA Vasculitis of the Skin
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Introduction: IgA Nephropathy (IgAN) is the most common type of primary glomerular disease worldwide. About 25-30% of IgAN patients develop end-stage kidney disease within 20-25 years. IgA vasculitis (IgAV) is a small-vessel vasculitis that affects multiple organs including the skin and kidneys. Renal involvement occurs in 45 to 85% of adults with IgAV. Despite the similarities between IgAN and IgAV, most IgAN trials excluded those with vasculitis. Here we report a case of rapidly progressive glomerulonephritis (RPGN) secondary to IgAN in a patient presenting with IgAV involving the skin.

ThP-PO712
Minimal Change Nephrotic Syndrome in an Elderly Female with Acute Onset Type 1 Diabetes
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Introduction: Concurrent type 1 diabetes (T1D) and idiopathic nephrotic syndrome (NS) are rare, and most previously reported cases were in children. Recently, a younger adult who developed minimal change NS (MCN) several months after acute-onset of T1D was reported 1). Moreover, human leukocyte antigen (HLA) A24, Bw52, Bw61, DR2 and DR9 has been described to be associated with T1D and renal disease 2).

Case Description: An Asian 78-year-old female with anti-glucagon-like protein 2 decarboxylase (GAD) 65 antibody-positive acute onset T1D, anti-thyroidperoxidase Hashimoto thyroditis, and fatty liver disease, diagnosed them three years ago then treated with mci insulin and po leptoglobin 3), was admitted again to our section due to bilateral leg edema as well as remarkable body weight gain. Her serum albumin was decreased to 1.8 mg/dL. Laboratory data show Hb 12.2 g/dL, TP 4.7 g/dL, Cr 1.11 mg/dL, eGFR 36.8 ml/min/1.73m², Na 132 mEq/L, K 5.7 mEq/L, TcH 353 mg/dL, LDL-c 165 mg/dL, T4 9.09 ng/dL, TSH 13.81 mU/L, Hba1c 6 %, normo-complement proteins, D-dimer 9.23 ng/mL, UACR < 30 mg/gCr; UP 7.9 g/L with selectivity index 0.18, β2-microglobulin 27.1 mg/L. Serum antibodies were positive in GAD 604 U/mL, TPO 168 IU/mL, Tg 123 IU/mL, whereas was negative in MPO/P3A- ANCA, GOM, nor staff as paraproteinemia. No deep vein thrombosis nor malignancy was shown in non-enhanced computed tomography imaging. Kidney biopsy detected minor glomerular abnormalities with 1/10 obsolescence glomeruli; No Kimmelstiel-Wilson nodule was shown. Diagnosis of MCN was made with incidence described above. Her HLA typing was A24, A26, B62, B54, and DR9. Given methylprednisolone (mPSL) 500 mg/day intravenously (IV) for 7 days, then PSL 40 mg/day orally, CR was achieved but renal function was 1/10 obsolescence kidneys; No acute interstitial inflammation, diabetic nephropathy, and hypertensive kidney injury. Based on the patient's clinical manifestations, history of thymoma, and auto-immune antibodies were negative. Chest CT showed a mass in the anterior mediastinum. The patient underwent a right posterior hepatic lobectomy in 2020. The pathology revealed a thymoma type B2. Other past history includes hypertension and diabetes. Based on the patient's clinical manifestations, history of thymoma, and acute interstitial inflammation, diabetic nephropathy, and hypertensive kidney injury. Methylprednisolone was administered 240mg/d *3d, followed by prednisone 30mg/d and rituximab 375mg/m²/week * 4 weeks. Remission was achieved one month after completion of the RTX course. Interestingly, the thymoma shrank only on the CT scan.

Discussion: We report a case of minimal change nephrotic syndrome associated with T1D, and recent literature suggests that there is a high association between T1D and renal disease.

TH-PO713
Rituximab in the Treatment of Thymoma-Related Minimal Change Disease
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Introduction: Thymoma may cause autoimmune-related kidney disease. This article presents two cases of thymoma-related kidney disease treated with oral prednisone in combination with rituximab. Remission of proteinuria were achieved, and shrinkage of the thymoma mass was observed on the CT scan.

Case Description: Case 1: A 67y male was admitted because of foamy urine and edema. Lab tests revealed hypothyminemia and proteinuria. Scr increased progressively, while auto-immune antibodies were negative. Chest CT showed a mass in the posterior mediastinum. The patient underwent a right posterior hepatic lobectomy in 2020. The pathology revealed a thymoma type B2. Other past history includes hypertension and diabetes. Based on the patient’s clinical manifestations, history of thymoma, and acute interstitial inflammation, diabetic nephropathy, and hypertensive kidney injury. Methylprednisolone was administered 240mg/d *3d, followed by prednisone 30mg/d and rituximab 375mg/m²/week * 4 weeks. Remission was achieved one month after completion of the RTX course. Interestingly, the thymoma shrank only on the CT scan.

Case 2: A 67y male was admitted because of foamy urine and edema. Lab tests showed a 24h urine protein of 8.78g. Plasma albumin was 16.9g/L, eGFR was 53mL/min/1.73m².

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The patient claimed a history of thrombosis, and underwent thrombectomy in 2014. PET-CT showed a left pleural and carotid-symphatic angle lymph node, and anterior chest wall subcutaneous metastases. The patient claims a history of hypertension. The final diagnosis based on clinical manifestations and renal biopsy was thrombosis-related MCD, hypertensive kidney injury, and AIIN. Steroid therapy (methylprednisolone 120mg/d, d8-11, followed by prednisone 40mg/d) combined with RTX (375mg/m2/week 4wks) was administered. The patient’s proteinuria gradually decreased two months after RTX treatment, the urine protein was 0.67 g/24h at the latest follow-up. In addition, there was remission of the patient’s thrombocytemia.

Discussion: Experience in treating thrombosis-related nephropathy with RTX is limited, our cases report the effectiveness of RTX in both MCD and thrombosis. This report highlights the potential role of RTX in the treatment of thrombosis-related nephropathy.

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an abnormal protein that precipitated when the plasma, but not serum, was stored at 4°C and redissolved at 37°C (Figure 1b). Liquid chromatography-tandem mass spectrometry revealed fibrinogen-α, -β, and -γ chains, and fibronectin. Despite adequate hydration, the patient’s renal function did not improve, and prednisolone (1 mg/kg/day) therapy was initiated and continued for 3 months, whereby the serum creatinine decreased to 1.9 mg/dl. However, the renal function of the patient decreased gradually thereafter to eventual kidney failure that necessitated hemodialysis.

Discussion: Cryofibrinogenemia can induce several organ dysfunctions, manifesting as mostly dermatological symptoms, as well as kidney involvement. Distinctive ultrastuctural findings of large microtubular structures on electron microscopy, plasma cryoprecipitates when cold, and proteomic analysis are crucial for diagnosing cryofibrinogen-associated glomerulonephritis.

TH-PO718
Unraveling the Mystery: A Case of Cryoglobulinemia
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Introduction: Cryoglobulinemia is a systemic inflammatory syndrome that generally involves small- to medium-sized vessel vasculitis due to cryoglobulin-containing immune complexes. The classification distinguishes three subtypes of cryoglobulinemic diseases. But at the same time, there are rare instances where there could be misleading classification of the disease due to the presence of two different underlying disorders. Here we report a case of type 2 cryoglobulinemic membranoproliferative glomerulonephritis with a detectable monoclonal IgM kappa in serum.

Case Description: A 70-year-old gentleman with a past medical history of chronic myelogenous leukemia presented with epigastric abdominal pain and melena. He was diagnosed with liver cirrhosis and spontaneous bacterial peritonitis. Additional workup revealed active hepatitis C infections, acute kidney injury with hematuria, sub-nephrotic proteinuria, active sediment on urine microscopy, elevated RF, serum immunofixation showing monoclonal gammapathy, IgM kappa type and urine immunofixation with lambda light chain band. A kidney Biopsy was performed that showed cryoglobulinemic glomerulonephritis. Due to monoclonal gammapathy, hematology performed a bone marrow biopsy, which returned 2-3% plasma cells. The diagnosis was felt to be more consistent with mixed/Type 2 Cryoglobulinemia secondary to HCV infection. The monoclonal gammapathy and the presence of Kappa-restricted B cells were felt to be an association rather than the cause of cryoglobulinemia. Therefore, he was not treated further with plasma cell-directed therapy. He received treatment with Rituximab, plasmapheresis, and steroids.

Discussion: This case highlights the importance of differentiating between different types of cryoglobulinemia that determines appropriate therapy. Detectable monoclonal gammapathy can be found in serum of patients with type II cryoglobulinemia. Although lymphoproliferative disorders are more closely related to type I cryoglobulinemia, it is essential to exclude monoclonal gammapathy in patients with mixed cryoglobulinemic glomerulonephritis to reveal hidden lymphoproliferative disease before the diagnosis of essential cryoglobulinemia can be made. This has implications for the management of such patients.

TH-PO719
Interstitial Inflammation and C3 Glomerulopathy Secondary to an Autoinflammatory Syndrome
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Introduction: Dual presence of histiocytic interstitial inflammation and C3 glomerulopathy (C3GN) are uncommon. We report a rare case of non-Langerhans cell histiocytosis associated acute kidney injury (AKI). (AKI)

Case Description: A 71-yr-old male was admitted to the hospital with anasarca and generalized weakness. Laboratory data were significant for anemia, AKI, hypercalcemia, and hypoalbuminemia. Physical examination was unremarkable. Laboratory data revealed Creatinine 1.1 mg/dl (eGFR 100 ml/min/1.73m²), protein to urine ratio (UPR) of 9.9 g/µ, UACR at 183 mg/g, serum albumin 2.7 g/dl. The urine was cloudy, and sediment analysis demonstrated no acanthocytes or lipid-laden oval fat bodies. Kidney biopsy showed normal glomeruli by light microscopy with unremarkable immunofluorescence staining and no significant glomerular abnormalities by electron microscopy. Additional studies were performed in our research laboratory to determine the cause of urinary turbidity. Upon addition of ether (a fat solvent), clearing of “cloudy” centrifuged urine occurred with layering of fat globules at the bottom. With addition of Sudan III stain, a red-stained fatty layer accumulated upon centrifugation. Urine assessed in a clinical laboratory showed elevated levels of triglycerides, cholesterol, and chylomicrons. Filaria serologies were negative. The patient was diagnosed with chyluria based on the urine TG level and ether test. MR lymphangiography showed abnormally dilated lymphatic channels in the left paraspinal region communicating with the left kidney. He underwent lymphangiogram with N-butyl cyanoacrylate glue embolization of the left perinephric lymphatic duct, and within 12 hours, the urine cleared to clear yellow. (Figure 1) Repeat labs 1 month after embolization showed UFCR of 0.07 g/g and serum albumin of 4.2 g/dl.

Discussion: Chyluria is a rare cause of nephrotic range proteinuria. Urine color and turbidity, absence of oval fat bodies, and non-selective proteinuria were early diagnostic clues, with urine TG confirming the diagnosis. Microscopic examination of the urine sediment is essential in evaluating patients with proteinuria.

TH-PO721
Compassionate Use of Pegcetacoplan in a Patient with C3 Glomerulopathy: A Case Report
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Introduction: Pegcetacoplan is a C3 complement inhibitor which is approved by the United States Food and Drug Administration for paroxysmal nocturnal hemoglobinuria and geographic atrophy secondary to macular degeneration. It is undergoing a phase III trial (Valiant trial, NCT05067127) which is assessing subcutaneous pegcetacoplan in patients with C3 glomerulopathy (C3G) or immune-complex mediated glomerulonephritis. Here, we discuss the case of a patient who did not qualify for the trial but was approved for compassionate use of pegcetacoplan.

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Case Description: A 26-year-old female was diagnosed with biopsy proven C3G with nephrotic range proteinuria over the course of about a year. Her renal function had deteriorated from estimated glomerular filtration rate (eGFR) of 64 to 22 ml/min/m², with proteinuria progressing from 1.5 to 2.7 gm/day, while being on prednisone and mycophenolic acid (MFA). Due to the inability to tolerate MFA (MFA induced enteropathy on colon biopsy), she was transitioned to tacrolimus and prednisone. The patient kept being hospitalized frequently due to acute kidney injuries (AKI), with five admissions over four months. Patient was not a candidate for the Valiant trial due to eGFR < 30 ml/min/m², 76% glomerular sclerosis (GS) and 60% interstitial fibrosis and tubular atrophy (IFTA) on the last biopsy. Therefore, a request for compassionate use of pegcetacoplan was submitted. It was approved after four months and started in September 2022. While being on pegcetacoplan for six months, the patient’s renal function remained stable (eGFR 19-22 ml/min/m², proteinuria 0.5-0.7 gm/day) and she did not require any hospitalizations. The medication was well tolerated without any serious adverse effects. In March 2023, the patient progressed to end stage renal disease (ESRD) and was started on hemodialysis.

Discussion: There is currently no approved therapy for C3G. Our patient had frequent episodes of AKI, multiple hospitalizations and did not meet the criteria for Valiant trial due to her low GFR. Pegcetacoplan might have delayed her progression to episodes of AKI, multiple hospitalizations and did not meet the criteria for Valiant trial.

TH-PO722
C3 Glomerulonephritis and Thrombotic Microangiopathy in a Patient with C3 Nephritic Factor
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Introduction: Complement-mediated kidney diseases include thrombotic microangiopathy (TMA), C3 glomerulonephritis (C3GN). TMA can occur due to complement dysregulation manifesting as hemolytic anemia, thrombocytopenia and kidney dysfunction. C3GN develops due to mesangiocapillary C3 accumulation. We report a case where both conditions developed in the same patient.

Case Description: A 76-year-old woman presented with shortness of breath and generalised edema. She had a history of hepatitis C infection. Laboratory testing showed creatinine 2.1mg/dl (eGFR 30 ml/min/1.73m²) and albumin 19 gm/L. Urinalysis showed hematuria and protein/creatinine ratio (uPCR) 1,100 gm/mol. Hepatitis C viral load was 5.52 x 10⁶ IU/ml. Other viral, autoimmune, cryoglobulin and parasite stains were negative. C3 was low 0.22 gm/L (0.9-1.8). C4 was normal. Kidney biopsy showed mesangial and endocapillary hyacellularity with double contours. IF showed granular C3 deposition in capillary and mesangium. EM showed subendothelial deposits, consistent with membranoproliferative glomerulonephritis. Renal parameters did not improve with hepatitis C treatment. C3 Nephritic Factor (C3NeF) was positive and Prednisolone and Mycophenolate were thus commenced with improvement of creatinine to 1.4 mg/dl and uPCR to 192 gm/mmol. One year later the patient presented with dyspnea, kidney failure (creatinine 14.1mg/dl) and features of TMA, with haemoglobin 63 g/L and platelets 133 x 10⁹/L. Haptoglobin was low (0.26 gm/L) and blood film showed schistocytes. ADAMTS13 level was normal. Hemodialysis commenced and Eculizumab was given with improvement in hematological parameters only. Complement genetic analysis (C3, C5, C1q, C4B) panel was negative. At four-year follow up, the patient remains dialysis-dependent.

Discussion: TMA and C3GN are disorders caused by complement defects, with the former from membrane-anchored complement activation and the latter from fluid-phase complement activation. C3NeF is a stabilizing antibody against complement C3c, a common step in multiple complement pathways, leading to complement-mediated disorders. Our patient had both TMA and C3GN. This illustrates the complexity and overlap of complement pathways.

TH-PO724
A Case of AA Amyloidosis Associated with “Skin Popping” Heroin
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Introduction: The differential diagnosis for renal disease in patients with substance use disorder can be broad. Etiology can be related to the substance itself, a contaminant of the substance, or a transmitted disease. The renal complications can be acute or chronic and include glomerular, interstitial, and vascular diseases. This case highlights the importance of distinguishing by kidney biopsy between different etiologies in patients with substance abuse.

Case Description: A 62-year-old man with history of Hepatitis C (treated 8 months prior), treated latent TB, chronic left ankle ulcer, and substance use disorder presented to the emergency room with right calf pain for 4 days. Per patient, he used heroin via “skin popping” a couple of times since his pain was severe, but denied using for 15 years prior. Exam with hyperkeratotic plaques on right ulnar palm, left heel ulcer, and lower extremity edema. He was found to have a new deep vein thrombosis in the right popliteal and posterior tibial veins. His laboratory workup revealed a serum creatinine of 5.5 mg/dL, from 1.0 mg/dL 5 months prior, urinalysis with 3+ protein and 2+ blood, and 14.8 grams of urine protein per 1 gram of urine creatinine. Hepatitis C viral load was undetectable. Other workup resulted during the hospitalization including HIV, Hep B, cryoglobulins, Anti-GBM, complements, ANCA, ANA, and ddDNA were negative. He had an abnormal SPEP and elevated free light chains ratio. Kidney biopsy revealed AA amyloidosis with preserved glomeruli and tubulointerstitial fibrosis less than 30%. Although serum creatinine did not significantly change during hospitalization, he remained with good urine output and did not develop indications to start dialysis.

Discussion: Given the broad differential diagnosis in patients with substance abuse, it is key to differentiate between them with a kidney biopsy. Renal amyloidosis should be considered in the differential diagnosis of heroin users when they present to the emergency room with right calf pain for 4 days. Per patient, he used heroin via “skin popping” a couple of times since his pain was severe, but denied using for 15 years prior. Exam with hyperkeratotic plaques on right ulnar palm, left heel ulcer, and lower extremity edema. He was found to have a new deep vein thrombosis in the right popliteal and posterior tibial veins. His laboratory workup revealed a serum creatinine of 5.5 mg/dL, from 1.0 mg/dL 5 months prior, urinalysis with 3+ protein and 2+ blood, and 14.8 grams of urine protein per 1 gram of urine creatinine. Hepatitis C viral load was undetectable. Other workup resulted during the hospitalization including HIV, Hep B, cryoglobulins, Anti-GBM, complements, ANCA, ANA, and ddDNA were negative. He had an abnormal SPEP and elevated free light chains ratio. Kidney biopsy revealed AA amyloidosis with preserved glomeruli and tubulointerstitial fibrosis less than 30%. Although serum creatinine did not significantly change during hospitalization, he remained with good urine output and did not develop indications to start dialysis.

TH-PO725
AL Kappa Amyloidosis with Rapidly Unfavorable Evolution: A Case of Renal, Hepatic, and Muscular Involvement with POEMS Syndrome and Unusual Autoantibody Activity
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Introduction: AL amyloidosis arises in the setting of plasma cell dyscrasia, with deposition of amyloidogenic misfolded immunoglobulin-light chains in peripheral tissues resulting in progressive organ dysfunction. Involved organs include kidneys, heart, liver, nervous system and gastrointestinal tract. A Case of Rapidly Unfavorable Evolution: A Case of Renal, Hepatic, and Muscular Involvement with POEMS Syndrome and Unusual Autoantibody Activity

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observed, despite the absence of thrombotic lesions on whole-body CT images. The patient was started on a cyclophosphamide-bortezomib-dexamethasone-daratumumab regimen, interrupted after four cycles, following the patient’s death only one month after the onset of nephrotic syndrome.

**Discussion:** We described a rare case of systemic amyloidosis with a rapidly unfavorable outcome with abrupt disease onset, in which organ involvement has rapidly progressed to multiorgan failure. If we exclude central nervous system involvement, polyendocrinopathies may be explained by concomitant POEMS. The significance of autoantibody positivity in the absence of clinical autoimmunity remains unclear, and raises the suspicion of a false positivity due to molecular mimicry.

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**TH-PO727**

**A Rare Case of Paraneoplastic Scleroderma Renal Crisis in a Patient with Squamous Cell Carcinoma of the Tongue**

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**Introduction:** Scleroderma Renal Crisis (SRC) is a life-threatening emergency that presents with hypertension, Acute Kidney Injury (AKI) andThrombotic Microangiopathy (TMA) in patients with Systemic Sclerosis (SSc). It is associated with 20% mortality at 6 months and 39-40% of patients requiring long term dialysis.1 Paraneoplastic Scleroderma Renal crisis (PSRC) is a rare subset of SRC that has been reported previously.2 We report a rare case of PSRC without history of SSc in a patient with squamous cell carcinoma of the tongue.

**Case Description:** 61-year-old male with history of squamous cell carcinoma of the tongue who was referred for evaluation of decreased oral intake for few days. He was noted to have tachycardia and hypertension (BP167/109 mmHg). Labs showed anemia, thrombocytopenia and serum creatinine of 1.5mg/dL (baseline 1mg/dL). Urinalysis showed small blood and 30 mg/dL protein with granular casts. Renal ultrasound indicated unremarkable. The patient was treated for severe acute tubular injury (ATN) from prolonged pre-renal state. Due to worsening renal function with a creatinine 8.9 mg/dL, the patient was initiated on hemodialysis. A renal biopsy was obtained revealing a widespread prominent mucoid intimal hyperplasia with severe occlusion and secondary changes of bloodless glomeruli. Mesangial lysis, acute tubular injury with focal ATN and minimal interstitial inflammation was seen. Repeat physical exam revealed thickening of the skin of the hands. Further testing revealed evidence of schistocytes, elevated LDH and positive RNA polymerase III. A diagnosis of PSRC was made and the patient was started on captopril. The patient continued to be dialysis dependent at the time of discharge.

**Discussion:** Paraneoplastic SCR has been reported in a few cases of lung, breast and abdominal cancers.3 The pathogenesis is postulated to be related to cancer induced profibrotic cytokines and growth factors leading to renal vascular damage.4 To our knowledge, there are no reported cases of squamous cell cancer associated PSRC. Our case adds to the literature of the rare PSRC in this patient population. This case highlights the importance of considering PSRC in the differential diagnosis of cancer patients presenting with AKI, TMA and higher than baseline blood pressure measurements.

**TH-PO728**

**A Case of Fibrillary Glomerulonephritis Presenting as Rapidly Progressing Glomerulonephritis in a Patient with Untreated Hepatitis C**

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**Introduction:** Fibrillary glomerulonephritis (FGN) is a rare progressive disease accounting for 0.5% to 1.4% of all native kidney biopsies. The diagnosis is established with renal biopsy demonstrating randomly oriented fibrils ranging 15-25 nm on electron microscopy, and negative Congo red staining. Recent discovery of DNAJB9 as a biomarker has been reliable for diagnosis, although its role in pathogenesis remains unclear. It is strongly associated with underlying malignancy, monoclonal gammopathy, autoimmune disease or infections. Progression remains poor with no established clinical guidelines to optimize therapy. Here, we describe a case of FGN presenting with rapidly progressive glomerulonephritis and crescents on biopsy in a patient with untreated Hepatitis C.

**Case Description:** A 64 yo. M with significant past medical history of hypertension, diabetes, dyslipidemia, smoker of 300 pack years. The patient presents to the hospital with edema and dyspnea. Initial work up showed AKI with creatinine of 4.52 mg/dL. Urinalysis displayed hematuria and proteinuria of 3+ and rising suspicion for an underlying GN. Serological work including anti-GBM, ANCA, Cryoglobulin, RF, HIV, Hepatitis A and B were negative. Hepatitis C antibody was positive, with quantitative RNA greater than 300,000 IU/mL. Electron microscopy from biopsy revealed randomly oriented fibrils ~ 15nm in diameter throughout the glomeruli. IF revealed IgG, C3, kappa/lambda light chains in the mesangium and along the GBM. IHC analysis showed negative Congo red and positive DNAJB9. Of the 46 glomeruli analyzed, 7 demonstrated cellular and fibrocellular crescents. Biopsy findings were consistent with FGN. He was started on pulse dose steroids followed by a taper and cyclophosphamide. Due to worsening renal function and volume overloaded state, he required initiation of diuresis. Despite starting treatment for Hepatitis C, there has been no evidence of renal recovery.

**Discussion:** Overall prognosis for FGN remains poor with approximately 40-50% of patients progressing to ESRD. Our case highlights the challenges with recognition and management of FGN as a cause of RPGN since clinical presentation is similar to other recognized etiologies. Despite treatment of RPGN and Hepatitis C, our patient had progression of disease emphasizing need for further trials and novel therapies.

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

**TH-PO729**

**An Atypical Case of IgG4-Related Disease (IgG4-RD) Manifesting as Extensive Abdominal Periarteritis and Membranous Nephropathy (MN): A Case Report and Literature Review**


**Introduction:** IgG4-DR is a progressive immune-mediated fibrotic disease characterized by tumor-like mass formation in many affected organs. Tubulointerstitial nephritis (TIN) with increased IgG4-positive plasma cells is the dominant feature of IgG4-related kidney disease. Here we present an atypical case of IgG4-DR, and a literature review of 18 cases on IgG4-related MN.

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

Underline represents presenting author.
Case Description: A 71-year-old man with a peptic ulcer was admitted with acute-onset leg edema and nephrotic syndrome. The laboratory data revealed serum albumin 1.9 g/dL, creatinine 1.1 mg/dL, and urinary protein 9.3 g/L. The renal biopsy showed granular staining in the capillary walls for IgG (IgG1) and negative PLA2R staining, suggesting secondary MN. Computed tomography (CT) scans revealed extensive wall thickening of the iliac and splenic arteries, and superior and inferior mesenteric arteries with dilatation. The findings of periarthritis, high serum IgG4 and IgE levels, and numerous IgG4-positive cells infiltration to interstitium led to the diagnosis of IgG4-RD. Our literature review of 18 cases on IgG4-related MN, including 1 case with aortitis, demonstrated that 10 cases achieved complete remission, and 8 achieved partial remission. The abdominal aorta, not the aorta itself. These features suggest a new phenotype of IgG4-related MN, indicating that it is a distinct entity from IgG4-related arteritis. Following the initiation of prednisolone (10 mg) and ARB, he achieved partial remission of proteinuria. We successfully controlled IgG4-RD and avoided the recurrence of nephrotic syndrome.

Discussion: This case, nephrotic syndrome and the outcome of typical manifestations, such as pancreatitis and sialadenitis made the diagnosis of IgG4-RD challenging. It was also unique in that extensive arteritis was confined to a major branch of the abdominal aorta, not the aorta itself. These features suggest a new phenotype of IgG4-RD. Our literature review of 18 cases on IgG4-related MN, including 1 case with aortitis, demonstrated that 10 cases achieved complete remission, and 8 achieved partial remission of proteinuria with various treatments such as corticosteroids, cyclosporinamide, and rituximab. Although the number of affected organs had no relation with the response of proteinuria, the complication of TN had an association with a good response.

TH-PO730

A Case of Renal Infarcts Followed by Renal Hematoma: The Importance of Angiography in the Diagnosis of Polyarteritis Nodosa
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Introduction: A renal infarct (RI) may go undiagnosed given its non specific symptoms; abdominal or flank pain, nausea and vomiting. Classically, it is attributable to cardiovascular causes, such as atrial fibrillation (AF), or to coagulopathies. Frequently, however, no underlying etiology is ascertained. Polyarteritis nodosa (PAN) is a medium vessel vasculitis not associated with antineutrophil cytoplasmic antibodies. Biopsy demonstrating necrotizing arteritis is the gold standard for diagnosis, and when it cannot be secured, angiography is an important tool to establish the diagnosis, exhibiting aneurysms or segmental stenosis of intrabrachial arteries.

Case Description: A 52-year old female, with a past medical history of abdominal pain with prior extensive work up, presents with acute on chronic abdominal pain, nausea, vomiting and 6 kg weight loss. Work up revealed a left RI. Telemetry was negative for AF, as a transesophageal echocardiogram for left ventricle thrombus. Her hospital stay was complicated by ongoing abdominal pain, repeated imaging showing a new large right RI. Hypercoagulable work up was negative. However, it was believed she was high risk for recurrent thrombosis, thus, initiated on Apixaban. After two weeks, she returns with abdominal pain and was discovered with a large right pericapsular hematoma with possible active bleeding. Given hemodynamic instability, she underwent a right renal angiogram that showed severe irregularity with multifocal areas of stenoses, dilatations and microaneurysms, also, large areas of devascularization, consistent with PAN. Hepatitis B serology showed prior immunization. She was treated with pulse dose steroid therapy and IV cyclophosphamide (total of 5 infusions), followed by PO prednisone 1mg/kg. Her abdominal pain ultimately resolved and she experienced no further thrombotic events.

Discussion: The underlying etiology of RI requires compressive investigation. Proper treatment warrants an evidence based practice. PAN is a rare entity, however usually complicates with RI. This case highlights the importance of prompt recognition, appropriate diagnostic investigation, and timely treatment.

TH-PO731

Histiocytic Glomerulopathy
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Introduction: Direct glomerular involvement by activated histiocytes is a rare histopathologic finding and may be associated with cryoglobulinemic glomerulonephritis, Langerhans cell histiocytosis (LCH) and hemophagocytic lymphohistiocytosis (HLH). We present a case of histiocytic glomerulopathy without a readily identifiable systemic cause.

Case Description: A 67-year female with recent cholecystectomy presented with abdominal pain and nausea. She was noted to have elevated alkaline phosphatase levels (1000 U/L) but with normal AST/ALT. She subsequently developed anasarca and anuria requiring dialysis. Kidney biopsy showed diffuse macrophage foam cells positive for CD68 in glomeruli (Image-1). Immunohistochemistry stains for CD1a and Langerin were negative making Langerhans cell histiocytosis unlikely. A bone marrow biopsy showed rare hemophagocytic macrophages. A broad serologic workup was performed and was mostly unremarkable. Although serology showed elevated IL-2 receptor alpha, hypoferritinemia, hypertriglyceridemia, and bone marrow with hemophagocytic macrophages; she did not meet full criteria for HLH. Due to concern for hypersensitivity reaction to metal clips placed during her cholecystectomy, she underwent laparoscopic removal. She was started on high dose methylprednisolone and then oral prednisone. Renal function improved and dialysis was discontinued.

Discussion: Histiocytic glomerulopathy is a rare entity categorized by the presence of macrophages in glomeruli. We present an idiopathic case which may have been triggered by a hypersensitivity reaction. Treatment options are limited and include steroids, plasmapheresis, and intravenous immunoglobulins (IVIG). Our patient responded to steroids in addition to removal of a potential underlying trigger. Six weeks after her initial presentation she remains off dialysis with excellent renal function.
Glomerular Diseases: Podocyte Biology - I

Factors of a Podocyte-Specific Injury Mouse Model with Inducible Yamanaka

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

**TH-PO734**
Deficiency of Melanocortin 5 Receptor Exacerbates Proteinuria and Podocyte Injury upon Glomerular Injury

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**Background:** Converging evidence suggests that therapeutic targeting of nonsteroidal melanocortinergic pathways represents a novel strategy for treating proteinuric glomerulopathies. However, the type of melanocortin receptor (MCR) mediating this beneficial effect remains controversial and uncertain. Recent work indicates that MC5R is expressed in glomerular cells and MC3R signaling may be involved in glomerular pathobiology. This study examined the possible effect of MC3R ablation in nephrin-negative serum (NTS)-elicited podocyte injury.

**Methods:** NTS nephritis was induced in MC3R knockout (KO) mice and wild-type (WT) littermates. Additional WT mice received treatment with a highly selective MC3R agonist or vehicle before NTS injury. Proteinuria, podocyte injury and glomerular damage were evaluated early in the heterologous phase of NTS nephritis.

**Results:** Despite no discernible phenotypes under physiological conditions, KO mice sustained exacerbated glomerulopathy upon NTS injury, as shown by heavier albuminuria. This was associated with worsened glomerular pathologic, characterized by glomerular hypercellularity, swelling of glomerular endothelial cells, and fibroinoid necrosis of glomerular capillary tufts, although glomerular depositional of the glomerular basement membrane-reactive heterologous rabbit IgG and C3b−9 membrane attack complex along the glomerular capillary loops were found to be comparable between the WT and KO groups after NTS insult. In parallel, KO mice exhibited more severe podocytopathy than WT mice after NTS injury, as evidenced by reduced numbers of WT-1 positive cells in glomeruli, as well as worsened podocyte injury, marked by loss of glomerular expression of podocyte homeostatic proteins such as podocin and synaptopodin. Conversely, to test if activation of MC3R signaling is sufficient to protect against NTS-elicited podocytopathy, WT mice with NTS nephritis were subjected to MC3R agonist by using a peptide mimetic selective agonist. This resulted in an attenuated proteinuria and an improved podocyte injury, as evidenced by preserved expression of podocyte marker proteins.

**Conclusions:** Our findings suggest that MC5R-mediated melanocortinergic signaling protects against proteinuria and podocytopathy upon glomerular injury, and may be harnessed as an actionable target for treating proteinuric glomerulopathies.

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

**TH-PO735**
Lower NBL1 Increases Kidney Function in a Glomerular Damage Model

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**Background:** Increased serum levels of neuroblastoma suppressor of tumorigenicity 1 (NBL1) have been associated with a faster decline in kidney function in patients with diabetic nephropathy (DN), and in vivo experiments suggest higher NBL1 levels lead to podocyte apoptosis. We aim to test whether there is a causal relationship between NBL1 and CKD by manipulating Nbl1 expression.

**Methods:** We generated an Nbl1 heterozygous knockout (Het) model in the C57BL/6J background (homozygous knockout is not viable) and confirmed lower NBL1 levels in these mice. We tested two kidney damage models. In the first model, we induced tubular damage using a low-dose cisplatin protocol. In the second model, we induced glomerular damage by manipulating a Col4a2 mutation through breeding.MC5R agonism in glomerular cells and MC3R signaling may be involved in glomerular pathobiology. This study examined the possible effect of MC3R ablation in nephrin-negative serum (NTS)-elicited podocyte injury.

**Results:** Despite no discernible phenotypes under physiological conditions, KO mice sustained exacerbated glomerulopathy upon NTS injury, as shown by heavier albuminuria. This was associated with worsened glomerular pathologic, characterized by glomerular hypercellularity, swelling of glomerular endothelial cells, and fibroinoid necrosis of glomerular capillary tufts, although glomerular depositional of the glomerular basement membrane-reactive heterologous rabbit IgG and C3b−9 membrane attack complex along the glomerular capillary loops were found to be comparable between the WT and KO groups after NTS insult. In parallel, KO mice exhibited more severe podocytopathy than WT mice after NTS injury, as evidenced by reduced numbers of WT-1 positive cells in glomeruli, as well as worsened podocyte injury, marked by loss of glomerular expression of podocyte homeostatic proteins such as podocin and synaptopodin. Conversely, to test if activation of MC5R signaling is sufficient to protect against NTS-elicited podocytopathy, WT mice with NTS nephritis were subjected to MC3R agonist by using a peptide mimetic selective agonist. This resulted in an attenuated proteinuria and an improved podocyte injury, as evidenced by preserved expression of podocyte marker proteins.

**Conclusions:** Our findings suggest that MC5R-mediated melanocortinergic signaling protects against proteinuria and podocytopathy upon glomerular injury, and may be harnessed as an actionable target for treating proteinuric glomerulopathies.

**Funding:** NIDDK Support

**TH-PO733**
A Podocyte-Specific Injury Mouse Model with Inducible Yamanaka Factors

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**Background:** Ectopic expression of the Yamanaka transcription factors Oct4, Klf4, c-Myc and Sox2 (OKMS) can reprogram somatic cells into pluripotent stem cells in vitro (Takahashi Cell 126, 2006). As shown recently for different tissues, in vivo expression of those factors can enhance regeneration and improve outcome after injury through partial cellular re-programming (Hishida Cell Rep. 39, 2022), even in non-muriotic cells (Le Nature 588, 2020). In order to apply this approach to podocytes and examine effects of OKMS on podocyte regeneration, we employed a podocyte-specific injury model (Guo J Am Soc Nephrol 23, 2012) and crossed it with a conditional and inducible OKMS mouse model, thereby generating podocyte-specific expression of the Yamanaka factors.

**Methods:** We crossed the previously published inducible diphtheria toxin receptor mouse (Buch Nat Methods 2, 2005) with a Podocin-Cre recombinase mouse (Moeller Genesis 35, 2003), and further with the ROSA26-rtTA(neo); OKMSch250-mouse (JAX stock #031012). We induced OKMS-expression in vitro in extracts of primary podocytes, as well as in vivo by 7-day application of doxycycline via drinking water. Furthermore, we determined urine albumin/creatinine ratios (ACR) and obtained histological samples to evaluate the extent of kidney injury after intraperitoneal diphtheria toxin (DT) injection in 5 different doses.

**Results:** To determine if OKMS can be induced, expression was first tested in vitro. Primary podocytes from OKMS<sup煺</sup>; rtTA<sup succesfully</sup>; Podocin-Cre<sup - mice showed increasing Oct4 and Sox2 expression over time, but no expression of Nanog after 6 days and no decrease in podocyte-specific markers, whereas primary podocytes from a OKMS<sup succesfully</sup>; rtTA<sup succesfully</sup>; Podocin-Cre<sup - mice exhibited expression of Nanog, as well as a decrease of Nphs1 and Nphs2, but an increase in WT1. In vivo, administration of 10 µg/kg and 7.5 µg/kg DT led to proteinuria with ACR levels over 50 g/g after 4 days as well as glomerulosclerosis and tubular casts on light microscopy after 4 weeks. Administration of 5 µg/kg, 2.5 µg/kg and 1.25 µg/kg showed later onset (60), lower levels and, after 14 days, a reduction of proteinuria.

**Conclusions:** We, hereby, provide a suitable mouse model to study the effect of Yamanaka-expression in a podocyte-specific injury model.

**Funding:** NIDDK Support, Government Support - Non-U.S.
Conclusions: Our preliminary results suggest that NBL1 is causal for decreased kidney function only in the model defined by glomerular pathology. Our next steps aim to determine what drives increased NBL1 expression, and the source of serum NBL1.

**TH-PO736**
Podocyte-Specific NRF2 Activity Protects Against Adravimycin-Induced Kidney Injury
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Background: NRF2 is a key regulator of antioxidant and detoxification pathways in the kidney. KEAP1 is an endogenous inhibitor of NRF2. Various cellular stressors alter KEAP1 binding to NRF2, leading to NRF2 nuclear translocation and upregulation of target antioxidant and detoxification genes. Unexpectedly, NRF2 enhancers increased proteinuria in CKD clinical trials. Our prior work also demonstrated that global NRF2 enhancement exacerbates proteinuria in mouse models of glomerular disease. The kidney cells mediating these effects are not known. Since podocytes are key cells maintaining the glomerular filtration barrier, we hypothesized that podocyte-specific NRF2 activity exacerbates proteinuria and glomerular injury.

Methods: We generated podocyte-specific KEAP1 knockout mice (Podo-KEAP1 KO) by crossing Podocin-Cre mice with Keap1 floxed mice. These mice exhibit increased NRF2 activity only in podocytes. We subjected Podo-KEAP1 KO and control littermates to either adriamycin or chronic angiotensin II infusion to induce glomerular injury and proteinuria. Kidney injury was assessed by histologic, biochemical, and molecular indices.

Results: Contrary to our expectations, Podo-KEAP1 KO mice were protected against adriamycin-induced kidney injury, as demonstrated by lower levels of proteinuria, the injury marker NGAL, and fibrosis. Results from glomerular isolates reveal significantly increased antioxidant (Nqo1 and Cat) and a trend to decreased inflammatory responses (Il-1β and Syp). The structure of vimentin fibers was deranged (65.2% to normal, p<0.05), and 14-3-3β in podocytes was expressed in the primary processes.

Conclusions: Although prior work demonstrated that global NRF2 enhancement worsens proteinuric CKD, we now show that podocyte-specific NRF2 enhancement protects against adriamycin-induced injury. This may be due to a specific effect of podocyte NRF2 activity to reduce glomerular oxidative stress in this model. Lack of effect in the angiotensin II model suggests a different mechanism of injury. Non-podocyte effects must also mediate CKD exacerbation in both models when NRF2 is globally enhanced. Future studies will determine the cell- and disease-specific effects of NRF2 in CKD, and whether podocyte-specific NRF2 can be targeted therapeutically.

**Funding:** Veterans Affairs Support, Other U.S. Government Support, Private Foundation Support

**TH-PO737**
14-3-3 Proteins Stabilize Vimentin and Actin Filaments to Maintain Primary and Foot Processes in Podocyte
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Background: 14-3-3 proteins are a ubiquitously expressed family of adaptor proteins. Despite exhibiting high sequence homology, several 14-3-3 isoforms have isoform-specific binding partners and roles. We reported that 14-3-3β interacts with FKBP12, a binding protein to tacrolimus, and synaptopin (Syp) to maintain the structure of actin fibers in podocytes (Yasuda et al., FASEB J, 2021). However, the functions of 14-3-3 proteins in podocyte injury models were not elucidated. The precise localization and differential role of 14-3-3 isoforms in glomerular are also unclear.

Methods: mRNA expression of 14-3-3s in kidneys was analyzed with RT-PCR, and their localization was investigated with immunohistochemical analyses. The interaction of 14-3-3s was analyzed by immunoprecipitation assay with the lysate of cultured podocytes. The expression of 14-3-3s in podocyte injury models was analyzed.

Results: 14-3-3β and 14-3-3σ were abundantly expressed in glomeruli. 14-3-3β in glomeruli was restricted in podocytes. 14-3-3σ in glomeruli was expressed in podocytes and mesangial cells. 14-3-3β is co-localized with Par3 at the slit diaphragm. 14-3-3β interacts with Par3, and the interaction was decreased by the transfection of FKBP12 in the foot processes, and a part of 14-3-3β and 14-3-3σ in podocytes treated with 14-3-3β siRNA interact with Par3, and the interaction was decreased by the transfection of FKBP12. The interaction of Par3–Parb was enhanced by the treatment of 14-3-3β siRNA (3 times to normal, p<0.05). The structure of F-actin was deranged (score 1.8 vs 3.1 of normal, p<0.05), and process formation was impaired (46.5% to normal, p<0.005) in the podocytes treated with 14-3-3β siRNA. 14-3-3β and Syp expression was decreased in podocyte injury models. 14-3-3σ in podocytes was expressed in the primary processes. 14-3-3σ interacted with vimentin but not with the actin-associated proteins FKBP12 and Syp. The structure of vimentin fibers was deranged (65.2% to normal, p<0.05), and process formation was impaired (40.1% to normal, p<0.005) in the podocytes with 14-3-3σ siRNA. 14-3-3σ and vimentin expression was increased in the early phase of podocyte injury but was decreased in the late stage.

Conclusions: 14-3-3 proteins play the roles in maintaining the primary and foot processes by stabilizing vimentin and actin filaments in podocyte.

**Funding:** Government Support - Non-U.S.
share a podocyte-parietal epithelial cell (PEC) transcriptome associated with renal repair and restoration.

Methods: The intersection set of podocyte-PEC genes (literature) and directionally aligned SRC genes were seeded into miRNet and Cytoscape for visualization of the shared transcriptome and identification of its functional attributes. Human SRCs (National Disease Research Interchange kidneys) were submitted to scRNA-seq to map gene expression and placed in culture and the supernatant quirked for secreted vascular endothelial growth factor A (VEGFA) and its angiogenic activity using a human umbilical vein endothelial cell (HUVEC) tube formation assay.

Results: car1, sis2, ltb1, lkg1, lkg2, npbs1, npbs2, vegfa, cdl4 and hes1 were expressed by both podocyte-PEC and SRCs and involved in kidney developmental functions including maintenance of undifferentiated nephron precursors, tubule and nephron formation, maturation of the glomerular barrier and formation of the glomerular capillary bed (A, B). VEGFA emerged as the hub gene within this network (C). SRCs expressed vegfa (D) and secreted VEGFA (0.75 to 3.02 ng/mL, mean=1.45 ng/mL) whose angiogenic activity was evidenced by HUVEC tube formation (E).

Conclusions: A Vegfa anchored podocyte-PEC transcriptome expressed by SRCs may recapitulate events associated with kidney development and mediate the preservation or improvement of glomerular integrity, renal microarchitecture and renal filtration observed in CKD models.

Funding: Commercial Support - ProKidney

TH-PO740

Podocyte Density, Rather than Podocyte Number per Glomerulus, is Associated with Kidney Outcomes in Obesity-Related Glomerulopathy

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Background: Obesity-related glomerulopathy (ORG) is a slowly progressing glomerular disease occurring in obese individuals. Podocyte injury and subsequent podocyte depletion are regarded as key processes in ORG progression. However, no previous study has assessed the longitudinal association between podometric and long-term kidney outcomes in ORG.

Methods: Podocyte number per glomerular volume (podocyte density) and podocyte number per glomerulus (podocyte number) in ORG patients were estimated using model-based stereology. The associations between these podometries at the diagnostic biopsy and subsequent kidney outcomes (30% decline in eGFR) were examined by log-rank tests and Cox proportional hazard analyses.

Results: Forty-one ORG patients with median age of 47 years, eGFR 63 mL/min/1.73m2 were analyzed. At biopsy diagnosis, ORG patients with podocyte density below the median value were older, predominantly male, and had larger body surface area, higher proteinuria, larger glomeruli, and lower podocyte number than ORG patients with higher podocyte density. During a median follow-up period of 3.9 years, 16 (39%) ORG patients reached a 30% decline in eGFR. Kidney survival in patients with lower podocyte density was significantly worse than in patients with higher podocyte density (P = 0.001), but there was no significant association between kidney survival and lower vs higher podocyte number (P = 0.3). Cox hazard analyses showed that podocyte density, but not podocyte number, was associated with kidney outcome after adjustment for clinical factors, including age, sex, proteinuria, and eGFR.

Conclusions: Our results indicate that lower podocyte density, rather than lower podocyte number, is a high-risk factor for progression of ORG. Confirmation in other ORG cohorts and potential generalizability to other glomerular diseases will require further studies.

Funding: Government Support - Non-U.S.

TH-PO742

Identification of Intercellular Communication Involved in the Progression of Tubulointerstitial Fibrosis Common to Podocyte Injury and Ischemia-Reperfusion Injury Models


Background: Tubulointerstitial fibrosis (TF) is the final common pathway of progressive chronic kidney disease. The fibrogenic niche, a specialized microenvironment that triggers the differentiation of renal myofibroblasts (MF), is one of the critical therapeutic targets for TF. However, it remains uncertain what kind of intercellular communication shapes the fibrogenic niche.

Methods: Podocyte-specific Tn1l knockout (Tnfl KO) in C57BL/6 background mice (Tnfl homozygous Tnfl flox: Tnfl-Cre) and an ischemia-reperfusion injury (IRI) model on C57BL/6 wild-type mice were used as animal models for TF. Tnfl homozygous Tnfl flox: Tnfl-Cre mice and sham-operated mice served as the controls. Kidney samples were collected on day 10 and week 5 after initiation of doxycycline induction for Tnfl KO mice and on days 2, 5, and 14 for the IRI model. The kidney samples were subjected to several analyses, including single-cell RNA sequencing (scRNA-seq).

Results: Histological examinations and real-time PCR analyses confirmed the development of TF lesions at week 5 in Tnfl KO mice and at day 14 in the IRI model. scRNA-seq analyses of a combined dataset from the two animal models identified 21 cell clusters. As TF progressed, clusters of injured proximal tubules (Inj-PT), impaired Henle’s loops, MFs, and inflammatory cells appeared in common in both animal models. CellChat analyses of the inter-cluster communication revealed the closest communication between the Inj-PT and MF clusters. The communication between these two clusters included cxcl10, il17a, and itgav/itgb1 signaling. The Inj-PT cluster expressed high levels of Haver1 that encodes kidney injury molecule 1.
Conclusions: These results indicated that Hdac1-positive proximal tubular cells contribute to podocyte loss in animal models. Although these experiments are required, these intercellular communications may contribute to developing a fibrogenic niche.

TH-PO743
Interleukin (IL)-27-Induced Podocyte Injury in Minimal Change Nephrotic Syndrome (MCNS)
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Background: We have previously demonstrated that relapse in MCNS was associated with decreased monocyte expression of CD14 and downregulation of proinflammatory cytokines in lipopolysaccharide-stimulated monocytes. This study aimed to identify the dysregulated monokines in disease relapse and subsequently to investigate the proteinuria-inducing mechanism in an experimental rat model and cultured human podocytes.

Methods: Monocytes were isolated from 5 MCNS patients in relapse (MCNSRelapse) and remission (MCNSRem) using monocyte isolation kit II. Monocyte transcription profile was performed using Illumina Human Ref68 chips. Plasma IL-27 levels were measured in 14 MCNS patients in relapse and remission and 20 healthy controls. Experimental rat model was created through electroporation of IL-27 plasmid DNA in Wistar rats. The role of IL-27 in human podocytes was examined through cell RhoA/Rac1 and STAT3 activities. Statistical analysis was done using Mann-Whitney test and Wilcoxon signed rank test for paired data.

Results: Monocyte transcriptomes in MCNSRelapse involved regulation of IL-1 signaling, RhogTPTases regulation of actin cytoskeleton, toll-interleukin receptor (TIR)-domain-containing adapter-inducing interferon-β (TRIF) and IFN-induction pathways. Analysis of monokine gene expression showed a 2.7-fold increase in IL27 expression in MCNSRelapse. Plasma IL-27 levels were also significantly higher in MCNSRelapse (1.5±0.19 ng/ml) compared to MCNSRem (0.95±0.13 ng/ml) (P<0.05) and controls (0.89±0.14 ng/ml) (P=0.01). Similarly, in an IL-27 overexpression rat model, both 24-hour urine albumin excretion (409±34 vs 251±34 µg, P<0.005) and plasma triglyceride levels (362±27 vs 27±2 mg/dL, P=0.02) were significantly higher at Day 70, compared to control rats. This was associated with upregulation of glomerular pSTAT3 expression in IL-27 transfected rats. Additionally, IL-27 stimulation in human podocytes resulted in phosphorylation of both STAT1 and STAT3 as well as 1.56-fold increase in activated Rac1 level.

Conclusions: The IL-27 overexpression rat model demonstrating podocyte injury possibly through activation of STAT3 and Rac1 as shown on podocyte culture experiments.

Funding: Government Support - Non-U.S.

TH-PO744
Disrupting Circadian Control of Autophagy Induces Podocyte Injury and Proteinuria
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Background: Diabetic kidney disease (DKD) remains the most common cause of end-stage kidney disease in the USA, and is characterized by mitochondrial dysfunction, increased circulating serum mtDNA levels, and activation of STING, a DNA-sensing innate immune adaptor, expressed in podocytes. Mitochondrial DNA (mtDNA) has been previously described to activate STING signaling in renal tubular cells in DKD, leading to autoinflammation. We hypothesize that loss of mitochondrial transcription factor A (TFAM) and impairment of PTEN-induced putative kinase 1 (PINK1) mediated mitophagy triggers mtDNA leakage and causes podocyte injury in DKD.

Methods: Adult C57BL/6 mice and podocyte specific Clock knockout mice (podocyte-Clock–/–) were used to construct the type II diabetes model in vivo. Primary podocytes were cultured in 20mM high glucose. Chromatin immunoprecipitation (ChIP) qPCR analysis and dual-luciferase reporter gene assay were used to elaborate association between Clock and autophagy.

Results: The rhythmic oscillations of Clock were disappeared in high glucose treated podocytes, and strongly with myoblasts in both animal models. The podocyte specific Clock knock out mice at age 3 months and 8 months showed deficient autophagy, loss of podocytes and increased albuminuria. Chromatin immunoprecipitation (CHIP) sequence and PCR analysis indicated Clock binding to the promoter regions of Beclin 1 and Atg12. CHIP-qPCR analysis also confirmed the binding of Clock and autophagy gene promoter reduced when exposed to high glucose. Deletion Clock in podocyte could aggravate podocyte injury and proteinuria in diabetic mice. The autophagy in podocyte-clock–/– diabetic mice was lower than that of control diabetic mice.

Conclusions: Our findings demonstrate that clock-dependent regulating autophagy is essential for podocyte survival. The loss of circadian control autophagy plays an important role of podocyte injury and proteinuria.

Funding: Government Support - Non-U.S.

TH-PO745
Reduced Glycolytic ATP Production Is Responsible for Irreversible Podocyte Injury in Nephrotic Syndrome
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Background: Energy metabolism is essential for cellular function and homeostasis, and the kidney is a high energy-consuming organ, making it susceptible to injury due to aberrant energy metabolism. Podocyte energy metabolism is also critical for homeostasis under physiological condition, but its role in stress condition, especially in nephrotic syndrome involving circulatory permeability factors, is unclear. Therefore, to clarify the role of energy metabolism in injured podocytes, we examined changes in podocyte energy metabolism by circulating humoral factors of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS).

Methods: Cultured human podocytes were treated with biopsy-proven MCD and FSGS patients’ or healthy subjects’ sera, analyzed for cell apoptosis by flow cytometry, and real-time ATP production rates in glycolysis and mitochondrial respiration using a Seahorse Extracellular Flux Analyzer. In addition, metabolic analysis of serum-treated podocytes by GC-MS was performed to obtain an overview of energy metabolism. Isolated mouse glomeruli from Adriaymphcin nephropathy were also evaluated.

Results: FSGS patients’ sera significantly induced apoptosis in human podocytes compared to MCD patients’ or healthy subjects’ sera. There was a correlation between decreased glycolytic ATP production and the rate of cell apoptosis in podocytes treated with FSGS patients’ sera. In addition, treatment with low concentrations of glycolytic inhibitors partially reduced apoptotic podocyte apoptosis, despite increased mitochondrial ATP production in podocytes treated with MCD patients’ sera. Metabolic analysis also showed that glycolytic metabolites were reduced in podocytes treated with FSGS patients’ sera compared to MCD. Glycolytic enzymes were also decreased in mouse glomeruli isolated from Adriaymphcin nephropathy.

Conclusions: These data suggest that irreversible podocyte injury is associated with disruption of metabolic compensatory mechanisms, particularly reduced glycolytic ATP production.

Funding: Government Support - Non-U.S.

TH-PO746
STING Activation by Mitochondrial DNA Triggers Podocyte Injury in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) remains the most common cause of end stage kidney disease in the USA, and is characterized by mitochondrial dysfunction, increased circulating serum mtDNA levels, and activation of STING, a DNA-sensing innate immune adaptor, expressed in podocytes. Mitochondrial DNA (mtDNA) has been previously described to activate STING signaling in renal tubular cells in DKD, leading to autoinflammation. We hypothesize that loss of mitochondrial transcription factor A (TFAM) and impairment of PTEN-induced putative kinase 1 (PINK1) mediated mitophagy triggers mtDNA leakage and causes podocyte injury in DKD.

Methods: 16-week-old control (db/+ ) and diabetic (db/db) mice were used. Glomeruli were isolated to determine the expression of OXPHOS complex subunits, TFAM, PINK1 and TOM20, a biomarker for mitochondrial mass. Mitochondrial morphology was evaluated by TEM. Free mtDNA levels were measured in plasma, urine and cytosolic fraction from kidney cortex. Treatment with nuclear DNA (mDNA) or mtDNA was performed in vitro (10 ng, 30 min) using immortalized control human podocytes and in vivo (5 mg/kg, 24h) using control and STING knockout mice, followed by pSTING/STING expression and phenotypical analyses.

Results: We found that db/db mice have decreased glomerular TFAM expression and increased PINK1 expression in the mitochondrial fraction of db/db mice kidney cortices. Mitochondria morphology was indicative of dysfunction on TEM analysis, which was confirmed by increased expression of OXPHOS complex II (SDHA), and loss of mitochondrial mass marker TOM20. Db/db mice were also found to have increased mtDNA in the cytosol of kidney cortices, as well as in blood and urine. Treatment with mDNA led to increases in pSTING expression in vitro and the development of albuminuria and foot process effacement in vivo, while STING −/− mice were protected from renal injury.

Conclusions: Our data suggest that loss of TFAM accumulation of PINK1 contributes to pathologic leakage of mtDNA into the circulation and cytosol causing albuminuria and podocyte injury.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO747

RIPK3 Promotes Mitochondrial Fission and Dysfunction via PGAM5-Drp1 Signaling During Diabetic Podocyte Injury
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Background: Receptor-interacting protein kinase (RIKP3) is an essential molecule for necroptosis and its role in kidney fibrosis has been investigated using various kidney injury models. However, the relevance and the underlying mechanisms of RIKP3 of podocyte injury in DKD are poorly understood. In this study, we investigated the role of RIPK3 in kidney injury of DKD and elucidated the underlying mechanism.

Methods: We evaluated the association of RIPK3 on clinical indices of DKD in the kidneys from diabetic mice and animals. To investigate the role of RIPK3 in glomerular damage of DKD, diabetes was induced by a high-fat diet in RIPK3 knockout (KO) mice and cultured podocytes were stimulated with high glucose with or without RIPK3 inhibitor GSK872.

Results: RIPK3 level was upregulated in podocytes and plasma from human DKD cohort. Such upregulation was correlated with podocyte loss, albuminuria, and poor renal outcome. RIPK3 deficiency in DKD mice improved albuminuria, podocyte numbers, and renal histopathological features including foot process effacement and glomerular basement membrane (GBM) thickening. Increased mitochondrial fragmentation, upregulated mitochondrial fission-related proteins such as phosphoglycerate mutase family member 5 (PGAM5) and dynamin-related protein 1 (Drp1), and mitochondrial dysfunction were decreased in RIPK3-depleted diabetic podocytes both in vitro and in vivo. By contrast, RIPK3 overexpression was sufficient to decrease oxygen consumption rate and increase PGAM5 expression and mitochondrial fragmentation due to mitochondrial translocation of Drp1.

Conclusions: RIPK3 is associated with diabetic podocyteopathy, likely by regulating mitochondrial fission via PGAM5-Drp1 signaling. Targeting RIPK3 might be a promising therapeutic option for treating DKD.

Funding: Government Support - Non-U.S.

TH-PO748

Dapagliflozin Exerts Senomorphic Effects on Adriamycin-Induced Podocyte Injury via Modulation of Complosome
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Background: Recent clinical and experimental studies demonstrate that Sodium-glucose co-transporter 2 inhibitors (SGLT2i) exert reno- and cardiovascular protection independently of the hypoglycaemic effect. SGLT2i treatment rapidly reduces proteinuria preserving renal function in the long term. The mechanisms underlying the renal protection of SGLT2i are not fully understood. PODOs are the cornerstone of the underlying mechanisms.

Methods: We have a direct effect on Podocytes (PODO) after Adriamycin (ADR) injury investigating the association of TRPM4 with TRPC6, a monomeric calcium channel that is downstream of the mitochondrial translocation of Drp1. The kinetics of the expressions of TRPM4, TRPC6, and podocyte functional molecules in vitro were investigated in human cultured podocytes. The effect of silencing studies with siRNA were performed with cultured podocytes. The effect of the expression of mitochondrial translocation of Drp1.

Results: TRPM4 was identified as a molecule downregulated in PAN and panone-dependent podocytes. The study with 9-phenanthrol clearly showed that functional molecules were detected yet.

Conclusions: The expression of TRPM4, TRPC6, and podocyte functional molecules in vitro were significantly increased in PAN- and panone-dependent podocytes. TRPM4 functional knockdown with siRNA clearly promotes the expression of TRPC6 (139.76% ± 10.04; P<0.05) in vitro. Dapa repairs ADR-induced PODO injury by recovering of PODOs’ F-actin, increasing Nephrin (mRNA: 179.24% ± 9.02; P<0.05) in vitro. Dapa repairs ADR-induced PODO injury by recovering of PODOs’ F-actin, increasing Nephrin (mRNA: 179.24% ± 9.02; P<0.05) in vitro. Dapa repairs ADR-induced PODO injury by recovering of PODOs’ F-actin, increasing Nephrin (mRNA: 179.24% ± 9.02; P<0.05) in vitro. Dapa repairs ADR-induced PODO injury by recovering of PODOs’ F-actin, increasing Nephrin (mRNA: 179.24% ± 9.02; P<0.05) in vitro.
TH-PO751

Nephrin, Podocin, and Nephrin Encoding mRNAs Are Dysregulated by Alternative Polyadenylation During Podocyte Injury


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Background: Podocyte injury and proteinuria are hallmark characteristics of glomerular disease. Nephrin and Podocin are critical regulators of the structure and function of podocytes and the glomerular filtration barrier. We hypothesized that these important components of the slit diaphragm could be dysregulated at the level of mRNA processing during podocyte injury and glomerular disease.

Methods: Glomerular alternative mRNA polyadenylation was detected using APATrap analyses of the RNASeq data from porcine aminonucleoside (PAN) and adriamycin (ADR)-induced nephropathy models of podocyte injury and glomerular disease, mimicking human minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), respectively.

Results: Nephrin (encoding for Nephrin) mRNA presented with a significant shift from proximal to distal usage of the polyadenylation (pA) site in its 3' untranslated region (3' UTR) in both PAN (12.7% shift vs healthy control) and ADR (24% shift vs healthy control) -induced glomerular disease models. The Nephrin mRNA pA site shift to distal site and lengthening of the 3' UTR during injury was also validated by 3' Rapid Amplification of cDNA Ends assay. In contrast, a reverse shift was detected on the Nephrin (encoding for Podocin) mRNA in the ADR-induced nephropathy model (9.2% shift vs healthy control) only. The pA shift in Nephrin mRNA to a more distal site during injury results in increased introduction of target sites for miRNAs (miR-376a-5p, miR-466c-5p and miR-466d), which might affect its localization, stability and translation. Nephrin mRNA also showed a shift to a more distal site (~13% shift vs healthy control) in both PAN and ADR -induced glomerular disease models, exposing additional 415 nucleotides to mRNA targeting. On the other hand, a shift in Nephrin mRNA (pA site from distal to proximal during injury results in introduction of the pA site) in its last coding exon upstream of the STOP codon, which might affect its stability by the mRNA non-STOP decay pathway.

Conclusions: Alternative mRNA polyadenylation of Nephrin, Nephrin and Kirre1 mRNAs during podocyte and glomerular injury could result in their altered levels or function, with potential implications towards the dysregulation of podocyte structure and function and disruption of glomerular filtration barrier.

Funding: Private Foundation Support

TH-PO752

Podocyte Injury in Human Primary Membranous Nephropathy: Evidence Supporting a Role for Complement

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Background: Primary membranous nephropathy (PMN) is the leading cause of nephrotic syndrome in adults and a common cause of end-stage kidney disease (ESKD). The Heymann’s nephritis rat model of PMN shows that proteinuria is complement-mediated. However, the pathogenic role of complement in human PMN remains unclear. We aim to demonstrate that complement activation can have both structural and functional effects on podocytes.

Methods: An in-vitro model of immortalized human podocytes (from Moin Saleem, Bristol, UK) was used for all the experiments. Cells were exposed to 25% serum of 19 PMN patients (from the Toronto Glomerulonephritis Registry). Complement deposition was assessed by immunofluorescence (IF). As positive control, cells were pre-sensitized with anti-CDS9 and exposed to 25% normal human serum (NHS) to induce complement activation. Changes in intracellular calcium were monitored using a fluorescent dye (Fluo 3-AM), acquiring images every 20 seconds (up to 10 minutes) by confocal microscopy. Calcium influx in mitochondrial membrane potential were measured by flow cytometry. Intracellular adenosine triphosphate (ATP) changes were analyzed by bioluminescence. Actin cytoskeleton re-arrangements were evaluated by IF. Wound healing assays were performed to study functional effects on cell migration.

Results: Incubation with 25% PMN serum led to deposition of both C3b and C5b9 on the cell surface, which was significantly higher compared to controls (p < 0.05). Complement activation induced a significant rise in the intracellular calcium levels. Loss of mitochondrial membrane potential was also observed, together with intracellular ATP decrease, disruption of the actin cytoskeleton and impaired cell migration. Effects of both structure and function of podocytes were reversed by inhibition of the terminal complement pathway.

Conclusions: Complement is active in PMN, leading to both structural and functional effects on podocytes. Effects can be reversed by inhibition of the terminal complement pathway. Further studies are needed to fully understand the consequences of complement activation on the podocyte energy machinery and the rationale for the use of complement inhibitors in PMN. Our research may identify novel molecular treatment targets with the potential of improved patient outcomes and quality of life.

TH-PO753

Podocyte Injury Marker EGR1 in Lupus Nephritis

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Background: We have discovered that early growth response 1 (EGR1) is expressed in injured podocytes from an early stage in animal studies. Additionally, we have observed that EGR1 expression in podocytes correlates with proteinuria, urinary nephrin/podocin mRNA levels, and glomerular podocin expression in patients with glomerular diseases. These findings suggest that EGR1 could potentially serve as a marker of podocyte injury. The objective of this study is to investigate the relationship between EGR1 expression in podocytes and the activity of lupus nephritis (LN).

Methods: We recruited patients diagnosed with LN by kidney biopsy at Jikei University Hospital, Tokyo, between January 2001 and March 2020. Patients under 20 years and those with fewer than 8 glomeruli were excluded. We collected the SLE disease activity index (SLEDAI), estimated glomerular filtration rate (eGFR), and urinary protein excretion (UPE) levels from the patients’ medical records during kidney biopsy. We measured the percentages of glomeruli with podocytes expressing EGR1 (%EGR1glo), sclerotic glomeruli (%SGS), glomeruli with endocapillary hypercellularity (%Endo), and glomeruli with cellular/fibrillar crescents (%Cres), as well as tubulointerstitial damage from the kidney biopsy specimens. %EGR1glo was compared with these parameters using Spearman’s rank correlation coefficient, and %EGR1glo between LN classes was compared using the Kruskal-Wallis test. Multiple comparison corrections were conducted using Holm-Bonferroni method.

Results: Seventy-five patients were included in this study (84% female, median age 38 [interquartile range 31–50] years, SLEDAI 17 [14–22], eGFR 86 [60–103] mL/min/1.73 m², UPE level 1.49 [0.57–3.23] g/d, and %EGR1glo 14.3 [8.8–26.8]%). LN classes were 4 Class I, 8 Class II, 44% Class III, 36% Class IV, and 8% Class V. %EGR1glo showed correlations with SLEDAI, eGFR and UPE level (rho = 0.419, 0.358, and 0.45; P = 0.003, 0.018, and <0.001, respectively). In the histological analysis, %EGR1glo was significantly higher in Class IV than in the other classes (vs Class I + II, P <0.001; vs Class III, P <0.001; and vs Class V, P = 0.004). %EGR1glo correlated with %Endo and %Cres (rho = 0.566 and 0.580; P <0.001 and <0.001, respectively), but not with %GS or tubulointerstitial damage.

Conclusions: EGR1 expression in podocytes was associated with the activity of LN, especially with acute lesions.

Funding: Government Support - Non-U.S.

TH-PO754

Podocyte Injury Induces Rapid Collagen Degradation Within Mesangial Cells

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Background: Glomerulosclerosis, characterized by accumulation of extracellular matrix (ECM) proteins, is primarily caused by podocyte injury. In our investigation of a mouse model of podocyte injury, we frequently observed mesangiolysis in sclerotic glomeruli. Our hypothesis is that mesangial collagen undergo degradation subsequent to podocyte injury. This study aimed to characterize the process of collagen degradation following podocyte injury.

Methods: Podocyte injury was induced in transgenic mice expressing hCD25 in podocytes through the injection of hCD25-directed immunotoxin, LMB2. Denatured collagen was visualized using Collagen hybridizing peptide (CHP), a specific binder of unfolded collagen chains, and imaged with LSM880. Collagenolytic activities was assessed by quenched fluorogenic DQ-Gelatin or DQ-Collagen IV. CHP staining was intensified in glomeruli seven days after the induction of podocyte injury preceding the establishment of sclerotic lesions. The intensity of glomerular CHP staining correlated with the severity of glomerular injury and was localized in mesangial cells labeled by Igta8. Notably, intense glomerular CHP staining was absent in decellularized sections, while hydroxyproline (HP) staining persisted (Figure). The primary CHP staining was partially co-localized with MEK1/2 or GAPDH, but not with LAMP1, a lysosome marker, or with ERp72, an ER marker, suggesting that CHP is present in the cytoplasm. Collagenolytic activity in glomeruli with podocyte injury was found to be elevated in parallel with CHP staining.

Conclusions: These findings indicate that podocyte injury triggers and promotes degradation of collagen and accumulation of denatured collagen within mesangial cells. Further investigation is required to elucidate the detailed process involved.

Funding: Government Support - Non-U.S.

Figure
Glomerular Diseases: Podocyte Biology - I

TH-PO755

The Mouse Nephrotoxic Serum (NTS) Model to Screen Novel Drugs for Reversal of Podocyte Injury


Background: Kidney podocyte drug targets are being studied for treatment of diabetic kidney disease (DKD) and chronic kidney disease (CKD), requiring screening models to test agents for efficacy testing. Nephrotoxic serum (NTS) causes nephritis driven by immune complex-mediated inflammation of the kidneys. Methods of induction vary widely: kidney immunogen used, source of antigen or pre-immunization, dose of NTS, and/or mouse strain. A new batch of commercially available NTS (Proเทค, San Antonio, TX) has been validated for rats but not mice. Characterization of this mouse model will facilitate rapid screening podocyte targeting agents for DKD/CKD.

Methods: An IV dose range of new Proเทค NTS was tested in four strains of mice. Female C57Bl/6 and DBA/1 mice were chosen for more testing. Kidney injury model induction was tested using single or multiple sequential daily NTS injections. Disease model severity was assessed measuring serum creatinine, BUN, urine albumin to creatinine ratio (UACR) and Luminex Kidney Injury Panels. Upon establishing mouse strain sensitivity to NTS, the effect of clinically approved standard of care agents lisinopril or losartan to preserve kidney function was assessed.

Results: One dose of new NTS did not replicate reported body weight effects in mice; small UACR effects were noted but less than published literature. In contrast, two or three daily NTS injections caused an increase serum creatinine, BUN and UACR, with sensitivity of DBA1 mice being greater than C57 mice. Comparing fold-increase in UACR to PBS control mice, two doses of NTS induced 6.8±1.7 and 149±64 fold-increases, and three doses of NTS induced 217±36 and 292±117 fold-increases, in C57 and DBA1 mice respectively. Lisinopril or losartan treatment were both able to attenuate the NTS-induced kidney injury by over 65%, as assessed by UACR changes, in either 2- or 3-dose NTS injury paradigms in DBA1 mice, with a concomitant improvement in tissue histopathology.

Conclusions: The new Proเทค NTS was validated for use in mice to generate a screening model for podocyte injury. The differential sensitivity of C57 vs DBA1 mice, and the ability to alter the disease severity in each model by modifying the NTS-injection protocol will permit tailoring the degree of injury relevant to the research question.

Funding: Commercial Support - Janssen Pharmaceutical Companies of J&J

TH-PO756

Nucleophosmin Translocation Detects Early Podocyte Injury

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Background: Podocyte loss is common in diverse glomerular diseases. However, the lack of injury markers limits elucidation of the pathophysiologic processes that cause podocyte loss. Nucleophosmin (NPM) mediates regulated kidney cell death, and its translocation from the nucleus to the cytosol is an early marker and trigger of ischemic injury in tubular epithelial cells. Based on these observations, we tested the hypothesis that NPM translocation reflects podocyte injury. In our preliminary study, we detected NPM translocation as a novel marker of podocyte injury in cell injury models, and in human glomerular disease.

Methods: In vitro, podocytes were exposed to diverse insults known to injure podocytes including oxidative stress, adriamycin, and hyper-osmolarity. NPM translocation was evaluated by immunofluorescence and immunoblotting of cytosolic podocyte extracts. To assess NPM translocation in humans, kidney biopsy tissue from diabetic nephropathy patients was stained for NPM and established podocyte markers.

Results: NPM translocation was detected in cultured podocytes after oxidative stress, or exposure to either adriamycin, or hyper-osmolarity (Figure 1). Podocyte NPM translocation was also observed in patients with established diabetic kidney disease (Figure 2).

Conclusions: NPM translocation reflects acute podocyte injury in vitro and podocyte injury in diabetic glomerulopathy. Regulated cell death mediated by NPM may be a primary pathologic mechanism of podocyte loss. NPM is also a rational therapeutic target in glomerular diseases to reduce the dropout of the limited number of podocytes residing in the human kidney.

TH-PO775

Targeting Membrane Lipid Peroxidation Rescues Podocyte Dysfunction in Cystinosis

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Background: Cystinosis is a rare, incurable, autosomal recessive lysosomal storage disease caused by mutations in the CTNS gene and leading to lysosomal cystine accumulation in all cells of the body. While cystinosis is considered as a prototype of proximal tubular dysfunction, the disease also affects glomerular podocytes and presents with increased podocyte losses into urine and glomerular proteinuria at early disease stages. Cysteamine, the current standard of care treatment, decreases lysosomal cystine accumulation but does not reverse podocyte injury. Thus, we aimed at investigating other pathogenic mechanisms than mere cystine accumulation involved in glomerular dysfunction in cystinosis.

Methods: Immortalized cystinosis patient-derived podocytes, healthy podocytes and CTNS knockdown podocytes were used and the results were validated in our newly in-house developed fluorescent ctnszebrafish larvae model (I-fabh:DBP-eGFP;CTNS). To understand the impaired podocyte functionality, static and dynamic permeability assay, tracer metabolomics analysis (LC-MS), flow cytometry, RT-qPCR, western blot, chemical and dynamic roGFP2 redox-sensing fluorescent probes were used.

Results: Cystinosis podocytes present decreased adhesion, increased permeability and enhanced ferroptosis cell death caused by an accumulation of mitochondrial ROS-driven lipid membrane peroxides. Moreover, these cells show fragmented mitochondrial network with impaired energy and TCA cycle metabolism and decreased expression of superoxide scavenging enzyme SOD2. Targeting mitochondrial ROS with MitoTEMPO in combination with cysteamine or lipid peroxidation with Liproxstatin-1 improved podocytes dysfunction in vitro and rescued proteinuria in cystinosis zebrafish larvae.

Conclusions: Mitochondrial dysfunction leading to increased ROS production and subsequent lipid peroxidation drive podocyte detachment and ferroptosis and plays a key role in podocyte injury in cystinosis. Targeting these mechanisms represents a new therapeutic perspective for nephropathic cystinosis.

TH-PO758

Exploring the Pathogenicity of an Anillin Coding Variant in Proteinuric Kidney Disease

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Background: Mutations in slit diaphragm proteins and regulators of actin dynamics are implicated in the pathogenesis of proteinic kidney disease (proKD). Coding variants of Anillin (ANLN), a scaffolding protein found at slit diaphragms, have been associated with FSGS, but mechanisms are unknown. The aim of this study is to investigate the pathogenicity of ANLN coding variants identified in individuals with proKD.

Methods: Expression of ANLN relative to proteinuria was assessed in bulkRNAseq profiles of microdissected kidney tissues from NEPTUNE (n=238 glom, n=316 tub) and living donor (n=8, 10) cohorts. WGS data in NEPTUNE (n=620) were interrogated for ANLN coding variants; allele frequencies were compared to gnomeAD. Kidney organoids
A Modular Intracellular Hierarchical-Responsive Nanocarrier Enables Dual Targeting for High Therapeutic Efficacy in Kidney Diseases
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**Background:** Single-drug nanocarriers that can improve targeting capability and reduce drug toxicity compared with free drugs demonstrate a promising strategy for disease treatment. However, due to cell heterogeneity during disease progression, dosing heterogeneity, drug resistance, and instability of nanocarriers in the blood circulation, achieving dual targeting of different injured cell subsets while reducing drug dosage and maintaining treatment efficacy remains challenging. In addition, developing nanocarriers is a complex and time-consuming process; there is a desire for a universal nanocarrier for various diseases, especially complex diseases. Here, we have successfully designed a modular nanocarrier capable of delivering drugs with a reduced effective dosage of one-tenth that of single-drug nanocarriers.

**Methods:** The dual-drug targeting nanoparticles consist of three main modules: a PEG nanosphere, an antibody, and two drugs. We first construct a non-targeted PEG nanoparticle encapsulating drug A. Then, the podocyte-specific antibody Nephrin was modified onto the nanoparticle surface. Finally, drug B was coupled to the antibody. The dual-targeting dual-drug nanoparticles were injected into mice to evaluate their toxicity compared with free drugs. We explored the targeting of the nanoparticles using organ imaging and other methods. We established three kidney disease models in mice to compare the effects of dual-targeting nanoparticles at different concentrations.

**Results:** Dual-targeting nanoparticles loaded with different drugs demonstrated dual targeting of glomeruli and tubules. To treat acute kidney injury, we utilized the independence of dual targeting of injured cell subsets while reducing drug dosage and maintaining treatment efficacy. We observed reduced tubular injury in the acute kidney injury model, recovered podocyte foot processes in the PAN model, and reduced cancer foci in the ccRCC model. These results show that dual-drug-loaded nanomaterials have an excellent ability to address complex disease presentations.

**Conclusions:** The dual-drug delivery system can flexibly adapt to treating various diseases by modifying the particle size, surface antibodies, and drugs.

**Funding:** Clinical Revenue Support

**TH-PO760**

Oxysterol-Binding Protein-Like 7 Deficiency in CKD
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**Background:** OSBP7Ps have been implicated in various processes such as cholesterol transfer from the endoplasmic reticulum to the Golgi, and cholesterol efflux. Previous studies have shown that OSBP7L deficiency leads to decreased autophagy in other cell types, which may impact lipid trafficking and podocyte function. The purpose of this study was to investigate OSBP7L in podocytes as a potential therapeutic target in podocyte disease and its potential as a therapeutic target. OSBP7L’s involvement in autophagy and endoplasmic reticulum stress suggests that its deficiency may contribute to the development of CKD.

**Methods:** The study utilized immortalized mouse podocytes and a Tet[fl-fmD: DBP:eGFP]zebrafish model to investigate the effects of OSBP7L deficiency on the development and progression of podocyte disease and measure the effect of OSBP7L on glomerular filtration. We determined OSBP7L protein levels in metabolic and non-metabolic mouse models of CKD using western blot. OSBP7L deficient podocytes and zebrafish were generated and the impact of OSBP7L deficiency on ER stress markers, autophagy, and morphological changes was analyzed.

**Results:** The results show that OSBP7L protein levels were reduced in the renal cortex of metabolic and non-metabolic mouse models of CKD. OSBP7L deficiency leads to an increase in apoptosis levels and ER stress markers in podocytes and a decrease in autophagic flux. Additionally, an increase in lipid droplet levels is observed in OSBP7L deficient podocytes, but this increase was found to be cholesterol independent. Knocking down OSBP7L expression in Tg[fl-fmD: DBP:eGFP]zebrafish leads to increased proteinuria and a slight edema phenotype. The findings suggest that OSBP7L plays a role in regulating autophagy and ER stress in podocytes and contributes to the progression of CKD.

**Conclusions:** OSBP7L is important for maintaining podocyte homeostasis and its potential as a therapeutic target in CKD. The results indicate that OSBP7L deficiency may contribute to the development of podocyte disease and its potential as a therapeutic target in CKD. The results indicate that OSBP7L deficiency may lead to lipid accumulation inside the podocyte and contribute to the progression of CKD.

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

**TH-PO761**

Steroid-Dependent Minimal Change Disease in an Adult Responsive to Rituximab
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**Introduction:** The patient is a 30M diagnosed at age 27 with minimal change disease. His clinical course was complicated by multiple relapses following an initial treatment with full dose steroids (60mg per day) per clinical guidelines. He ultimately progressed to steroid dependent disease. Consequently, the patient was prescribed Rituximab, which he received a clinical and serologic response, with almost full remission of proteinuria. However, after steroids were tapered off, the patient suffered three more relapses of his minimal change disease over the course of the ensuing fourteen months. After the last relapse, steroids were unable to be weaned (remained on 5 mg PO daily). A CT scan of the chest returned unremarkable for lymphadenopathy or any findings suspicious for lymphoma. The patient sought a second opinion with a nephrologist at Westchester Medical Center. Upon initial evaluation in November 2020, urine protein to creatinine ratio was elevated. The patient had a history of steroid dependent disease in 2019, and he was treated with a course of full dose steroids by his primary nephrologist. After steroids were tapered, the patient's proteinuria increased to 10mg PO daily prior to the appointment. Creatinine 0.86 and UPCR 4mg/g. Once again, he was started on full dose steroids for treatment, with subsequent improvement in proteinuria. However, by April 2022, the patient once again ended lower extremity swelling and forty pound weight gain. The patient had increased his dose of prednisone to 10mg PO daily prior to the appointment. Creatinine 0.86 and UPCR 4mg/g. Once again, he was started on full dose steroids for treatment, with subsequent improvement in proteinuria. However, by April 2022, the patient's creatinine was 1.1 and UPCR 0.04mg/g.

**Discussion:** Minimal change disease is a rare clinical entity in adult patients. The patient presented is a unique case presented with relapsing minimal change disease (confirmed by two separate biopsies) that ultimately became steroid dependent. This case provides an example of successful response to Rituximab as an alternate agent for minimal change disease in treatment resistant patients.

**TH-PO762**

Uncovering the Role of Cyclic G-Associated Kinase (GAK) in Regulating the Podocyte Cytoskeleton
Patricia Bunda, Xuexei Tian, Kazunori Inoue, Shuta Ishibe. Yale University, New Haven, CT.

**Background:** Podocytes are terminally differentiated epithelial cells that are integral components of the glomerular filtration barrier (GFB). These cells have specialized interdigitating structures called foot processes, characterized by a complex network of actin filaments. Damage to podocytes leads to cytoskeletal reorganization and morphological changes, which ultimately result to foot process effacement and disruption of the GFB. In 2020, our group previously identified subsets of chronic kidney disease (CKD) patients, with significantly reduced expression of cyclic G- associated kinase (GAK).

**Methods:** We subsequently generated a podocyte specific Gak knockout mouse (Gakflfl Pod-Cre-Dmo) mice, which developed foot process effacement, progressive proteinuria, and profound glomerulosclerosis. To further interrogate the role of GAK in podocytes, we utilized a mouse model, which enables transgenic expression of a truncated GAK protein consisting only of the 62-kDa C-terminus end (Gak-C62−/−). We then generated the C62/Gak KO mouse model by crossing the Gak-C62−/− mice to our podocyte specific Gak KO mouse.

**Results:** Interestingly, our preliminary data showed that the C62/Gak KO mice rescued the proteinuria and glomerulosclerosis phenotypes, and podocyte foot processes were also maintained, suggesting a novel role of the C-terminal domain of GAK in maintaining podocyte morphology and function.

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

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podocytes. This morphological change in vitro was again rescued in podocytes isolated from the C2G-Gal KO mouse. To elucidate the mechanism of rescue, we also performed a co-immunoprecipitation combined with shotgun proteomics experiment to identify potential binding partners of the C-terminal end of GAK. Remarkably, our results suggest a novel interaction between GAK and lymphocyte-specific protein 1 (LSP1), a known actin-binding protein that regulates the podocyte foot process.

Conclusions: Together, these results further support the integral role of GAK, specifically its 62-kDa C-terminal residue, in regulating podocyte foot processes and podocyte dysfunction.

Funding: NIDDK Support

TH-PO763

Soluble CD93 Contributes to Podocyte Activation in Minimal Change Disease

Cologne, Germany

Background: Minimal Change Disease (MCD) is considered a podocytopathy, but subtle endothelial injury may also be present. CD93, a protein primarily expressed in endothelium, mediates focal adhesion kinase (FAK) activation in endothelium and can be shed during inflammation. We tested the hypothesis that glomerular endothelium releases CD93 in response to podocyte activation, and that CD93 is detectable in MCD.

Methods: We tested for CD93 in human kidney tissue (immunofluorescence), urine, and sera (ELISA) from 27, 57 and 48 children, respectively, with MCD during relapse. Patients without glomerular disease served as controls (n=9 for kidney tissue, n=19 for soluble CD93). We cultured human glomerular endothelial cells (HGEC) with human sera and measured CD93 (extracellular domain) in cell lysates by western blot. Additionally, we exposed HGEC to human sera and, following washing steps, we measured CD93 (ELISA) in serum-free supernatants. By co-immunoprecipitation, we studied CD93 and podocyte FAK (pFAK) integrin interaction. Human podocytes were also treated with recombinant CD93 (rCD93) and human sera, with β1 integrin (Mab13) and CD93 blocking antibodies, respectively, and we assessed FAK activation by western blotting.

Results: Compared to controls, CD93 expression was higher in MCD glomeruli and colocalized with endothelium (p<0.0001). Soluble CD93 was higher in urine (~10-fold) and serum (~1.5 fold) from MCD patients in relapse compared to controls (p<0.0001 for both). MCD sera in replate stimulated cultured human GEC to release CD93. CD93 was higher in supernatants and lower in cell lysates from GEC previously exposed to MCD sera in culture. pFAK activation compared to controls (p<0.01). CD93 bound to podocyte β1 integrin and replate FAK activation (Figure 1a, p<0.05 at 6 hours). MCD sera in relapse caused podocyte FAK activation, which was mitigated by adding a CD93 antibody to sera (Figure 1b, p=0.01).

Conclusions: MCD sera trigger the release of soluble CD93 from GEC and this, in turn, contributes to podocyte activation.

Funding: Private Foundation Support

TH-PO764

The Direct Effect of Mycophenolate Mofetil on Podocytes in Nephrotic Syndrome

Cologne, Germany

Background: Mycophenolate mofetil (MMF) is applied in proteinuric kidney disease. Recently, MMF contributes to improvement of Ca2+ levels and amelioration of the disorganized actin cytoskeleton in podocytes. These data extend the knowledge of direct effects of immunosuppressants on podocytes that may contribute to a more effective treatment of proteinuric glomerulopathies with the least possible side effects.

Conclusions: Here, we provide evidence that MMF has a substantial direct effect on podocytes, including the amelioration of the disorganized actin cytoskeleton in podocytes. This finding has broad implications for the use of MMF, as it suggests a potential mechanism by which this drug may reduce proteinuria.
TH-PO767

MHC Class I Molecules and Dendrin Are Upregulated in Primary FSGS Podocytes
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Background: The pathophysiology of primary focal segmental glomerulosclerosis (FSGS) is incompletely understood, and differentiation between FSGS subtypes remains challenging. We used single-cell transcriptomics to identify new pathways that are specifically deranged in primary FSGS podocytes.

Methods: We performed single-nucleus RNA-seq (10x Genomics Chromium) on cryopreserved kidney biopsy cores from patients with primary FSGS (n=9, all nephrotic, maladaptive FSGS (n=9, none nephrotic), proteinuric plasmin (PLA2R)-positive membranous nephropathy, n=3), and healthy controls (pre-perfusion biopsies, n=4).

Results: We identified 194,594 nuclei, of which 3,660 were podocytes expressing canonical marker genes (Figure 1A). Differential gene expression analysis between primary FSGS podocytes (n=1,635 nuclei) and all other podocytes (n=2,025 nuclei) showed significant upregulation of genes encoding major histocompatibility complex (MHC) class I proteins (HLA-A, HLA-B, HLA-C, and HLA-E) and dendrin (DIN) (Figure 1B-C). Overexpression of MHC class I molecules has previously been observed in autoimmune diseases such as diabetes mellitus. We hypothesize that presentation of self-antigens in primary FSGS podocytes via MHC class I proteins may either be an initiating event, triggering production of a pathogenic permeability factor, or alternatively an adaptive response to earlier podocyte injury. Dendrin, which interacts with slit diaphragm proteins, translocates to the nucleus in injured podocytes, triggering apoptosis in mouse models of FSGS, thereby making it a promising new target in human primary FSGS.

Conclusions: MHC class I molecules and dendrin represent two novel differentially expressed pathways that could aid in further distinguishing different FSGS subtypes.


TH-PO768

Shear Stress on Podocyte Foot Processes Arising from Flow in Filtration Slits Studied by Numerical Flow Simulations
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Background: The glomerular filtration barrier is exposed to flow dynamic forces arising from filtration pressure (tensile stress) and filtration flow (shear stress). Filtrate flow acts on podocyte cell bodies in Bowman’s space and on foot processes (FPs) lining the filtration slit. Besides the filtration slit, the corresponding filtration parameters of the rat kidney. The filtration unit consists of fenestrated endothelium, the GBM, and two opposing halves of FPs bridged by the slit diaphragm (SD). The GBM and SD were regarded as porous media.

Methods: We used numerical flow simulations to study forces arising from glomerular filtration. Simulations were run with a realistic model of a filtration unit and the corresponding filtration parameters of the rat kidney. The filtration unit consists of fenestrated endothelium, the GBM, and two opposing halves of FPs bridged by the slit diaphragm (SD). The GBM and SD were regarded as porous media.

Results: Modeling the GBM and SD as one homogeneous porous medium, a peak wall shear stress of 6.2 Pa on FPs in the filtration slit was found; pressure dropped by 2.5 mm Hg across the SD. Increasing filtration slit width from 30 to 40 mm reduced peak wall shear stress by only 9% to 59.4 Pa. Modeling GBM and SD as two separate homogeneous porous media with an increased viscous resistance of the SD further increased the pressure drop across the SD, but also wall shear stress on FPs. Two factors were revealed: (a) that may account for the high levels of wall shear stress: 1) convergence of filtrate flow out of the GBM into the filtration slit (similar to a nozzle), 2) transition from a porous medium (GBM, SD) with a rather uniform velocity profile into free flow (Bowman’s space) with a developing parabolic velocity profile.

Conclusions: Our data demonstrate that FPs are likely to experience high levels of wall shear stress in the filtration slit that markedly exceed levels of endothelial wall shear stress. Shear stress on FPs represents the only flow dynamic force that directly tends to disconnect viable podocytes from the GBM—a hallmark of podocyte loss in many glomerular diseases.

Funding: Government Support - Non-U.S.

TH-PO769

YAP and TAZ in Podocytes: Twins Distinguished by Single-Nucleus Transcriptomic Analysis
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Background: Podocyte homeostasis and the maintenance of the filtration barrier relies on the balanced activity of YAP and TAZ, the two effectors of the Hippo signaling pathway. Previous studies showed an increase of YAP and TAZ during glomerular disease. Additionally, specific deletion of YAP and TAZ in adult podocytes increases susceptibility to induced injury, suggesting a protective role. However, the exact molecular mechanisms underlying these observations remain unclear. Here, we investigate the individual roles of YAP and TAZ in podocytes in vivo.

Methods: We generated generic mouse models in which YAP, TAZ, or both were knocked out specifically in podocytes (pKO). The mice were deeply characterized including kidney function, slit diaphragm morphology and survival. To gain insights into pathomechanisms leading to podocyte disease and to differentiate processes unique for YAP and TAZ, we performed single-nucleus RNA Sequencing (snRNASeq) of isolated glomeruli of mice of different ages and stages of disease.

Results: YAP pKO mice present a heterogenous disease onset until 12 weeks old, with a phenotype resembling focal segmental glomerulosclerosis (FSGS) with proteinuria and reduced slit diaphragm length. TAZ pKO mice displayed a tendency towards a reduced slit diaphragm length without developing proteinuria. Notably, when breeding mice to obtain both YAP and TAZ knockout alleles, no viable offspring was produced with less than two of the four YAP/TAZ alleles, suggesting compensational mechanisms. Immunostainings supported this hypothesis. The snRNASeq analysis revealed similar patterns in YAP and TAZ pKO mice, further confirming their overlapping functions.

Subsequent cell communication network analysis provided first evidence on disturbed signaling pathways that could contribute to the phenotypic differences observed between YAP and TAZ pKO mice.

Conclusions: While YAP and TAZ have a high level of similarity and are considered homologous twins, their roles in podocytes are distinct, as only the specific deletion of YAP leads to FSGS. Strikingly, combined YAP/TAZ activity above a certain threshold is indispensable for podocyte homeostasis, as the combined knockout is not viable. With this study we merely applied snRNASeq unique and compensatory functions of YAP and TAZ in podocyte homeostasis and injury.

TH-PO770

Multi-Ethnic Genome-Wide Association Study (GWAS) for Idiopathic Nephrotic Syndrome Identifies Susceptibility Loci Across the Life Span, Response to Therapy, and Genetic Ancestry
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Background: Large-scale genetic association studies for idiopathic nephrotic syndrome cause by focal segmental glomerulosclerosis and minimal change disease are lacking, especially for forms of disease that are unresponsive to immunosuppressive treatments. To address this knowledge gap, we conducted a large-scale genome-wide association study (GWAS) for common variants with paired exome sequencing. GWAS was conducted first on the entire cohort and then in subgroups based on age of onset, ancestry, and response to therapy. Analyses were conducted again after removal of cases harboring diagnostic/response to induced injury, suggesting a protective role. However, the exact molecular mechanisms underlying these observations remain unclear. Here, we investigate the individual roles of YAP and TAZ in podocytes in vivo.

Methods: We generated generic mouse models in which YAP, TAZ, or both were knocked out specifically in podocytes (pKO). The mice were deeply characterized including kidney function, slit diaphragm morphology and survival. To gain insights into pathomechanisms leading to podocyte disease and to differentiate processes unique for YAP and TAZ, we performed single-nucleus RNA Sequencing (snRNASeq) of isolated glomeruli of mice of different ages and stages of disease.

Results: YAP pKO mice present a heterogeneous disease onset until 12 weeks old, with a phenotype resembling focal segmental glomerulosclerosis (FSGS) with proteinuria and reduced slit diaphragm length. TAZ pKO mice displayed a tendency towards a reduced slit diaphragm length without developing proteinuria. Notably, when breeding mice to obtain both YAP and TAZ knockout alleles, no viable offspring was produced with less than two of the four YAP/TAZ alleles, suggesting compensational mechanisms. Immunostainings supported this hypothesis. The snRNASeq analysis revealed similar patterns in YAP and TAZ pKO mice, further confirming their overlapping functions.

Subsequent cell communication network analysis provided first evidence on disturbed signaling pathways that could contribute to the phenotypic differences observed between YAP and TAZ pKO mice.

Conclusions: While YAP and TAZ have a high level of similarity and are considered homologous twins, their roles in podocytes are distinct, as only the specific deletion of YAP leads to FSGS. Strikingly, combined YAP/TAZ activity above a certain threshold is indispensable for podocyte homeostasis, as the combined knockout is not viable. With this study we merely applied snRNASeq unique and compensatory functions of YAP and TAZ in podocyte homeostasis and injury.


FSGS and APOL1 HR genotypes, the strength for association to chromosome 4 increased and a total of 15 reached genome-wide significance (ADAMTS1; OR=1.53, P=2.73 x 10^{-5}). Ancestry-specific and sub-phenotype analyses according to the age at onset and response to glucocorticoid treatment resulted in validation and replication of loci for SSNS (e.g. CALHM1, CLEC4A), and several novel HLA loci (for adult-onset and non-Mendelian SSNS).

Conclusions: Interim results demonstrate multiple novel loci for INS, including pleiotropic risk alleles that predispose to NS across different sub-phenotypes, and loci specific to ancestry, age of onset, and response to therapy.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO771

Regulation of Podocyte Adhesion by SEL1L-HRD1 ERAD via Integrin Xiaojing Wei, You Lu, Ling Qi. University of Michigan, Ann Arbor, MI.

Background: Podocytes are specialized epithelial cells crucial for the kidney glomerular filtration barrier. They form interdigitating foot processes with neighboring podocytes in the kidney glomerulus to filter the blood. Adhesion of podocytes to glomerular basement membrane (GBM) is key to the formation of foot process and filtration function. Impairment of this process causes podocyte detachment, proteinuria and glomerulosclerosis in humans. While homeostasis in the endoplasmic reticulum (ER) has been generally recognized as important for cellular function, our understanding of ER homeostasis in podocytes remains unclear. Endoplasmic reticulum-associated degradation (ERAD) is the primary mechanism for the clearance of misfolded ER proteins by cytosolic proteosomal degradation. The SEL1L-HRD1 protein complex represents the most conserved ERAD pathway. However, the role of SEL1L-HRD1 ERAD in podocyte function remains poorly understood.

Methods: The podocyte-specific SEL1L-deficient mice were generated. Mouse body weight and survival curve were recorded. Urine samples from mice at 1, 3, and 5 weeks of age were collected to assess the abundance of albumin and WT1. Kidneys from wild-type (WT) and SEL1L-deficient mice were collected for ultrastructure observation by scanning electron microscopy (SEM) and transmission electron microscopy (TEM), the abundance and cellular location of the integrin subunit ITGA3 by immunofluorescence staining and western blot.

Results: Compared with WT mice, SEL1L-deficient mice showed lower body weight and premature renal failure with a median lifespan of 14 weeks. More albumin and detached podocytes were observed in SEL1L-deficient mice. Moreover, SEL1L-deficient mice showed damaged glomeruli and severe foot process effacement based on SEM and TEM. In terms of molecular mechanism, ITGA3, an important podocyte adhesion receptor, was accumulated in the ER, not exit to podocyte membrane, in the absence of SEL1L-ERAD.

Conclusions: Our data demonstrate SEL1L-ERAD regulates podocyte attachment on the glomerular basement membrane via degrading misfolded integrin subunit, ITGA3.

Funding: NIDDK Support, Private Foundation Support

TH-PO772

Identification of Circular Dorsal Ruffles as Signal Platforms for the AKT Pathway in Glomerular Podocytes Sei Yoshida. Nankai University, Tianjin, China.

Background: Circular dorsal ruffles (CDRs) are rounded membrane ruffles induced by growth factors to function as precursors of the large-scale endocytosis called macropinocytosis. In addition to their role in cellular uptake, recent research using cell line systems has shown that CDRs/macropinosomes regulate the canonical AKT/mTORC1 growth factor signaling pathway. However, as CDRs have not been observed in tissues, their physiological relevance has remained unclear. Here, we first report that CDRs are expressed in glomerular podocytes ex vivo and in vivo, and we visually captured the transformation process to macropinocytosis.

Methods: Ultra-high resolution scanning electron microscopy (SEM) and confocal microscopy were used to confirm if CDRs are expressed at the surface of mouse glomeruli and isolated glomeruli. Podocyte cell line MPC5 was used for further imaging analysis as well as biochemical assays to test if CDRs regulate the AKT pathway.

Results: High-resolution SEM of mouse kidney tissue showed that glomerular podocytes displayed CDR-like structures in vivo (Fig. 1A, arrows). In total, 21 glomeruli from five mice were examined using SEM. CDR-like structures formed in 25.38% of the podocytes (n=528). Moreover, epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) induced CDRs in MPC5 cells. Inhibition of CDRs significantly mitigated GF-induced AKT phosphorylation and attenuated mTORC1 activation in cells. Confocal microscopy showed that AKT signaling components localized to CDRs. Importantly, we utilized isolated mouse glomeruli for ex vivo experiments and found that podocytes express CDRs as macropinocytic cups after EGF stimulation (Fig. 1B, arrows), regulating the AKT pathway.

Conclusions: Our results demonstrate the physiological role of CDRs as signal platforms for the AKT/mTORC1 pathway in podocytes at the tissue level. As mTORC1 plays critical roles in podocyte metabolism and aberrant activation of mTORC1 triggers podocyte detachments, the outputs from this study strongly suggest that targeting CDR formation could represent a potential therapeutic approach for these diseases.

Funding: Government Support - Non-U.S.

TH-PO773

Dual Deletion of Guanylyl Cyclase-A and p38 Mitogen-Activated Protein Kinase (MAPK) in Podocytes with Aldosterone Administration Causes Glomerular Intra capsular Thrombosis Sayaka Suzio,1 Hiroyuki Yamada,2 Akira Ishii,1 Yukiko Kato,1 Ryo Yamada,1 Keita P. Mori,1 Shoko Ohno,1 Takaya Handa,1 Akiie Ikushima,1 Takuya Ishimura,1 Taji Matsusaka,1 Motoko Yanagita,1 Hideki Yokoi,1 1Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 2Department of Primary Care & Emergency Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 3Department of Molecular Life Sciences, Tokai University School of Medicine, Isehara, Japan.

Background: Previously, we demonstrated that podocyte-specific guanylyl cyclase-A (GC-A; natriuretic peptide receptor 1; NPR1) conditional KO (pod-GC-A cKO) mice with aldosterone exhibit podocyte injury, and that pharmacological inhibition of p38 MAPK ameliorates it. However, the effects of genetic deletion of p38 MAPK in podocytes have been unknown.

Methods: We generated podocyte-specific p38 MAPK and GC-A double KO (pod-GC-A cKO) mice, and tested them with aldosterone and high salt without nephrinopathy (B-ALDO). Next, we focused on PAI-1 (SERPINE1) and administered PAI-1 neutralizing antibody to pod-double cKO mice. In vitro, we examined how podocytes in which p38 MAPK was deleted by CRISPR/Cas9 system and GC-A was suppressed by sirNA. Then, we cultured human p38 MAPK-null podocytes transfected with si-NPR1 in the upper layer and wild-type glomerular endothelial cells (GE) in the lower layer, with PAI-1 inhibitor in the transwells.

Results: Unexpectedly, B-ALDO-treated pod-double cKO mice resulted in elevation of serum Cr, massive albuminuria and severe foot process effacement in addition to intracapillary fibrin thrombi indicating endothelial damage. PAI-1 was increased in podocytes and treatment with PAI-1 neutralizing antibody ameliorated intracapillary thrombus formation in B-ALDO-treated pod-double cKO mice. In vitro, knockout of p38 MAPK and suppression of GC-A in human cultured podocytes upregulated SERPINE1, TGFβ1, and FN1. Deletion of p38 MAPK and inhibition of GC-A in podocytes in the upper layer upregulated TGFβ1 in the GE in the lower layer, indicating that some humoral factors derived from podocytes could work as cell-to-cell mediators. The treatment with PAI-1 inhibitor decreased TGFβ1 in both podocytes and GE.

Conclusions: Podocyte-specific deletion of p38 MAPK and GC-A exacerbated glomerular endothelial cell injury as well as podocyte damage which was ameliorated by PAI-1 neutralizing antibody. PAI-1 in podocytes is one factor that disrupts the podocyte-endothelial crosstalk, suggesting that p38 MAPK and GC-A play indispensable roles in podocytes.

TH-PO774

Podocyte Infolding Glomerulopathy: Insights from Proteomics by Laser Microdissection and Mass Spectrometry Ling Hong,1 Zhihua Zheng,1 Wenfang Chen.2 The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, China; 2The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China.

Background: Podocyte infolding glomerulopathy (PIG) is a newly recognized rare glomerular injury. The potential mechanism of this injury pattern remains unclear.

Methods: 10 cases diagnosed with PIG and 5 minimal change disease (MCD). 4 donor kidney biopsy specimens at Kingmed Diagnostics were analyzed by laser scanning microdissection and mass spectrometry (LMD/MS). The clinicopathological features, especially the ultrastructural changes were reviewed.

Results: 10 cases were divided into 2 groups according to immunofluorescence, IC-PIG group and non-IC-PIG group. The differentially expressed protein, α-actinin4 (ACTN4), was detected by LMD/MS in 10 PIG glomeruli (P=0.005) with 9 controls, among the top 20 proteins. The displacement of ACTN4 into the GBM was confirmed by the confocal microscope. Interestingly, Tubulin Beta-4 Chain (TUBB4A) was only detected in the isolate group.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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TH-PO775

Single-Cell Transcriptional Analysis Reveals the Effect of Anti-PLA2R and Anti-THSD7A Sera on Human Glomerular Cells

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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults due to the deposition of anti-podocyte antibodies in the glomerular subepithelial space. Several podocyte proteins have been identified as targets of these autoantibodies, with PLA2R and THSD7A being the most prominent. We investigated the specific effect of anti-PLA2R and anti-THSD7A on glomerular cells using single cell transcriptomics on a human glomerulus-on-a-chip (GOAC) system.

Methods: GOACs were generated using human primary podocytes and glomerular endothelial cells and cultured with human serum from MN patient with anti-PLA2R or anti-THSD7A antibodies for 72 hours. Sera from healthy individuals were used as a control. Samples from three different individuals were used for each group. Albumin leakage assay was performed on GOAC to confirm injury. Single cell RNA-seq analysis (scRNA-seq) was performed on cells retrieved from the GOAC. Downstream analyses were done using UMAP, gene and pathway enrichment, and intra- and inter-cluster comparative transcriptomics.

Results: Exposure to anti-PLA2R and anti-THSD7A sera from MN patients induced injury on the GOAC as confirmed by albumin leakage. scRNA-seq analysis showed robust activation of the complement pathway in both cohorts. Preliminary analysis also suggested activation of podocyte injury pathways with changes in genes involved in slit diaphragm formation being more prominent in cells exposed to anti-THSD7A sera vs the anti-PLA2R. At the same time, GEC displayed an enrichment in genes involved in proliferation and metabolic changes under both conditions compared to healthy sera, suggesting a broader effect of MN sera that extends beyond direct podocyte damage.

Conclusions: The combined use of the GOAC and transcriptomics allows to investigate molecular and transcriptional changes affecting podocytes and GEC when both exposed to MN sera. This approach can help unraveling glomerular mechanisms of injury in MN, thus providing potential new targets for the treatment of nephropathies and other glomerular diseases.

Funding: NIDDK Support

TH-PO776

Multi-Institutional Study of Anti-Nephrin Autoantibodies in Post-Transplant Focal Segmental Glomerulosclerosis Recurrence

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Background: Post-transplant recurrence of focal segmental glomerulosclerosis (fSGS) is a major challenge in kidney transplantation. Recently, we reported very early pathological changes in podocytes and possible roles of circulating anti-nephrin antibodies (abs) in a patient with fSGS (Hattori et al, Am J Transplant, 2022). To confirm these preliminary results, we performed a multi-institutional study.

Methods: 14 Japanese kidney transplant recipients with childhood-onset primary FSGS who had stored plasma samples and graft biopsy specimens were analyzed. All patients underwent whole exome sequencing and no pathogenic variants in FSGS-related genes were identified. Circulating anti-nephrin abs were measured by ELISA and the cut-off levels were defined as 231 U/mL, the maximum antibody levels among the controls (9 genetic FSGS patients, 13 membranous nephropathy patients, 4 lupus nephritis patients and 13 healthy controls). Dual immunofluorescence staining of nephrin and IgG or ShcA, an adaptor protein of phosphorylated nephrin, was performed using the structured illumination microscopy.

Results: There were 10 fSGS and 4 non-recurrent (non-fSGS) patients. In fSGS patients, median (interquartile range) anti-nephrin abs before transplant or during a post-transplant recurrence were markedly high at 950 (839, 1123) U/mL. Graft biopsies showed punctate IgG deposition co-localizing with nephrin that showed altered localization and increased expressions of ShcA. Eight of 10 fSGS patients achieved remission, and graft biopsies after remission showed normal nephrin expression and no signals for IgG and ShcA. Anti-nephrin abs decreased to 261 (121, 398) U/mL in 4 patients with available samples at remission. In non-fSGS patients, anti-nephrin abs were comparable with the controls regardless of the timing of sample collection. Their graft biopsies showed normal nephrin expression and no signals for IgG and ShcA.

Conclusions: Our results suggest that anti-nephrin abs are associated with fSGS via nephrin phosphorylation. Larger studies including other ethnicities are required to confirm this finding and to determine the prevalence and incidence of post-transplant FSGS recurrence associated with anti-nephrin abs.

Funding: Government Support - Non-U.S.
Identification of Novel Small Molecules for Podocytopathies Using a High-Throughput Screen for KLF15 Agonists

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Background: Krippel-Like Factor 15 (KLF15) is a glucocorticoid-responsive, zinc-finger transcription factor that is critical for maintenance of podocyte differentiation. Previous studies demonstrate that podocyte-specific induction of KLF15 attenuated kidney injury and improved overall survival in proteinuric murine models. Here, we developed a high-throughput screen (HTS) to identify novel KLF15 agonists for podocytopathies.

Methods: We developed a HTS using human podocytes expressing a dually reporter, firefly luciferase reporter directed at the KLF15 promoter and renilla luciferase, and tested the NCi1 small molecule library (2542 compounds). Hit-to-lead optimization was conducted using a Structure-Activity Relationship (SAR) study. Lead KLF15 agonists were tested in cultured human podocytes and the proteinuric murine models: LPS, Nephrotropic Serum (NTS) Nephritis, and HIV-1 transgenic (Tg26) mice.

Results: HTS assay exhibited high reproducibility with low variability (signal to background = 3.22 and a low Z-score = 0.56). We identified 16 hits with > 2.5-fold change in KLF15 reporter activity and an EC50 < 100nM. Based on cell viability and “lead likeness” of the hits, SAR study was conducted to synthesize novel leads with improved efficacy and low cell toxicity. The novel lead, BT503, demonstrated improved cell viability in cultured human podocytes and reduced proteinuria and podocyte effacement in mice treated with LPS. BT503 treatment in NTS and Tg26 mice also attenuated kidney injury (proteinuria, serum creatinine, urea nitrogen), podocyte and glomerular injury, and interstitial fibrosis. Concurrent treatment with BT503 in cultured human podocytes and mice also reduced the deoxanethasone dose required to restore podocyte injury. Subsequent RNA-sequencing, in-silico drug-docking studies, and western blot analysis in cultured podocytes demonstrate that the salutary effects of BT503 and induction of KLF15 are mediated through NF-kB signaling.

Conclusions: To date, this is the first study to develop a KLF15 HTS using human podocytes to identify and optimize novel small molecules, and subsequently demonstrate their therapeutic efficacy in cultured podocytes and proteinuric murine models with a mechanism of action.

Funding: NIDDK Support, Veterans Affairs Support

SGLT2 Inhibitor Suppresses Progression of Obesity-Related Nephropathy Induced by Podocyte Hypertrophic Stress

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Background: We recently reported that podocyte hypertrophic stress occurred relatively early during the onset of nephropathic progression in a rat model of type 2 diabetes-related nephropathy. In this study, we evaluated the progression of obesity-related nephropathy and podocyte hypertrophic stress and the efficacy of an SGLT2 inhibitor (SGLT2i) in obese rat models.

Methods: To investigate the ORN progression, we used 8-week-old Zucker fatty (ZF) rats exhibited non-diabetic obesity model (n = 6), and Zucker lean (ZL) rats as a control model (n = 6). Kidney biopsies and urine samples were collected at 16, 24, and 32 weeks of age. Next, to investigate the effect of an SGLT2i, ZF rats were divided into two groups (SGLT2i: n = 6, non-treated: n = 6); beginning at 12 weeks of age, both groups were fed the same amount of diet. From 24 weeks of age, the SGLT2i group received canagliflozin 10 mg/kg/day for 8 weeks. Kidney issues and urine samples were collected at 32 weeks of age. We measured urinary sediment podocin (U-sed pod) mRNA using qRT-PCR, glomerular volume (GV), podocyte volume (PV), and podocyte density (PD) to evaluate the podocyte injury.

Results: ZF rats were significantly heavier than ZL rats during the entire observation period. The urinary protein (UP) excretion level in ZF rats began to significantly increase at 16 weeks of age and became 20-fold greater than the level in ZL rats at 32 weeks of age. Significant increases in the GV, PV, and U-sed pod mRNA level, along with a decrease in PD, were observed in ZF rats from 16 to 32 weeks of age. Neither non-treated nor SGLT2i groups were hyperglycemic, and no changes in blood pressure occurred during the observation period. Compared with non-treated group, SGLT2i group exhibited significant weight loss, approximately 50% decrease in UP, significant reductions in the GV and PV, and increased PD (p < 0.01), and decreased U-sed pod mRNA (p < 0.01). SGLT2i group exhibited a significant increase in urinary sodium excretion (p < 0.01) and restored creatinine clearance to the level in control group.

Conclusions: Quantitative and morphological assessment of podocytes suggest that podocyte hypertrophic stress causes ORN progression. An SGLT2i may suppress podocyte hypertrophic stress by inhibiting glomerular hyperfiltration, and progression of ORN.

Funding: Government Support - Non-U.S.
TH-PO782
Exetimibe Restores the Communication Between Lipid Droplets and Mitochondria via Modulation of Plin5

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Background: Podocyte lipid accumulation contributes to glomerular diseases such as diabetic kidney disease (DKD) and Alport Syndrome (AS). These excess lipids, such as cholesterol and fatty acids, are esterified and stored as cholesterol ester and triglyceride in lipid droplets. Excessive FFA catabolism resulting from excessive lipolysis of TG is a major contributor to cell lipotoxicity. Perilipin 5 (PLIN5) is an LD-related protein that plays a critical role in regulating TG lipase activity and the interactions between LD and mitochondria, where it protects mitochondria from excessive exposure to FFA. Here we test the hypothesis that PLIN5 expresses in podocytes and that PLIN5 deficiency in AS causes excessive TG breakdown and the loss of LD-mitochondrial contact, thus contributing to kidney failure.

Methods: In vitro, Immortalized AS podocytes and WT podocytes were established and characterized in our laboratory by breeding the Col4a3KO mice (Jackson Laboratory) to H-2kb-Ata58 transgenic mice (Charles River). PLIN5 expression was determined by RT-PCR and western blot analysis in podocytes from Col4a3KO mice when compared to controls. TG lipolysis and FFA quantification were determined and normalized to protein content. LD-Mitochondrial contact was determined by TEM analysis. PLIN5 expression was studied in kidney cortexes, and the effect of Exetimibe on PLIN5 modulation, on LD-Mitochondrial contact, and on podocyte injury was studied in vitro and in vivo. 

Results: We demonstrate that PLIN5 is expressed in podocytes, and the expression of PLIN5 is significantly decreased in AS podocytes compared to WT podocytes (p<0.01). AS podocytes also showed significantly increased rates of TG lipolysis (p<0.05), intracellular free fatty acids (p<0.05), and apoptosis (p<0.01) when compared to WT podocytes. AS podocytes had a reduced number of LD-mitochondrial contacts (p<0.05), implying apoptosis. Moreover, Exetimibe, which restored LD-Mitochondrial contact in vitro (p<0.05) and improved kidney function in vivo, was found to restore PLIN5 expression in vitro and in vivo (p<0.05). Our findings suggest that podocyte PLIN5 deficiency causes podocyte injury in AS through excessive TG lipolysis and inefficient FA transfer from LD to mitochondria. Exetimibe improves LD-mitochondria communication by restoring PLIN5 expression.

Funding: NIDDK Support

TH-PO783
Expression Evaluation of TRPC6 and PODXL Genes in Podocyte Cell Culture After Albumin Overload with and Without Porciney-Aminoglycoside Damage

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Background: Proteinuria is a prognostic marker for kidney disease and one of the main symptoms of podocyteopathies. This study aimed to evaluate the relative expression of TRPC6 and PODXL genes with albumin overload in vitro.

Methods: Human podocyte cultures were exposed to progressive 0.3, 20 and 40 mg/mL of albumin for 24h with and with 15 µg/mL exposure to porcine aminoglycoside (PAN) for 12h. qPCR was performed with RPLP0 as endogenous control. The phenotype recovery was evaluated, either with gradual (removing 25% every 24h of total overload) or abrupt (removing all albumin in the first 24h) regeneration conditions. SDS-page and Western Blot were performed to evaluate protein expression. Statistical analysis was performed with ANOVA and Tukey’s a posteriori test (p<0.05) (n=5).

Results: The rate of PODXL gene transcript was higher than control in 40 mg/mL of albumin without PAN and in 0, 20 and 40 mg/mL of albumin with PAN (p<0.0001). Phenotype recovery was observed after gradual removal of albumin overload at 20 mg/mL with PAN. Similar results were observed for protein expression, both in progressive and regressive conditions (p<0.05). For TRPC6 gene, there was a decrease in expression after progressive albumin exposure with 3, 20 and 40 mg/mL without PAN (p<0.0001) and an increase expression in 20 and 40 mg/mL with PAN treatment (p<0.0001). Phenotype recovery was observed in gradual and abrupt regressive conditions.

Conclusions: When podocytes are injured, podocalyxin is released in vesicles that are excreted in the urine and used as an early glomerular disease biomarker. Therefore, we believe that this mechanism might explain why the phenotype was not recovered in the 40 mg/mL condition. Regarding TRPC6’s increased expression after PAN exposure, it might increase Ca2+ influx leading to apoptosis, aggravating podocyte damage after proteinuria insult.

Funding: Government Support - Non-U.S.

TH-PO784
Defects in CLVS1 Gene Increase Glycolytic Activity in Cultured Human Podocytes

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Background: Increased oxidative stress is a common feature of chronic kidney disease. We have shown that the homozygous H310Y variant in the gene encoding clavesin-1 (CLVS1) is a cause of steroid sensitive nephrotic syndrome and disrupts podocyte endocytosis as well as binding of clavesin-1 to an antioxidant transporter. Human podocyte cells lines with CLVS1 knockout (KO) and homozygous H310Y knockin (KI) displayed increased levels of reactive oxygen species (ROS) and apoptosis that could be rescued by treatment with corticosteroids as well as ROS inhibitors. However, the precise effects of CLVS1 deficiencies on the metabolic profile of podocytes is unknown.

Methods: To identify differences in podocyte metabolic function due to deficiencies in CLVS1, we used an Agilent Seahorse XF Analyzer to examine KI/ KO, homozygous CLVS1 H310Y KI, corticosteroid treated KI/ H310Y KI, and control podocytes. Assays designed to measure ATP production, mitochondrial respiration, and glycolysis were used to examine differences between cell groups (N=15 for each).

Results: CLVS1 KO and H310Y KI podocytes displayed a more energetic cell phenotype compared to controls that included a higher level of overall ATP production and increased glycolytic activity (p<0.0001 for each). An almost two-fold increase in glycolysis, glycolytic capacity and glycolytic reserves were observed in KO and KI podocytes compared to controls (p<0.0001 for each). These levels were unaffected by steroid treatment. Differences in mitochondrial respiration were relatively minimal between control and CLVS1 KO or KI podocytes. However, increases in non-glycolytic acidification and non-mitochondrial oxygen consumption were observed in KO and KI podocytes (p<0.0001 for each), suggesting that additional physiological abnormalities may be present as well.

Conclusions: Defects in CLVS1 increase glycolysis-mediated ATP production in podocytes. Glycolysis is a key component of podocyte metabolic activity, particularly in foot process regulation and elevated ROS levels can induce a shift towards increased glycolytic activity. However, further studies are required to determine if this altered metabolic activity contributes to podocyte dysfunction due to deficiencies in CLVS1 or if it is a survival response to other cellular abnormalities including increased ROS levels.

Funding: Other NIH Support - NICHHD

TH-PO785
Elucidation of the Molecular Mechanism of Albuminuria Improvement by Nonsteroidal Mineralocorticoid Receptor (MR) Antagonists Focusing on Podocyte Calcium (Ca2+) Dynamics

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Background: MR activation in podocytes has been linked to the progression of glomerular and podocyte injuries in diabetic kidney disease (DKD). In the FIDELIO-DKD study, non-steroidal MR inhibitors showed a significant reduction in the development of renal outcomes compared to placebo. However, there are still many unknown aspects regarding MR activation in DKD. Transient Receptor Potential Canonical (TRPC) channels in podocytes have been implicated in various kidney diseases, including hereditary nephrotic syndrome. We hypothesized that increased TRPC activity and expression due to MR activation in podocytes contribute to glomerular damage in DKD. We investigated the molecular mechanism of finerenone’s effect on improving albuminuria in DKD.

Methods: C57BL/6 mice (control) and diabetic Akita mice (Akita) were used in the study. Four groups were created: Control-Nx (Nx; one nephrectomized), Control-Nx+HS (high salt diet), Akita-Nx+HS, and Akita-Nx+HS+fineurone. The mice were sacrificed at 17 weeks of age, and specimens and tissues were analyzed. In vivo imaging using two-photon laser microscope was performed to confirm changes in albumin leakage from glomeruli. Additionally, cultured podocytes were used to assess the effect of aldosterone (Aldo) stimulation on TRPC5 expression, reactive oxygen species (ROS) production, Ca2+ influx, and actin rearrangement. Podocin-GCaMP5d/Tomato mice, which specifically express the calcium sensor protein GCaMP in podocytes, were used to study the effect of Aldo stimulation on Ca2+ influx.

Results: The Akita-Nx+HS group exhibited abnormal podocyte morphology and significantly increased albuminuria. Increased intraglomerular ROS production was observed along with clear changes in albumin leakage from glomeruli. In cultured podocytes, Aldo stimulation induced increased TRPC5 protein expression, ROS production, Ca2+ influx, and actin rearrangement. Similar Ca2+ influx was observed in Podocin-GCaMP5d/Tomato mice. These changes were ameliorated by MR and TRPC5 inhibitors.

Conclusions: The study demonstrated that MR activation in podocytes contributes to glomerular damage in DKD via increased TRPC5 expression and activity, and MR inhibitors like fineurone improve podocyte Ca2+ dynamics and reduce damage in DKD.

Funding: Commercial Support - Bayer
TH-PO786

Multidimensional Characterization of Renal Biopsies Integrating Podocyte Morphology with Clinical and Histopathological Features

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Background: Podocyte foot process effacement and loss of glomerular filtration slits are common pathological changes observed in many chronic kidney diseases (CKD). Accurate measurement of podocyte morphology requires electron microscopy or advanced super-resolution light microscopy. Here, we used three-dimensional-structured illumination microscopy (3D-SIM) to quantify glomerular filtration slits in residual diagnostic biopsies of the NURTURE CKD cohort. We integrated this measure of podocyte foot process morphology with other clinical and histopathological features to enable future precision diagnostics and patient stratification strategies.

Methods: Histological sections of formalin-fixed, paraffin-embedded kidney biopsies were stained for podocin and nephrin and analyzed using the 3D-SIM Podocyte Exact Morphology Measurement Procedure (PEMP). Filtration slit densities (FSD) and filtration slit lengths (FSL), which describe the density and extent of the glomerular filtration network, were derived from a median of 17 glomeruli per sample for 69 NURTURE CKD patients of various etiologies.

Results: The 3D-SIM investigation revealed different patterns of intra- and intersample variance with distinct, etiology-dependent distributions, likely reflecting common disease mechanisms. While samples from primary glomerular diseases showed a reduced median FSD and FSL with low intrasample variance, samples from secondary glomerular diseases displayed increased intrasample variance, suggesting distinct patterns of glomerular injury and disease progression. Moreover, podocyte morphology was strongly correlated with urinary protein and albumin creatinine ratios, but independent of other histopathological features, including glomerulosclerosis ratios and interstitial fibrosis and tubular atrophy scores.

Conclusions: Assessment of podocyte morphology in NURTURE kidney biopsies supports FSD and FSL as independent and precise histopathological estimators of foot process effacement and glomerular integrity, revealing etiology-specific features of disease. Further investigation of clinical time series and renal survival data, will uncover the potential of PEMP for kidney precision diagnostics and risk prediction.

Funding: Commercial Support - Evotec SE

TH-PO787

Role of Colony-Stimulating Factor-1 Receptor in Driving Parietal Epithelial Cell Activation in Focal Segmental Glomerulosclerosis

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Background: Parietal epithelial cells (PECs) are renal progenitor cells similar to bone marrow-derived mesenchymal stem cells (MSC). In focal segmental glomerulosclerosis (FSGS), activated PECs contribute to extracellular matrix deposition. Colony stimulating factor-1 (CSF-1), a hematopoietic growth factor, acts through its specific receptor, CSF-1R, and has been implicated in various glomerular diseases. However, its role in PEC activation is still unknown. In this study, we studied the CSF-1/CSF-1R pathway in dysfunctional activation of PECs in FSGS.

Methods: CSF-1R expression was assessed in FSGS patient biopsies and in adriamycin (ADR)-induced FSGS mouse model. ADR-induced animals were further treated with a recombinant CSF-1R inhibitor, GW2580 or KG2227 (n=5–7). CSF-1R expression, localization in the glomerulus and its relevance to glomerulosclerosis were examined, as well as de novo CD44 formation and its correlation with the ERK1/2 pathway. Human kidney progenitor cells were treated with CSF-1 (n=6/group) to observe migration and proliferation changes and to identify potential key interactors of CSF-1 through RNAseq. Genes of interest were validated in the FSGS model.

Results: CSF-1R was upregulated in PECs and podocytes in FSGS biopsies. In vitro, results showed that PECs constitutively expressed CSF-1R. CSF-1 treatment induced CSF-1R upregulation and transcriptional changes in genes associated with PEC activation. CSF-1/CSF-1R activated the ERK1/2 pathway, upregulated CD44 while both ERK and CSF-1R inhibitors reduced CD44 expression. CSF-1 promoted proliferation and migration while suppressing podocyte differentiation. These results were validated in the ADR-induced FSGS model. Treatment with specific CSF-1R inhibitors demonstrated strong therapeutic effects. CSF-1 also promoted interferon (IFN)-related gene transcription in human PECs.

Conclusions: This study provides the first evidence of the involvement of the CSF-1/CSF-1R pathway in FSGS in humans and supports potential therapeutic use of CSF-1R inhibitors in FSGS treatment.

TH-PO788

AMPK Activation Ameliorates Angiotensin II-Induced Downregulation of Podocyte ZO-1

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Background: Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases and induces podocyte apoptosis. ZO-1 (zona occludens-1) protein as a component of the slit diaphragm plays a pivotal role in glomerular permeability by connecting slit diaphragm structure and actin cytoskeleton. AMP-activated protein kinase (AMPK), as a sensor of cellular energy status, has been known to play an important role in the pathophysiology of metabolic diseases, including diabetes, and its renal complications. We investigated the role of AMPK on the changes of ZO-1 of podocyte induced by Ang II.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and AMPK-related agents. The changes of ZO-1 and permeability were observed by confocal imaging, western blotting, and permeability assay in the presence of Ang II.

Results: Ang II induced the fusion of microvilli and the gap pores on podocytes, which were improved by AICAR, an AMPK activator. Ang II also reduced and disrupted the intercellular ZO-1-staining, resulting in increased podocyte intercellular permeability. The intensities of fluorescences and bands of ZO-1 protein were decreased by Ang II in a dose-dependent manner by confocal microscopy and western blot analysis, respectively. AICAR and metformin, AMPK activators, ameliorated the abnormal distributional changes and the protein of ZO-1. Losartan, Ang II type I receptor blocker, also ameliorated the decrease of ZO-1 protein.

Conclusions: Our findings suggest that Ang II induces the relocation and suppression of podocyte ZO-1 via Ang II type I receptor which is ameliorated by AMPK-activating agents.

TH-PO789

Pre-Transplant Nephrin Autoantibodies Predict Post-Transplant Recurrent Focal Segmental Glomerulosclerosis (FSGS)

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Background: Focal Segmental Glomerulosclerosis (FSGS) following renal transplant occurs commonly and can lead to early graft failure. Evidence supports a recipient derived circulating factor(s) that leads to early post-transplant recurrence however its identity has remained elusive. The recent discovery of nephrin autoantibodies in minimal change disease (MCD) led us to hypothesize that nephrin autoantibodies pre-transplant may predict early recurrence in FSGS.

Methods: Single center retrospective study of 16 consecutive patients undergoing renal transplant for biopsy proven primary podocytopathy from the Centre Hospitalier Regional Universitaire de Lille between 2012 and 2019. Circulating anti-nephrin antibodies were evaluated pre-transplant by indirect ELISA. Recurrent FSGS was diagnosed on biopsy and the presence of nephrin antibodies was evaluated by immunofluorescence (IF).

Results: The median age of disease onset and transplant were 19 years (IQR 8.5-31.25) and 31 years (IQR 23.5-43.75) respectively. Disease recurrence was seen in half of the patients and occurred early, within 1 day, in 62.5% (n=5/8). One quarter (n=4/16) of the patients were serologically positive for nephrin autoantibodies at the time of transplant (Fig 1) and as expected, this was universally associated with disease recurrence (n=4/4) and constituted the majority, 80% (n=5/6) of those with early recurrence. There was no concordance with anti-nephrin antibodies in the renal biopsies. Approximately one third (n=5/16) of the patients underwent pre-transplant plasma exchange (PE) and the majority (n=5/4) were serologically negative for nephrin autoantibodies. Post-transplant recurrence occurred in 2 of 5 patients and one of them was anti-nephrin antibody positive despite preemptive PE.

Conclusions: The presence of circulating nephrin autoantibodies at the time of transplant was universally associated with post-transplant early recurrence and were identified within the kidney disease. Our findings support an important role for nephrin autoantibodies in the pathogenesis of recurrent FSGS. In those patients undergoing pre-emptive PE this is would be an important biomarker to guide treatment as one patient who recurred despite PE has persistent circulating nephrin autoantibodies.

Funding: Private Foundation Support

TH-PO790

Characterization of a Novel Human Podocyte Cell Line as a Model for CKD Drug Development

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Background: Podocytes are terminally differentiated epithelial cells which act as a crucial component to form the glomerular filtration barrier. There are a number of challenges in working with human and mouse podocytes in culture due to drug discovery programs as most cell lines do not present a typical podocyte morphology that is comparable with the in vivo situation, and some of the podocyte markers are not expressed in these cell lines. In this study, we characterized a novel human podocyte cell line...
PODO/TERT 256 from Evercyte that has several advantages over long-standing SV40 JPHS1, SYNPO, PODXL, WT-1, KIRREL, KIRREL3 from detectable by qPCR. Expression of the nephrin, podocin, synaptopodin and podocalyxin proteins were confirmed by western blotting and immunofluorescent staining. The localization to the cellular membrane for synaptopodin and nephrin was confirmed by immunofluorescent staining. RNA profiling study indicated that this cell line possesses podocyte characteristics. Nephrin expression was stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA) and suppressed by glucose. The cells demonstrated susceptibility to puromycin aminonucleoside (PAN) induced injury. Cell adhesion assays confirmed the suitability of this novel podocyte cell line for functional studies.

Conclusions: Characterization of novel podocyte cell line PODO/TERT 256 (Evercyte) confirmed expression of multiple podocyte-specific markers on RNA and protein levels. This new podocyte cell line will become a powerful tool for identification of the novel therapeutic targets and discovery of the new drugs for CKD.

Funding: Commercial Support - Janssen Research & Development

TH-PO791
Urinary Podocin Cell Count in Relation to Glomerular and Tubular Damage Markers in Patients with Primary Nephrotic Syndrome
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Background: Progressive renal failure in patients with glomerular disease is driven by podocyte depletion. Several methods have been proposed to monitor urinary podocyte loss. Here, we investigated the process of podocyte depletion in patients with primary membranous nephropathy (MN) by flow cytometric detection of Podocin-positive cells in urine.

Methods: We included 27 patients with MN. Urinary cell pellets were processed and stained for Podocin and subsequently counted using FACS. Urinary protein and creatinine levels were determined from the same portion of urine. Normal values of urinary Podocin-positive cells were obtained in urine samples of 13 healthy controls.

Results: Mean urinary podocyte count (Podocin-positive cells) was significantly higher in patients compared to healthy controls. Podocyte excretion showed significant correlations with urinary protein (r = 0.71), glomerular damage marker IgG (r = 0.75) and the tubular damage markers α1-microglobulin (r = 0.66) and β2-microglobulin (r = 0.43), all corrected for creatinine.

Conclusions: Urinary excretion of Podocin-positive podocytes was significantly increased in patients with MN, and correlated significantly with protein/creatinine ratios and glomerular and tubular damage markers. We conclude that this method can be used to monitor the process of podocyte depletion, and potentially the impact of treatment. We are planning prospective studies to evaluate the prognostic value of urinary Podocin-podocyte excretion in patients with PNS.

Funding: Government Support - Non-U.S.

TH-PO792
Value of Repeat Renal Biopsies in Lupus Nephritis in Two Large Inner-City Hospitals in New York
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Background: Class transition is common in lupus nephritis (LN) patients and may affect treatment. While the initial biopsy is indicated for the diagnosis, the role of repeat renal biopsies during renal flares is controversial. We retrospectively evaluated the histopathological and treatment changes associated with repeat renal biopsies in LN patients.

Methods: Fifty-six LN patients with at least 2 renal biopsies were included from Jacobi Medical Center and Montefiore Medical Center in Bronx, NY. Statistical analysis was performed using STATA 18 (StataCorp).

Results: The study cohort consisted of 80.4% (45/56) female, 48.2% (27/56) Black, and 42.8% (24/56) Hispanic patients, with a mean age of 26.4 ± 13.1 at the initial biopsy. The most common LN classes were proliferative, accounting for 62.9% and 80.8% of the identified classes in the 1st and 2nd biopsies respectively. There were no differences between the mean activity indices between the 1st and 2nd biopsies (1.89 ± 2.11 vs 2.10 ± 2.07, p = 0.666). Mean chronicity indices were significantly higher in the 2nd vs. 1st biopsies (5.05 ± 2.60 vs 2.69 ± 2.19, p < 0.001). Class switch occurred in 52% (26/50) of the repeat biopsies. Among the proliferative classes, 35% (11/31) had class switch within the proliferative categories (mixed class to III or IV or vice versa, or III to IV or vice versa), 6% (2/31) transitioned to class V, and 3% (1/31) to class II. Eighty percent (8/10) of the mixed III/IV-V class remained histologically unchanged in the repeat biopsies. Among non-proliferative classes, 75% (6/8) transitioned to proliferative classes (III, IV, or III/IV-V). Class switch during flares occurred more frequently in the non-proliferative classes compared to the proliferative classes (63% vs 45%, p = 0.013). In the end, 64% of patients had escalation in their immunosuppression, 17% had de-escalation, and 19% had no change.

Conclusions: Repeat biopsies were found to be particularly important in those with non-proliferative class of LN at the initial biopsy since transition to proliferative class occurred in a majority of these cases. Further, a class switch occurred in more than half the patients and a majority of the patients had an escalation of therapy, suggesting the benefit of repeat biopsies during flare in our largely minority population.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Identification of Unique Molecular “Fingerprints” of Systemic Lupus Erythematosus (SLE) and Evaluation of Kidney Function Using Urine Raman Spectroscopy and Chemometrics

TH-PO793

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Background: SLE, a pan-systemic inflammatory disease, can have a deleterious effect on renal function. Timely detection and management of renal dysfunction is highly desirable, since many patients develop disease at an early age and inflammatory nephropathies can be relentlessly progressive.

Methods: We developed a Raman spectroscopic technology (Rametrix® molecular uranalysis) to detect SLE systemic/renal effects by analysis of patient urine. It is based on chemometric analysis of the Raman spectrum of urine and detects metabolite differences. The technology is not designed specifically to detect cell degradation products (DP), such as nucleic acid DP, but can be harnessed to probe and quantify them through the biochemistry of urine and that Rametrix® analysis could detect renal dysfunction via urine molecular ‘fingerprinting’. We applied Rametrix® analysis on 587 urine specimens collected from 82 patients with biopsy-proven (80/82) and/or laboratory-validated SLE markers. Paediatric age was 8-21 years of age (median age 14.5) and 77.5% female. Most patients were African-American (183/587), Latino (162/587) or Caucasian (129/587). Serial longitudinal urine samples were obtained on multiple individuals. A renal SLEDAI-2K score was correlated to Rametrix® findings. Using chemometric analysis of urine Rametrix® spectra, we compared urine spectra from urine of healthy controls (203), patients with CKD (20), COVID19 patients (118), bladder cancer patients (19) and Lyme disease patients (20).

Results: Rametrix® molecular uranalysis distinguished SLE-associated changes in urine composition with predictive metrics (accuracy, sensitivity, specificity, PPV, and NPV) ranging between 73-97%. A correlation between changes in urine Raman spectra and physician assessment of disease (SLEDAI-2K) was also found through computational analysis. Urine spectra from SLE and COVID19 patients showed notable Rametrix® spectral similarities, suggesting common inflammatory pathways (interferonopathies).

Conclusions: Raman molecular uranalysis can be useful to detect and manage SLE and renal dysfunction.

Funding: Commercial Support - Rametrix Technologies, Inc.

Establishment of Diagnostic Criteria for Tubulointerstitial Nephritis with IgM-Positive Plasma Cells (IgMPC-TIN)

TH-PO794


Background: We proposed the IgMPC-TIN disease concept in 2017, and this disease concept is gradually gaining recognition in Japan. However, there are no clear diagnostic criteria for diagnosing IgMPC-TIN. We attempted to develop diagnostic criteria for IgMPC-TIN from both clinical and histological parameters or from only clinical parameters using cases collected from multiple institutions. A total of 115 renal biopsy specimens were collected from 61 patients with suspected IgMPC-TIN and 57 patients with other interstitial lesions from our hospital and national collaborating centers, and we performed double staining (IgM and CD138) using the immunoenzymatic method. Patients with M protein in their blood or urine and patients with diabetes mellitus were excluded as exclusion criteria. Then several nephrologists classified each case that did not meet the exclusion criteria from +3 (usual IgMPC-TIN) to $ (not IgMPC-TIN at all). Based on 49 cases judged as $ and 56 cases judged as $, a decision tree-based diagnostic algorithm was created in JMP. Finally, the sensitivity and specificity of the diagnostic criteria created were calculated.

Results: The diagnostic criteria consisting of histological and clinical parameters, the most important requirement was a maximum IgMPC infiltration count of $ $, followed by the presence of prominent highly atypical cholangitis (PBC). For diagnostic criteria consisting only of clinical parameters, the most important requirement was a serum IgM level of $ $ higher, followed by the presence of Fanconi syndrome. Sensitivity and specificity of each diagnostic criterion were $ $ and $ $, respectively. Importantly, no association between renal vasculitis (ptc and v correlating with severe kidney injury) and any glomerular lesion in historical section was found. However, capillaritis (ptc, p=0.0002) and arteritis (v, p=0.0069), affecting 5/49 (10.2%) and 11/49 (22.4%) of renal biopsies, respectively. Therefore, we here aimed to expand our current knowledge focusing on interstitial vasculitis in ANCA GN by systematic histological scoring of vascular lesions analogous to Banff. A total number of 49 kidney biopsies with confirmed renal involvement of AAV at the University Medical Center Göttingen were retrospectively included between 2015 till 2020. A renal pathologist evaluated all biopsies and was blinded to clinical data collection and analysis.

Results: Since previous studies established that crescentic ANCAGN associates with severe kidney injury and acute deterioration of kidney function in AAV, we systematically scored interstitial vasculitis in association with requirement of renal replacement therapy (RRT). Among all active and chronic tubulointerstitial lesion scores analogous to the Banff scoring system, the only association between severe kidney injury requiring RRT was observed for interstitial vasculitis in AAV reflected by peritubular capillaritis (ptc, p=0.0002) and arteritis (v, p=0.0069), affecting 5/49 (10.2%) and 11/49 (22.4%) of renal biopsies, respectively. Interestingly, no association between renal vasculitis (ptc and v correlating with severe kidney injury) and any glomerular lesion in ANCA GN (also correlating with severe kidney injury) was observed, thereby confirming that interstitial vasculitis contributes to severe kidney injury independent of ANCA GN. By contrast, short-term renal recovery from RRT was equal in both groups, suggesting a distinct association with acute decline, if kidney function at disease onset.

Conclusions: Taken together, by using the Banff scoring system we here expand our current knowledge of renal interstitial lesions in AAV revealing peritubular capillaritis and arteritis as important histological alterations associated with severe kidney injury in a considerable subset of AAV.

TH-PO795

ANCA-Associated Kidney Disease in a Child with History of Presumed IgG4-Related Disease

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Introduction: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and IgG4-related disease (IgG4-RD) are immune disorders with distinctions in patient presentation, prognosis, and management, that can share clinical and laboratory features. While ANCA positivity excludes IgG4-RD in the 2019 ACR/EULAR classification, this criterion is not uniformly applied, and AAV can form inflammatory masses in various organs and show increase in IgG4+ plasma cells, similar to IgG4-RD. This case highlights challenges in AAV and IgG4-RD diagnoses in a child.

Case Description: A 5-year-old female with previously normal kidney function presents with nausea, diarrhea and acute kidney injury with hematuria and proteinuria. Her only medical history is of a left orbital mass a year ago, diagnosed as IgG4-RD based on elevated serum IgG1 (1270 mg/dL) and biopsy with sclerosing fibrosis with IgG4+ plasma cells and eosinophil, and treated with steroids with complete mass resolution. On this admission, she has a positive MPO ANCA (1:80) with pertinent negatives of normal serum C3, C4, total IgG, and IgG4, and negative ANA and anti-dsDNA. A kidney biopsy shows chronic active pauci-immune crescentic glomerulonephritis and acute tubulo-interstitial nephritis with up to 14 IgG4+ plasma cells $ $, and focal tubular basement membrane (TBM) deposits (Image). She is treated with pulse steroids and rituximab with no kidney function improvement, in contrast to most cases of IgG4-RD.

Discussion: Pauci-immune crescentic GN with positive ANCA are characteristic for kidney AAV, and in retrospect, suggest the orbital mass may have represented the initial manifestation of AAV despite orbito mass histology with increased IgG4+ plasma cells and elevated serum IgG4 at diagnosis. The additional features of TBM deposits and increased IgG4+ plasma cells in the kidney biopsy highlight further potential for confounding morphologic overlap between AAV and IgG4-RD, for which correlation with ANCA testing is essential.

TH-PO796

Interstitial ANCA-Associated Vasculitis Associated with Severe Kidney Injury Independent of Glomerulonephritis

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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis affecting multiple organ systems, including the kidney. Although crescentic ANCA glomerulonephritis (GN) is a common histological finding reflecting glomerular small vessel vasculitis, it is reasonable that manifestation of AAV could also contribute to interstitial small vessel vasculitis. Therefore, we here aimed to expand our current knowledge focusing on interstitial vasculitis in ANCA GN by systematic histological scoring of vascular lesions analogous to Banff.

Methods: A total number of 49 kidney biopsies with confirmed renal involvement of AAV at the University Medical Center Göttingen were retrospectively included between 2015 till 2020. A renal pathologist evaluated all biopsies and was blinded to clinical data collection and analysis.

Results: Since previous studies established that crescentic ANCA GN associates with severe kidney injury and acute deterioration of kidney function in AAV, we first systematically scored interstitial vasculitis in association with requirement of renal replacement therapy (RRT). Among all active and chronic tubulointerstitial lesions analogous to the Banff scoring system, the only association between severe kidney injury requiring RRT was observed for interstitial vasculitis in AAV reflected by peritubular capillaritis (ptc, p=0.0002) and arteritis (v, p=0.0069), affecting 5/49 (10.2%) and 11/49 (22.4%) of renal biopsies, respectively. Interestingly, no association between renal vasculitis (ptc and v correlating with severe kidney injury) and any glomerular lesion in ANCA GN (also correlating with severe kidney injury) was observed, thereby confirming that interstitial vasculitis contributes to severe kidney injury independent of ANCA GN.

Conclusions: Taken together, by using the Banff scoring system we here expand our current knowledge of renal interstitial lesions in AAV revealing peritubular capillaritis and arteritis as important histological alterations associated with severe kidney injury in a considerable subset of AAV.
TH-PO797
Transthyretin Amyloidosis with Biopsy-Proven Renal Involvement
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Background: Systemic amyloidosis is a cluster of disorders characterized by tissue deposition of amyloid (highly ordered fibrils composed of low molecular weight subunits of a variety of proteins). Transthyretin (TTR) amyloidosis (ATTR) is either an autosomal dominant inherited condition (ATTRv, where v stands for “variant”) or a non-hereditary disease due to misfolding of wild-type TTR (ATTRwt). ATTR is likely underdiagnosed due to its clinical variability and lack of specific symptoms or biomarkers. The first aim of the study is to emphasize the importance of suspecting ATTR when facing certain clinical manifestations in association with renal impairment and urinary abnormalities. Furthermore, renal biopsy provides crucial information for a correct diagnosis and treatment approach.

Methods: We report 5 cases of biopsy-proven renal ATTR deposition in patients presenting with mild to moderate renal impairment and mild urinary abnormalities. The TTR precursor has been confirmed in kidney specimens by immunohistochemistry. Genotyping was carried out in every patient.

Results: The presence of amyloid was found in all patients, with different distribution (1-3 pericapsular and vascular; 2 vascular; 4 mesangial, vascular, in tubular basement membrane and in the interstitium of cortex and medulla; 5 pericapsular, vascular and interstitial). On genetic analysis three patients were wild-type (1-2-5), one carried the c.424G>A (p.(Val142Ile)) mutation (#3) and the last one the Val30Met mutation (#4).

Conclusions: Suspicion of ATTR should be considered in patients with increase in serum creatinine, mild proteinuria and cardiac and peripheral nerve symptoms. This can be of utmost importance in elderly patients in whom a monoclonal gammopathy of undetermined significance can co-exist and drive a wrong diagnosis of primary light chain amyloidosis (AL), that could lead the clinician to undertake inappropriate treatments. Renal biopsy and genetic sequencing are both critical in diagnosing ATTR. Finally, we suggest distinguishing in the context of the ATTR deposition disease an ATTR nephropathy characterized by mesangial accumulation of amyloid, that impacts functional and urinary assessment, from isolated deposition in small vessels without specific clinical consequences, albeit critical for ATTR diagnosis.

TH-PO798
Microplastics: First Proteomic Analysis on Kidney Tubular Cells
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Background: Microplastics (fragments < 5 mm in diameter) and nanoparticles (< 1 µm) are ubiquitous in the environment. Microplastics (MPs) absorb environmental pollutants, such as bisphenol A (BPA), and release them into tissues increasing their toxicity. Their presence has been proved in human blood and human tissues, such as placenta and lung, and in cirrhotic liver. Biological effects of MPs are inflammation, oxidative stress and alteration of metabolic pathways. We performed proteomic analysis to evaluate the toxicity of polyethylene (PE) and bisphenol-A (BPA) MPs on renal tubular cells (HK-2).

Methods: HK-2 cultures were exposed to BPA, PE Microspheres (PE-MP) and MP combined with BPA. We performed a proteomic analysis by mass spectrometry (MS). Analysis of data were performed using unsupervised hierarchical clustering using multidimensional scaling, non-linear support vector machine (SVM) learning, and partial least squares discriminate analysis. In SVM learning, a fourfold cross-validation approach was applied to estimate the prediction and classification accuracy.

Results: Analysis showed a clear differentiation of the HK2 proteome based on conditioning and identified a “core” of proteins, significant at ANOVA and above the 95th percentile for “fold increase” and significant at T-Test compared with controls, highly discriminatory between groups. A final set of 5 proteins was selected to be validated for distinguishing features. PPIAL4C accelerate the folding of proteins. Nephronecetin is involved in cellular adhesion. GDF15 is a markers of stress conditions. IGFBP7 is a biomarker of acute kidney damage. CDKN1C is a negative regulator of cell proliferation.

Conclusions: MP and BPA significantly modify the protein expression in renal tubular cells. These findings highlight the urgent need for additional research into the toxic effects of plastic debris on human kidneys and the eventual link to kidney diseases.

TH-PO799
Magnetic Resonance Imaging Contrast Agents: Confounded Exposures Matter
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Background: Gadolinium-induced systemic fibrosis involves the monocyte chemoattractant protein-1/C-C chemokine receptor 2 pathway. Observational analyses measuring the risk of nephrogenic systemic fibrosis universally discounted exposures to multiple brands. The patients who contact the Kidney Institute of New Mexico report exposure to various brands or American College of Radiology Group 2 agents. Using our rodent model, we examined the pathology and metal retention of combined Group1/2 exposures.

Methods: We treated rodents for one week with Omniscan and three weeks of Dotarem (and vice versa) according to our standard, published protocols. Specimens were analyzed using conventional histology and electron microscopy. We quantified gadolinium with ICP-MS (Nexion 300D, Perkin-Elmer).

Results: Confounded treatments (Omniscan followed by Dotarem or vice versa) led to the formation of intracellular nanoparticles in the renal proximal tubules.

Conclusions: Measuring the incidences of gadolinium-induced complications has been artificially reduced by excluding confounded contrast agent exposures. Our results demonstrate that Le Chatellier’s principle must be entertained in estimating the risk from magnetic resonance imaging contrast agents. Because routine magnetic resonance imaging contrast agent administration leads to gadolinium-rich nanoparticles in the brain and the kidney, defending particular brands is a fragile position.

Funding: NIDDK Support, Other NIH Support - UL1TR001449, Veterans Affairs Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Mixed exposures to class 1 and 2 magnetic resonance imaging contrast agents (Omnisan, Dotarem) led to intracellular gadolinium-rich nanoparticles in the renal proximal tubule. Transmission electron microscopy, Hitachi H7700. Kidney gadolinium levels were similarly elevated regardless of the magnetic resonance imaging contrast agent treatment group. *** P < 0.001, ANOVA, TukeyHSD.

**TH-PO800**

**Intersectin 1 and Intersectin 2 Localize with IgG Deposition in Glomeruli**

Naomori Kumagai, Tomomori Kondo, Yuji Matsumoto, Yohei Ikezumi. Fujita Health University, Toyoake, Japan.

**Background:** Intersectin 1 (ITSN1) and intersectin 2 (ITSN2) are multifunctional proteins and are causative gene for steroid-sensitive nephrotic syndrome. However, their expression in glomeruli remains unclear. IgG deposition cause glomerular injury and play a pivotal role in glomerular diseases such as membranous nephropathy and lupus nephritis. However, the molecules associated with IgG deposition remain unclear.

**Methods:** IFTN, IFTSN2, and IgG were co-stained with immunofluorescence staining for renal biopsy specimens of pediatric patients with glomerular diseases such as steroid sensitive nephrotic syndrome, steroid resistant nephrotic syndrome, IgA nephropathy, Henoch-Schönlein nephropathy, membranous nephropathy, and lupus nephritis.

**Results:** IFTSN1 and IFTSN2 stained at the same site and with the same intensity as IgG regardless of the type of disease. In membranous nephropathy and lupus nephritis, IFTSN1 and IFTSN2 stained strongly at the IgG stained site with the same intensity as IgG, especially in glomerular capillary. In other kidney diseases such as IgA nephropathy, Henoch-Schönlein nephropathy, steroid sensitive nephrotic syndrome, and steroid resistant nephrotic syndrome, IFTSN1 and IFTSN2 stained weakly at the IgG stained site with the same intensity as IgG.

**Conclusions:** IFTSN1 and IFTSN2 seem to express in glomeruli in response to IgG deposition, since they stain at the IgG stained site with the same intensity as IgG regardless of the type of disease. They are considered commonly associated with IgG deposition regardless of the type of disease, which cause glomerular injury. It remains to elucidate the pathophysiological role of IFTSN1 and IFTSN2 in glomerular injury caused by IgG deposition.

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

**TH-PO801**

**Fast Molecular Profiling of Kidney Biopsy Tissue by Gene Profiling from Biopsy Transport Medium**

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**Background:** Molecular assessment by targeted gene profiling of kidney biopsy tissues is gaining traction in kidney pathology, particularly kidney transplant biopsies (e.g. with the Nanostring B-HOT panel). A critical downside of molecular assessment from FFPE tissues is its turnaround time and same-day diagnostics is currently not feasible. Timely and tailored treatment requires the support of faster and more sensitive molecular assessment and we therefore studied the use of biopsy transport medium (BTM) used to transfer kidney biopsies from the clinic to the pathology ward.

**Methods:** We utilized tumor-free tissues from complete nephrectomy to cut tissues into small strips, imitating the size of a renal biopsy. These biopsies were stored in PBS to mimic the process of biopsies transport at our department. We optimized RNA isolation by comparing different RNA isolation methods, centrifuge speeds, and storage times of the biopsies in the BTM. We checked the quantity and integrity of the RNA and performed qPCR with different biomarkers. We validate the reliability of BTM by comparing gene expression in BTM and frozen tissues from the same kidney. Finally, from a cohort of regular biopsies, RNA was isolated using BTM.

**Results:** Our results showed that different RNA isolation methods, centrifuge speeds, and different storage time up to 24 hours did not have a significant effect on RNA quality and yield. In a preliminary assessment, we were able to measure cell-specific genes by RT-qPCR, representing T cells, B cells, macrophages, and even podocytes. The average RNA yield from regular biopsies was 165ng with RIN values around 7. As an example, CD68 expression of BTM correlated with the CD68 expression of tissue from their corresponding kidneys (N=5, r=0.902, p<0.05).

**Conclusions:** Our results demonstrate that we can obtain relatively large amounts of RNA with sufficient quality from BTM, and that gene expression analysis from BTM is practically feasible as we were able to measure the expression levels of cell-specific genes within 5 hours after arrival. BTM represents an interesting new source for rapid molecular assessment and a potentially feasible alternative to molecular assessment on FFPE tissues without the need for an extra biopsy core. Further research should validate its potential in discriminating clinically relevant diagnosis and/or quantification of disease activity.

**TH-PO802**

**Development and Validation of a Multilayer Segmentation Model to Quantify Chronic Changes on Kidney Biopsy**

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**Background:** Semiquantitative visual assessment of chronic structural changes is clinically relevant but has limited reproducibility. To better quantify chronicity, we developed a multilayer artificial intelligence (AI) model for the automated detection of glomerular, tubulointerstitial, and vascular chronic changes. These were correlated with similar measures of chronic changes derived from HistoQC, a histopathological computer software, and was annotated independently by 7 human validators and by the AI model. Then, for each of the 203 WSIs, the objects and regions detected by the AI model were used to calculate chronic changes. These were compared with similar measures of chronic changes derived independently using human annotations.

**Results:** The final model assigned 20 classes across 9 nested layers (Figure 1). The F1 score for AI vs human was 95% and for human vs human was 96%. The correlation between AI model vs human measures was r=0.92 for glomerular volume, r=0.90 for cortex per glomerulus, r=0.92 for % globally sclerotic glomeruli, r=0.82 for AI % tubular atrophy vs. human % interstitial fibrosis/tubular atrophy, and r=0.72 for % artery stenosis from internal thickening.

**Conclusions:** A multilayer AI model for the segmentation of 20 different classes on PAS-stained WSIs facilitate the quantification of kidney chronicity indices.

**Funding:** NIDDK Support
Background: Renal biopsy is a crucial procedure for diagnosing kidney diseases, and the quality of obtained tissue samples is essential for accurate diagnosis. On-site evaluation of biopsy specimens has been shown to increase the diagnostic yield. However, there is a trend of omitting on-site assessment when a nephropathologist is not readily available, leading to decreased yield. We hypothesized that evaluation of biopsy specimens by a nephropathologist on-site would improve specimen adequacy in the absence of a pathologist.

Methods: Electronic medical records of patients who underwent kidney biopsy from 2019 to 2022 were reviewed. Demographic, clinical, and biopsy-related data were collected. Biopsy specimens were evaluated by a nephropathologist on-site, and the final pathology report was provided by different pathologists. Adequacy of the specimens was assessed based on the number of glomeruli observed under light microscopy, immunofluorescence, and electron microscopy.

Results: The average age of the study sample was 50, range between 20-72 years of age. 19 of all patients were women. 5 out of 30 biopsies were performed under CT guidance. Adequate number of glomeruli were found in 27 biopsies; 2 of them had 6 glomeruli in LM, the other had a total of 3 glomeruli. A minimum of 1 glomerulus was available for IF and EM. 2 specimens were deemed adequate by nephrologist but inadequate by pathologist. 1 specimen was deemed inadequate by both nephrologist and pathologist. Average glomerular yield was 26. Median glomerular yield was 40 glomeruli total. The most common pathologic diagnoses were secondary FSGS and diabetic nodular glomerulosclerosis.

Conclusions: Adequate biopsy samples are crucial for accurate diagnosis and monitoring of kidney disorders. Previous studies have shown that on-site assessment of biopsy specimens improves yield outcomes. In this study, evaluation of specimens by a nephropathologist on-site showed nearly 100% correspondence with pathologists’ assessments. Our findings suggest that nephropathologists’ evaluation of gross biopsy specimens can positively impact biopsy yield in institutions lacking nephropathologists. Further research with larger cohorts is needed to validate these findings and assess the generalizability of this approach.

TH-PO804

Biopsy: Features of Initial KPMP Participants with CKD and Diabetes or Hypertension
Christine P. Limonte,1 Yunbi Nam,2 Zoltan G. Laszik,3 Laura Barisoni,3 Joel M. Henderson,2 Gearoid M. McMahon,4 Isaac E. Stillman,5 Jonathan J. Taliercio,5 Miguel A. Vazquez,6 Brooke Berry,7 Emilio D. Poggio,8 Charles E. Alpers,9 Sylvia E. Rosas,9 Ian H. de Boer.1 For the Kidney Precision Medicine Project Medicine.1 University of Washington, Seattle, WA; 2University of California San Francisco, San Francisco, CA; 3Duke Medicine, Durham, NC; 4Boston University School of Medicine, Boston, MA; 5Brigham and Women’s Hospital Department of Medicine, Boston, MA; 6Beth Israel Deaconess Medical Center, Boston, MA; 7Cleveland Clinic, Cleveland, OH; 8The University of Texas Southwestern Medical Center, Dallas, TX; 9Joslin Diabetes and Endocrinology Research Center, Boston, MA.

Background: The Kidney Precision Medicine Project (KPMP) is obtaining biopsy samples in people with common causes of CKD and AKI for complete clinical, histopathological, and molecular characterization. Here we report findings from the first set of adjudicated CKD biopsies.

Methods: KPMP enrolled adults with CKD and diabetes or hypertension with eGFR 30-59ml/min/1.73m², UACR >30mg/g, or UPCR >150mg/g. Standardized clinico-pathological adjudication by KPMP nephrologists and kidney pathologists was completed for 39 participants enrolled 2019-2022. Clinicians completed surveys to assess impacts of biopsy results on diagnosis and management.

Results: Participants’ mean age was 59 years, 59% were female. Mean eGFR was 53ml/min/1.73m² and median UACR was 96mg/g. Among participants with diabetes and CKD (N=28), 15 (54%) had a primary diagnosis of diabetic nephropathy, 3 (11%) had vascular nephrosclerosis, 2 (7%) had other glomerular diseases, and 8 (29%) participants had non-specific biopsy findings for which no primary diagnosis could be determined. Among those enrolled with hypertension and CKD (N=11), 5 (46%) had vascular nephrosclerosis and 6 (55%) had non-specific findings. A range of glomerular, tubulointerstitial, and vascular findings was observed (Table). 26% of clinicians stated results were different than expected and 77% stated results affected prognostic discussions.

Conclusions: Kidney biopsies in people with common causes of CKD show a broad range of histopathology and may have clinical utility. Unexpected and non-specific findings precluding a definitive diagnosis are often present. Biopsies influenced prognostic discussions between participants and their providers.

Funding: NIDDK Support

TH-PO805

Automated Foot Process Width (FPW) Measurements Using a Deep Learning (DL) Model Are Interchangeable with Stereology and Correlate with Kidney Functional and Structural Variables
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Background: Increased FPW is a key measure of podocyte (PC) health and injury. Unbiased stereology, the current gold standard, is time consuming and not widely available. To address this, we developed a DL model for automated FPW measurement.

Methods: A U-Net variant model was trained to semantically segment the PC-glomerular basement membrane interface (PGBMI) and filtration slits. A cloud-based application was developed for users to upload systematic electron microscopy (EM) images, view and download the results. The model was applied to EM images of biopsies from Fabry disease (FD) patients (n=56), type 2 diabetes (T2D) (n=15), minimal change disease (n=10), and controls (n=17). The results were compared with unbiased stereology measurements by expert technologists (ET).

Results: DL and ET FPW measurements were correlated and not statistically different in all of the groups. Bland-Altman plot confirmed method interchangeability. Measurement time/biopsy was reduced from ~8 hours (ET) to <1 min (DL). In male (M) FD patients, both DL and ET measured FPW correlated directly with age, urine protein/creatinine (PCR), podocyte volume (VPC) and volume of FD inclusions per PC (V(Inc/PC)). However, only DL FPW correlated inversely with PC numerical density. In female (F) FD patients, only DL FPW directly correlated with PCR, VPC and V(Inc/PC). In the T2D group, both DL and ET FPW correlated directly with fractional volume of mesangial matrix per glomerulus. However, only DL FPW directly correlated with urine protein.
albumin/creatinine, and fractional volume of mesangium per glomerulus, and VPC, and inversely correlated with filtration surface density.

Conclusions: Our novel and validated DL model for EM FPW measurements can make this important biomarker widely accessible for research and clinical applications.

Funding: NIDDK Support, Other NIH Support - NCATS

TH-PO806
Clinical Relevance of Computationally Derived Spatial Relationships Between Intertstitial Fibrosis and Tubular Atrophy (IFTA) and Peritubular Capillaries

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Background: The status of the tubulointerstitium and microvasculature is clinically relevant in glomerular diseases. While extent of interstitial fibrosis and tubular atrophy (IFTA) and peritubular capillaries (PTC) shape are independently associated with glomerular disease progression, the prognostic relevance of PTC shape features stratified by IFTA remains unknown.

Methods: N = 344 PAS-stained whole slide images (114 MCD/MCD-like, 132 FSGS, 61 MN and 37 IgAN) from the NEPTUNE/CureGN datasets were manually segmented for cortex and IFTA. A deep learning model was applied for PTC segmentation. The intersection between AI and human annotations of glomeruli had a Dice of 96%, precision of 99%, and recall of 93%. Glomerular volume was larger by AI than human (0.0303 vs .0027 mm3, p<0.001) as was cortex per glomerulus (0.080 vs .077 mm3, p<0.001). There were 52 progressive CKD events. Correlation of clinical characteristics with AI vs human estimates of glomerular volume is shown in Table 1. The risk of progressive CKD with glomerular volume (per SD) was 1.76 (95%CI 1.41-2.19) by AI and 1.89 (95%CI 1.61-2.23) by human and with cortex per glomerulus (per SD) was 1.82 (95%CI 1.49-2.21) by AI and 1.71 (95%CI 1.52-1.93) by human.

Conclusions: The AI approach provides efficient quantification of glomerular size measures comparable to a human approach.

Funding: NIDDK Support

Characteristics correlated with glomerular volume

<table>
<thead>
<tr>
<th>Human (µ±σ)</th>
<th>AI (µ±σ)</th>
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<tbody>
<tr>
<td>Age</td>
<td>69±1004</td>
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<tr>
<td>BMI</td>
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<td>24h protein</td>
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TH-PO807
A Comparison of Artificial Intelligence (AI) vs. Human-Derived Measures of Nephrone Size

Jaidip M. Jagtap,1 Andrew Janowczyk,2 Aleksandar Denic,2 Yijiang Chen,4 Muhammad Sohaib Asghar,1 Sumana Ramanathan,1 Aidan F. Mullan,1 Timothy L. Kline,1 Bradley J. Erickson,1 Laura Barisoni,1,4 Andrew D. Rule,1 Mayo Clinic Minnesota, Rochester, MN; 2Emory University, Atlanta, GA; 1Duke University, Durham, NC; 3Case Western Reserve University, Cleveland, OH.

Background: Enlarged nephrons as detected by glomerular volume and cortex per glomerulus (reciprocal of glomerular density) on kidney biopsy are prognostic for progressive CKD but require stereological calculations based on tedious human annotations. We sought to compare clinical associations with nephron size as calculated by AI versus human.

Methods: PAS-stained wedge section whole slide images (WSI) from nephrectomies (N=932) were manually annotated for cortex and non-sclerosed glomeruli using ImageScope software. A previously developed AI model for glomerular segmentation (NEPTUNE study) was applied to the same WSI. A threshold of 2000 µm2 for the smallest glomerular profile excluded false positives with the AI model. Clinical correlations and the risk of progressive CKD (kidney failure or a 40% decline in eGFR sustained for at least 3 months) was assessed using AI versus human derived glomerular volume and cortex per glomerulus.

Results: The intersection between AI and human annotations of glomeruli had a Dice of 96%, precision of 99%, and recall of 93%. Glomerular volume was larger by AI than human (0.0303 vs .0027 mm3, p<0.001) as was cortex per glomerulus (0.080 vs .077 mm3, p<0.001). There were 52 progressive CKD events. Correlation of clinical characteristics with AI vs human estimates of glomerular volume is shown in Table 1. The risk of progressive CKD with glomerular volume (per SD) was 1.76 (95%CI 1.41-2.19) by AI and 1.89 (95%CI 1.61-2.23) by human and with cortex per glomerulus (per SD) was 1.82 (95%CI 1.49-2.21) by AI and 1.71 (95%CI 1.52-1.93) by human.

Conclusions: The AI approach provides efficient quantification of nephron size measures comparable to a human approach.

Funding: NIDDK Support

Characteristics correlated with glomerular volume

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TH-PO808
Spatial Transcriptomic Analysis Reveals Altered Gene Expression in Glomerular Parietal Epithelial Cells Following Tubular Injury

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Background: In our previous study, we observed that acute tubular injury leads to the activation and transdifferentiation of parietal epithelial cells (PECs), resulting in a decrease in the ratio of columnar to flat PECs. In this study, our objective was to investigate the spatial tranascricomics of PECs following tubular injury.

Methods: We conducted experiments using wild-type (WT) mice and transgenic mice expressing the diphtheria toxin (DT) receptor in proximal tubular epithelial cells (PTECs). The mice were injected with DT at week 0 and week 1 and sacrificed after 6 weeks. Paraffin-embedded tissue sections were analyzed using the NanoString GeoMx DSP platform.

Results: Using fluorescent antibodies, we successfully isolated glomerular tuft and PECs and performed GeoMx spatial transcriptomics analysis. Principal component analysis (PCA) clearly distinguished tuft and PECs in both DT-treated and normal mice. In DT-treated PECs, we observed increased expression of 153 genes, including osteopontin (OPN), which showed enrichment in pathways related to actin cytoskeleton regulation, apelin signaling, the citric acid cycle, and respiratory electron transport. Immunostaining analysis (PCA) clearly distinguished tuft and PECs and performed GeoMx spatial transcriptomics analysis. Principal component analysis (PCA) clearly distinguished tuft and PECs in both DT-treated and normal mice. In DT-treated PECs, we observed increased expression of 153 genes, including osteopontin (OPN), which showed enrichment in pathways related to actin cytoskeleton regulation, apelin signaling, the citric acid cycle, and respiratory electron transport. Immunostaining

Conclusions: Our findings indicate that proximal tubular injury affects glomerular PECs, leading to their activation and altered gene expression. This study suggests potential pathways involved in the communication between tubular and glomerular compartments.

Funding: NIDDK Support
Histopathological Description of Sickle Cell Nephropathy of the Arab-Indian Haplotype

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Background: Sickle cell disorders are a group of autosomal recessive disorders characterized by the presence of the hemoglobin S (HbS) variant, which leads to sickling and hemolysis of the red blood cells. The inheritance of one variant gene, sickle cell trait (SCT), leads to a carrier state and milder form of the disease while having 2 genes leads to the more aggressive state of sickle cell disease (SCD). The main variants of HbS genes are the haplotypes present in the African race and the Arab-Indian (AI) haplotype, found in Saudi Arabia and central India. Sickle Cell Nephropathy (SCN) has been well characterized in the population of African descent. However, the histopathological changes of SCN have not been described in the patients of AI haplotype.

Methods: This was a retrospective analysis of all adult patients with sickle cell disorders (SCD/SCT) who underwent a kidney biopsy from January 2012 until May 2023. Histological specimens were retrieved and examined by a research histopathologist. Clinical and biochemical data were collected and analyzed at the time of biopsy and last follow-up.

Results: 22 kidney biopsies were identified, of which were excluded due to active lupus nephritis leaving 17 biopsies (12 SCD and 5 SCT). The mean age was 44 +/- 10 years, 8 were females (47%). The main indications for biopsy were unexplained raised creatinine (4/17) and proteinuria (13/17). The median hemoglobin S in SCD and SCT was 81% and 26%, respectively. Changes suggestive of SCN were only observed in SCD; the main findings were tubular hemosiderosis (92%), global sclerosis (83%), glomerular hypertrophy (75%), sickled RBCs (58%), FSGS lesions (42%), and duplication of the glomerular basement membrane (33%). None of the findings from SCT biopsies were consistent with SCN changes (2 diabetic glomerulosclerosis, 1 chronic glomerulonephritis, 1 normal glomerular architecture, and 1 cortical nerosis).

Conclusions: In patients with sickle cell disease in Saudi Arabia, where the AI haplotype is prevalent, the SCN histopathological changes were largely similar to the ones previously reported with the haplotypes in the African race. These changes were only present in SCD and are likely to reflect the nature of the repetitive damage.

Influence of Hospital Practices on Native Glomerular Pathologic Patterns: Insights from the Largest Kidney Biopsy Cohort in Thailand

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Background: We sought to explore the effects of kidney biopsy and glomerular pathologic patterns using the largest Thailand kidney biopsy registry.

Methods: Records of kidney biopsy registries from the Chulalongkorn University (one of the biggest university-based hospitals in Thailand) and the Kidney Center Bangkok Hospital (a center providing kidney pathology diagnostic service for all private and public hospitals in Thailand) between 2000 and 2014 were analyzed and classified into three groups: university practice (U), private practice (Pv), and public practice (Pb). Records from pediatric patients, kidney transplant, and repeated biopsies, and insufficient clinicalopathologic diagnoses were excluded from the study. One-way ANOVA was conducted to compare continuous variables among hospital types while Chi-Squared test and Fisher’s exact test were used for categorical variables.

Results: Out of 6,959 native kidney biopsies, 5,007 were eligible for analysis from 62 provinces covered all regions of Thailand over 15 years. University hospitals performed the highest number of kidney biopsies, followed by public and private hospitals. The three most common indications across all practice groups were nephrotic syndrome (NS), systemic lupus erythematosus (SLE, e.g., suspected lupus nephritis, morphologic diagnosis before making treatment decisions), and asymptomatic urinary abnormalities. U had a significantly higher proportion of biopsies due to SLE than the others (Image 1). In contrast, Pv performed biopsies with more indication of asymptomatic urinary abnormalities and unknown CKD than the others. Lupus nephritis was the most common pathological finding in U and Pb groups, while the Pv group was IgA nephropathy corresponding to the indications for biopsy.

Conclusions: The prevalence of pathologic diagnosis patterns is correlated well with the biopsy indication. Our findings highlight the influence of hospital practices on kidney biopsy indications and glomerular diagnoses.

Renal Malakoplakia: A Rare Disease Causing Acute Renal Failure

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Introduction: Malakoplakia is a rare chronic inflammatory condition characterized by granulomatous lesions, frequently involving the kidneys. We present a case of renal malakoplakia in the setting of Escherichia coli (E.coli) bacteremia leading to acute renal failure.

Case Description: A 36-year-old woman presented with vomiting and shortness of breath. Initial evaluation revealed hypotension, tachycardia, leukocytosis (22,000/µL), and acute kidney injury with elevated creatinine (6.4 mg/dL from a baseline of 0.6 mg/dL). Urogram showed blood, leukocytes, and bacteria, and a urine protein/creatinine ratio of 31 mg/mg. Computed tomography scan indicated fatty hepatomegaly and glomular nephromegaly. Urine and blood cultures grew E. coli. The patient was treated for septic shock with antibiotics and vasopressors. However, she developed oliguric acute renal failure and required continuous renal replacement therapy. Left kidney biopsy was pursued to evaluate the nephromegaly, which revealed multifocal microabscesses, parenchymal necrosis, fibrosis, calcifications, and an inflammatory infiltrate with histiocytic predominance, consistent with malakoplakia. Von Kossa stain confirmed the presence of numerous Michaelis-Gutmann bodies. Renal malakoplakia presents diagnostic considerations and therapeutic dilemmas. The choice of therapy for renal malakoplakia involves the balance between medical and surgical options.
Infection as a Trigger of Acute, Transient Glomerular Deposition of Clonal Immunoglobulins

TH-PO813

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Introduction: Glomerular deposition of clonal IgM, frequently in the form of intracapillary pseudohornbi, can be seen in Waldenström macroglobulinemia (WM) and type 1 cryoglobulinaemia (CG). Both are typically associated with B-cell lymphomas, particularly lymphoplasmacytic lymphoma (LPL). While infection is a frequent trigger of mixed (type 2 and 3) CG, its association with type 1 CG is uncommon. We report two cases in which striking lambda-restricted IgM deposits and acute kidney injury (AKI) occurred in the setting of systemic infections, with prompt resolution on treatment of the infection.

Case Description: Patient 1 was a 57-year-old female who presented with AKI following bowel perforation, treated with resection and antibiotics. Serum protein electrophoresis (SPEP) showed IgG kappa and IgM lambda M-proteins, without history of lymphoma. Patient 2 was a 59-year-old female with a 9-year history of an untreated, quiescent mature B-cell lymphoma, who presented with AKI, nephrotic range proteinuria, and hematuria, alongside a recent sore throat, presumptively treated with antibiotics for a respiratory infection. Her lab findings showed hypocomplementemia and faint IgM-lambda M-protein on SPEP. Neither patient was tested for cryoglobulins. Renal biopsies for both patients revealed glomerular capillary loops distended by abundant amorphous, eosinophilic and PAS-positive material, which stained strongly for IgM and lambda light chain on immunofluorescence and was granular and lacked substructure by electron microscopy. These findings were initially interpreted as concerning for renal manifestations of WM. However, after further investigation, neither patient exhibited LPL, and both patients experienced recovery of renal function following treatment of their respective infections (patient 2 also received a short course of steroids). Notably, patient 1 was diagnosed with a diffuse large B-cell lymphoma several years later.

Discussion: While infection may not be the root cause of clonal immunoglobulin production, these two cases suggest that it may serve as a trigger for glomerular deposition of clonal IgM in patients predisposed by underlying lymphoma. WM was initially suspected in both patients; however, the rapid normalization of renal function after resolution of infection indicates that they had undiagnosed type 1 CG triggered by infection.

TH-PO814

Nephropathy of Prematurity and the Crucial Role of Kidney Biopsy

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1Rochester Regional Health, Rochester, NY; 2Plainview Hospital, Plainview, NY.

Introduction: Nephrogenesis, the creation of nephrons, typically concludes before birth, yet in preterm infants it can extend up to 40 days post-birth. Nevertheless, these late-forming nephrons mature prematurely and remain abnormal. The exact influence of premature birth on nephrogenesis remains unclear. In light of this, we share a case of a young woman with signs of nephropathy attributed to her premature birth.

Case Description: A 22-year-old female with migraines and high blood pressure (230/150 mmHg) presented at an emergency department. Initial tests revealed normal CBC and CMP, but with elevated BUN (62 mg/dL) and creatinine (2.8 mg/dL). Mild proteinuria and a few red blood cells were noted. A renal ultrasound only found a small cyst in the right kidney. No stenosis was found, leading to further diagnostic workup. By the 5th day, with improved kidney function and controlled blood pressure, a renal biopsy was performed due to unclear AKI cause. The biopsy findings indicated acute tubular injury and Glomerulonephritis with secondary focal global and segmental glomerular sclerosis (Figures 1, 2). As the patient had no history of drug abuse, the prospect of nephropathy of prematurity was considered, which she confirmed, leading to the diagnosis of Chronic Kidney Disease due to nephropathy of prematurity.

Discussion: This case is unique due to hypertension and renal failure in a patient with a normal workup and kidney size. Nephropathy of prematurity should be considered in young adults presenting with renal failure and benign urinary findings. This case underlines the importance of vigilant follow-ups for early detection of renal diseases in young adults with proteinuria and high blood pressure but normal kidney size. The case raises the question of whether monitoring renal function in premature infants should be extended into adulthood. Kidney biopsy remains the definitive method for diagnosing unexplained CKD, emphasizing the role of vigilance follow-ups and consideration of underlying renal disease in young adults with proteinuria, high blood pressure, and normal kidney size.

Renal biopsy demonstrating IgG4 plasma cells.

TH-PO815

Systemic Immunoglobulin G4-Related Disease

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Introduction: Immunoglobulin G4-Related Disease (IgG4-RD) is an autoimmune condition that can result in systemic fibrosis and organ damage. Clinical manifestations include lymphadenopathy, atopy like symptoms, and is often found incidentally on imaging with diffuse or focal organ lesions. Serological findings can include elevated levels of immunoglobulins and low complement levels. A tissue biopsy is needed for diagnosis revealing IgG4 lymphoplasmacytic infiltration with variable degrees of fibrosis.

Case Description: A 79-year-old male with a PMHx of HTN, biliary stricture, asthma, and BPH presented with generalized fatigue, pruritus, and difficulty initiating urination for one month. Labs revealed a marked elevation of C4 and low C1q (C3 322, ALT 460, ALP 796, Tbilii 4), and anemia (Hgb 11.2). MRCP revealed a biliary duct stricture, chronic pancreatitis, and soft tissue swelling representing retroperitoneal fibrosis. ERCP with biliary stent placement and biopsies were performed, revealing lymphoplasmacytic infiltration and diffuse fibrosis. Renal biopsy revealed diffuse interstitial inflammatory IgG4 lymphoplasmacytic infiltration with interstitial nephritis. Total protein and globulin levels were elevated. SPEP/IFE revealed increased gamma globulins (2.1) with no monoclonality. Immunoglobulin G4 was elevated at 266.2 (4-46). IgG1 was elevated at 1185 (282-395), and low C4 levels.

Discussion: The patient was diagnosed with IgG4-RD and started on immunosuppression with prednisone and rituximab, complement levels were used to track responsiveness to treatment. Repeat serologic tests after immunosuppression revealed normalization of IgG, IgG1 and complement levels, with a CD19/20 count of zero, showing that his IgG4-RD was in remission. Early recognition and treatment of IgG4-RD is of utmost importance due to a fibrotic transition that is poorly responsive to treatment with resultant end organ damage.

Proliferative Glomerulonephritis with Monoclonal IgGλ Deposits, Characterized by Intracapillary λ-Containing Macrophages Infiltration

Natsumi Tsuge,1 Ichiro Kaiko,1 Anri Kaikoi,2 Yoshinori Takahashi,1 Shunsuke Tsuge,2 Satoshi Hara,1 Kiyoko Ito,1 Ichiro Mizushima,1 Mitsuhiro Kawano.1 ‘Kanazawa Daigaku Faozoku Byoin, Kanazawa, Japan; 2The Christ Hospital, Cincinnati, OH.

Introduction: Monoclonal gammopathy of renal significance (MGRS) encompasses kidney disorders caused by monoclonal proteins. We report a rare case of proliferative glomerulonephritis with monoclonal IgGλ deposits (PGNMD) in a patient with monoclonal gammopathy of undetermined significance (MGUS). Notably, the case is characterized by the infiltration of intracapillary macrophages containing λ immunoglobulin.

Case Description: A 69-year-old Japanese female with MGUS presented with renal dysfunction and proteinuria. She had a history of persistent proteinuria (urinary protein 3.4 g/g Creatinine), microscopic hematuria, and kidney dysfunction (serum Creatinine 1.3 mg/dL) for the past 2 years. Due to refractory symptoms, she was admitted to our hospital. On admission, her urinary protein was 1.1 g/day, with microscopic hematuria, and serum Creatinine 1.9 mg/dL. Immunofixation analysis detected monoclonal IgGλ in both serum and urine, while cryoglobulins were absent. Renal biopsy revealed diffuse endocapillary proliferative glomerulonephritis with subendothelial deposition. Immunofluorescence demonstrated IgG1, C3, and λ deposition with an infrange pattern, confirming the diagnosis of PGNMD. Remarkably, the intracapillary cells exhibited a foamy appearance and showed double positivity for CD68 and λ. Electron microscopy confirmed electron dense deposits (EDD) in the subendothelial area, and intracapillary foam cells contained EDD. Due to the presence of other life-threatening factors, the patient received renal protection therapy without anti-tumor treatment. Over a four-year period, renal dysfunction progressively worsened, with a serum creatinine level of 2.9 mg/dL and persistent proteinuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Discussion: We present a rare case of PGNMID characterized by the infiltration of intracellularly monoclonal immunoglobulins. The underlying pathophysiology remains unknown, but it may share similarities with crystal-soring histiocytosis, where macrophages engulf monoclonal immunoglobulins. To our knowledge, only one similar case has been previously suggested, suggesting that this histological finding could represent a novel manifestation of MGRS.

TH-PO817
How Factor H Deficiency Triggered Atypical Hemolytic Uremic Syndrome (aHUS) in a New Mother
Thien Ho, Erik Mai, Evelyn Bruner, Milos N. Budisavljevic. Medical University of South Carolina, Charleston, SC.

Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare form of thrombotic microangiopathy (TMA) causing dysregulation of the alternative complement system. aHUS presents with microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage, notably, renal failure requiring dialysis. Morbidity and mortality is preventable as treatments are now available. Yet, treatment is often delayed as aHUS is viewed as an exclusion diagnosis. Prior studies have shown that aHUS is associated with many genetic mutations of complement proteins. Of these, Factor H (CFH) were found in 25% of cases. We present an aHUS case of CFH deficiency in a postpartum patient.

Case Description: A 26 year old healthy female, who one week ago had a normal term vaginal delivery, presented with hypertensive emergency, MAHA, thrombocytopenia, and renal failure requiring dialysis. Initial labs showed deficient C3 levels and normal C4 levels. Plasmanephrosis was started for suspicion of Thrombotic Thrombocytopenic Purpura. Therapy was stopped when her ADAMTS13 returned normal. She was screened for infections, drugs, and malignancy, all were negative. A renal biopsy showed TMA with 10% cortical necrosis. Results of her complement panel showed dysregulation of the alternative pathway: low CFH and low alternative pathway levels. She was diagnosed with aHUS and treated with a C5 Inhibitor, Eculizumab. Eculizumab was given weekly and after her third dose, her hemolytic labs improved. After her 4th dose, her renal function was near complete recovery and dialysis stopped. Her dose now was every two weeks for a minimum of six months.

Discussion: C5 inhibitors have hugely improved renal survival. Our patient received Eculizumab with promising renal recovery. A 2010 study of 100 females with aHUS showed that 48% of cases involved CFH mutations. Another study assessed 273 aHUS patients and 139 had CFH dysfunction. We are learning that the defect affects more than one area on the CFH gene. Thus, the location of dysfunction affects the severity and treatment response making aHUS much more challenging to standardize.

TH-PO818
Lanthanum Gastropathy in Gastrectomy Specimen: A Case Report
University of Vermont Medical Center, Burlington, VT.

Introduction: Lanthanum carbonate is a non-calcemic phosphate binder that is used in end-stage renal disease (ESRD). It has few adverse effects due to its poor systemic absorption. Gastrectestinal lanthanum deposition was first reported in 2015 and is likely due to alterations in epithelial permeability from inflammation in chronic kidney disease. Endoscopy findings include gastritis, erosions, ulcers, and polyps, with a diffusely white mucosa and fine granular deposits. It is challenging to detect these findings in cases with minimal microscopic deposition and may be missed on biopsy.

Case Description: A 36-year-old with ESRD secondary to hypertension was started on lanthanum in 2017. She was evaluated by bariatric surgery in 2019 for sleeve gastrectomy and endoscopy was completed as part of the pre-operative workup. Findings were significant for gastritis and multiple gastric polyps. Biopsies demonstrated aggregates of histiocytes with granular eosinophilic material in the lamina propria. She underwent sleeve gastrectomy in 2022 in which the excised portion showed similar histologic findings. There have been no further studies or adverse events reported since the surgery.

Discussion: This case allows for the evaluation of a gross specimen as there have been no reports to date describing lanthanum gastropathy in specimens larger than biopsy. Not all patients taking lanthanum undergo endoscopic and histologic evaluation, but studies have found deposits in 60-85% of those evaluated. One case report found concurrent neoplastic changes, though this is the only description of such. The findings in this case were not consistent with neoplasm despite prolonged lanthanum use, but further studies must be conducted to determine long-term effects in patients with ESRD.
TH-PO820

Left Ventricular Diastolic Dysfunction by Echocardiography Is a New Predictor of Delayed Graft Function

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Background: Diastolic dysfunction (DD) is a common complication among end-stage renal disease (ESRD) patients. The ratio of early transmural flow velocity (E) to early diastolic velocity (e’) of the mitral annulus (E/e’) is related to left ventricular (LV) diastolic dysfunction (LVDD). Delayed graft function (DGF) is a detrimental complication after kidney transplantation (KT). It is unclear whether increased E/e’ predisposes a recipient to DGF.

Methods: A total of 574 patients were enrolled in this retrospective study. Two-dimensional echocardiography and Doppler imaging were performed. Multivariate logistic regression analyses were performed to calculate the OR (95%CI) for DGF. Model 1 included variables with P<0.05 in the multivariate logistic regression analyses. Model 2 was adjusted for demographic data (age and sex) and operation data (warm ischemia time and cold ischemia time). Model 3 (reference model) includes all the variables in Model 2 except E/e’. Discrimination was assessed by AUCs. Model performance was also evaluated by continuous net reclassification index (cNRI) and integrated discrimination improvement (IDI).

Results: 93 patients (16.25%) developed DGF. E/e’ was higher in DGF patients (14.07 ± 6.16 vs. 11.51 ± 4.23, P<0.001). Per 1 unit E/e’ increase (OR 1.13; 95%CI, 1.07-1.18). Compared with Model 3, Model 2 had better discrimination and reclassification (cNRI, 46.48%; 95% CI, 24.61%-68.34%; IDI, 4.36%; 95% CI, 1.81%-6.91%).

Conclusions: Our study found that higher E/e’ was an independent predictor of DGF. This may provide an important perspective on the management of waiting list patients. Our results recommend that clinicians should take measures to lower E/e’ before transplantation to lower DGF risks.

TH-PO821

Pre-Transplant Daratumumab (Dara) and Kidney Transplant Rejection

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Background: This study examined the post-kidney transplant outcomes of patients who received Dara, a monoclonal antibody against CD38 positive cells, pre-transplant. Concerns exist that Dara may increase the risk of rejection.

Methods: We identified solitary kidney allograft recipients who received Dara within 180 days pre-transplant in our center. Clinical and laboratory data were abstracted from the chart. Protocol biopsies are routine in our practice.

Results: Ten patients met inclusion criteria. Mean age was 60 (±10) range 36-73 years, there were 7 males, and 7 received a living donor transplant. Induction was with Basiliximab in 7, Alemuzumab in 2 & Anti-thymocyte globulin in 1. Maintenance immunosuppression consisted of a corticosteroid, tacrolimus, mycophenolate mofetil in 9 patients, Belatacept replaced tacrolimus in one patient and in one patient sirolimus was substituted for tacrolimus 26 months post-transplant due to microangiopathy. Last dose of dara was 22 (16,30) days prior to transplant. Three patients resumed dara: 11, 24, and 244 days post-transplant. Follow-up was 32 (±16) months. One patient did not undergo protocol biopsies due to systemic anticoagulation. The remainder had protocol biopsies at the predetermined time points. No graft losses occurred during follow-up. Two patients had subclinical borderline changes (i0, i1) at one year, and (i1, i3) on the two-year protocol biopsy. The latter, after reduction in immunosuppression due to CMV infection (Fig1). Another patient developed severe BK nephropathy that required significant immunosuppression reduction.

Conclusions: In our series of 10 patients, we did not observe any clinical acute cellular rejections. Two patient had subclinical borderline changes, one- and two-years post-transplant. Daratumumab did not appear to increase the risk of rejection.

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

TH-PO822

Role of Angiopoietins in Cardiovascular Disease (CVD) Outcomes of Kidney Transplant Recipients

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Background: Kidney transplant recipients have 30 times the risk of dying from cardiovascular disease (CVD). We tested the role of 2 vascular biomarkers, angiopoietin-1 and angiopoietin-2 (angpt-1, -2), in the development of CVD in deceased donor kidney transplant recipients.

Methods: This is an ancillary analysis of the FA VORIT study, evaluating the associations between baseline levels of angpt-1 and angpt-2 in the development of CVD and the secondary outcomes of graft failure (GF) and death in 2000 recipients. We used a Cox regression analysis to test the associations between biomarker quartiles and outcomes.

Results: Median age of participants was 52 IQR [45, 59] years with 37% women and 73% identifying as white. Median time from transplantation to biomarker measurement was 3.99 IQR [1.58, 7.93] years. Median time to the development of CVD was 3.7 IQR [2.89-5.25] years. Angpt-1 was not significantly associated with outcomes. Higher levels of angpt-2 (quartile 4) as compared to quartile 1 had about 2 times the risk of CVD, GF and death [aHR 1.85 (1.25 - 2.73), P<.01; 2.24 (1.36 - 3.70), P<.01; 2.30 (1.48 - 3.58), P<.01, respectively, (Figure 1)].

Conclusions: Angpt-2 may identify high-risk kidney transplant recipients for the development of CVD. This may aid in tailoring follow-up after transplantation to reduce the risk of CVD.

Funding: NIDDK Support
Impact of Hyperparathyroidism and Its Different Subtypes on Long-Term Graft Outcome: A Single Transplant Center Cohort Study

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Background: We retrospectively evaluated 871 renal transplant patients (RTx-p) transplanted in our unit from Jan-2004 to Dec-2020 assessing renal function and mineral metabolism parameters at 1, 6, and 12 months after RTx. Graft loss and death with functioning graft during follow-up (FU, 8.3[5.4-11] years) were checked.

Methods: At month-1, 79% had HPT, of which 63% with secondary HPT (sHPT) and 16% tertiary HPT (tHPT); at month-6, HPT prevalence was 80% of which sHPT 64% and tHPT 16%; at month-12 HPT prevalence was 77% of which sHPT 62% and tHPT 15%.

Results: In patients with sHPT, mean PTH exposure was strongly and independently associated with shorter long-term graft survival at every time point considered (Figure 1, PTH status at 12-months after RTx).

Conclusions: High PTH levels, and especially tHPT during 1st year of RTx seem to be associated with long-term graft loss.

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

Underline represents presenting author.

TH-PO823

Acute Phosphate Nephropathy: A Preventable Cause of AKI Among Kidney Transplant Recipients

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Introduction: Acute kidney injury (AKI) after a kidney transplant is an extreme emergency. It is associated with allograft loss and increased morbidity. Prompt recognition of reversible causes of AKI is important to prevent graft loss. We present a case of a kidney transplant patient who developed AKI secondary to acute phosphate nephropathy.

Case Description: A 37-year-old male with end-stage renal disease secondary to hypertension underwent a deceased donor kidney transplant. His pre-operative laboratory results include calcium of 8.2 mg/dl, phosphorus of 6.6 mg/dl, PTH of 835 pg/ml, and 25-hydroxyvitamin D of 18.6 ng/ml. His phosphate binder Sevelamer was discontinued after the transplant. He had an immediate graft function and an uncomplicated post-operative course. He was discharged on hospital day 4 with a creatinine of 1.1 mg/dl and phosphorus of 2 mg/dl. His immunosuppressants include Tacrolimus 7 mg twice daily, Mycophenolate 2400mg twice daily, and Prednisone 5mg daily. On follow-up, his blood work showed stable renal function but worsening hypophosphatemia of 1.4 mg/dl. He was initiated on oral phosphate supplementation. Two weeks later, he has a progressive worsening of AKI with creatinine trending up to 3 mg/dl. Due to concern for acute rejection, a kidney biopsy was performed which showed acute tubular injury with focal tubular necrosis, focal tubular subepithelial tubular calcium phosphate deposition, and calcium phosphate casts. There was no evidence of T-cell or anti-body mediated rejection. Phosphate supplementation was discontinued which subsequently improved the patient’s allograft function with his creatinine reaching a nadir of 1.8 mg/dl over the next 6 months.

Discussion: Hypophosphatemia is commonly seen after kidney transplantation. This case highlights that acute phosphate nephropathy secondary to oral phosphate repletion may cause AKI among kidney transplant patients. Nephrologists should be vigilant in managing hypophosphatemia following a kidney transplant. Unless hypophosphatemia is life-threatening, we recommend conservative management including high dietary phosphate intake. Oral phosphate supplementation should only be considered in patients who are symptomatic with persistent severe hypophosphatemia and once a patient is initiated, careful monitoring of serum phosphate level and kidney function is recommended.

TH-PO825

Rapid Point-of-Care Capillary Blood Assays for Monitoring Cystatin C Levels in Kidney Transplant Recipients

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Background: Frequent monitoring of tacrolimus (TAC), an FDA-approved immunosuppressant, and estimated glomerular filtration rate (eGFR) in kidney transplant recipients (KTRs) are necessary to prevent allograft rejection and toxicity. We propose to use cystatin C (CysC) concentration as a marker for estimating eGFR for KTRs. CysC concentration is independent of age, sex, and muscle mass, making it a valuable predictor of nephrotoxic risks associated with TAC in KTRs. IOS has partnered with a biotechnology and WIRFIR to develop a novel point-of-care (POC) enhanced lateral flow assay (ELFA) platform to determine levels of CysC from fingerstick capillary blood.

Methods: ELFA performance was assessed using standard calibration curves (SCCs) with spiked whole blood samples at various CysC levels. Method validation involved 17 KTRs, comparing ELFA measurements on fingerstick blood samples (n=3) to standard lab measurements of CysC from venous blood. SCCs indicated ELFA performed well in the same range of CysC concentrations as the standard lab measurements.

Results: SCCs indicated ELFA performs well in the 0.6-3.0 mg/L range for CysC. ELFA and standard lab measurements strongly correlated with r=0.88. ELFA analysis showed a mean difference (bias) of 0.13 mg/L for CysC between the two methods.

Conclusions: The ELFA platform delivers minimally invasive, convenient sampling in a POC device using capillary fingerstick blood from KTRs, and provides accurate, rapid measurements of CysC that have demonstrated good repeatability and strong correlation with laboratory standard reference measurements.

Funding: Other U.S. Government Support

TH-PO826

Performance of GFR Estimating Equations in Kidney Transplant Recipients of Various Races

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Background: We compared the performance of various estimated GFR equations in kidney transplant recipients of different races.

Methods: This single-center study compares eGFR with measured GFR at 1-year post-transplant.
Results: There were 1145 subjects with 1-year eGFR and mGFR data. Whites made up 59.6% of the population. There was a significant difference in eGFRcys and eGFRcr by race (p=0.007), but not eGFRcys (adjusted hazard ratio [aHR]: 1.62, 95% CI 1.05-1.92).

Conclusions: The study suggests that combined equations of creatinine-creatinine C performed better than creatinine-based equations and the cystatin C-based equations in all races. eGFRcys was lower than eGFRcr, was not associated with muscle mass but was lower on average than eGFRcr (52.5 ± 20.5 mL/min/1.73m²) was lower than observed in UK KTR populations. Over median follow-up of 4.8 (IQR 4.5 - 5.1) years, there were 14 deaths. Mean eGFRcys (40.9 ± 18.3 mL/min/1.73m²) was lower than eGFRcr (52.5 ± 21.0 mL/min/1.73m²; Figure). eGFRcys was lower than eGFRcr, but not associated with muscle mass but was strongly associated with mortality. As seen in the general population, eGFRcys is a valuable marker to stratify risk of death in KTR.

Funding: Private Foundation Support

TH-PO827
eGFRc, eGFRcys, Muscle Mass, and All-Cause Mortality in Kidney Transplant Recipients: Post-Hoe Analyses from a Randomized Controlled Trial

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Background: We explored eGFRc, eGFRcys and pectoral muscle mass cross-sectional area (PMA) in kidney transplant recipients (KTR) and assessed relationships: i) between parameters and ii) with all-cause mortality.

Methods: Participants were from the ViKTORIES randomised controlled trial (ISRCTN20120444) in prevalent KTR. eGFRc (2009) and eGFRcys (2012) were calculated from creatinine and cystatin C respectively at baseline. PMA was calculated as the mean pectoral muscle area from slice 1 (the first slice in which the full pectoral muscle became visible), 3 and 5 on non-contrast axial thoracic computed tomography (CT) scans taken at baseline. Follow-up data were extracted from the electronic record. Linear regression tested associations between eGFR measures and PMA. Cox proportional hazards models tested associations between eGFR measures, PMA and death.

Results: Of 90 ViKTORIES participants, 90 had available serum/plasma samples and 89 had CT data for analysis. Mean (±sd) age was 57.6 ± 9.6 years and 63 (70%) were male. The proportion with pre-existing cardiovascular disease (21.1%) and diabetes (22.2%) was lower than observed in UK KTR populations. Over median follow-up of 4.8 (IQR 4.5 - 5.1) years, there were 14 deaths. Mean eGFRcys (40.9 ± 18.3 mL/min/1.73m²) was lower on average than eGFRcr (52.5 ± 20.5 mL/min/1.73m²; Figure). eGFRcys was lower than eGFRcr, but not associated with muscle mass but was strongly associated with mortality. As seen in the general population, eGFRcys is a valuable marker to stratify risk of death in KTR.

Funding: Private Foundation Support

TH-PO829
Long-Term Outcome of Kidney Transplant Recipients with History of Complement-Mediated Thrombotic Microangiopathy

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Background: The long-term outcome of kidney transplant recipients with history of complement-mediated thrombotic microangiopathy (cTMA) is unknown.

Methods: We retrospectively studied all kidney transplant recipients with cTMA as primary disease or developed cTMA post-transplant between Jan 2000 and Dec 2020 in our center. We estimated the crude survival probability via Kaplan-Meier methods starting at date of transplant until graft failure or death. The adjusted hazard ratio (aHR) associated with primary cTMA was estimated using Cox regression models with time-varying cTMA effect and biopsy diagnoses included as time-varying variables.

Results: We identified 129 patients (20 with cTMA as primary disease) who had 460 biopsies. After a mean follow-up of 4.5 years, 73 started dialysis and 22 died. Compared to others, patients with cTMA were younger both at cTMA diagnosis and at transplantation (age at diagnosis, 28.9±16.3 vs 46.5±16.0 years; P<0.001). Crude survival probability is reported in Figure 1. After adjusting for non-linear age, sex, ethnicity, biopsy diagnoses, cTMA was associated with 4-fold increase in the hazard of transplant failure shortly after transplant (adjusted hazard ratio (aHR): 3.97 [95% CI:1.52-10.38; P=0.005]); then, the aHR decreased by 0.87 (95%CI: 0.77-1.00; P=0.046) per year elapsed since transplantation (Figure 2). Banff diagnoses were all associated with increased hazard of transplant failure: grade 1 & 2 TCMB, borderline rejection, and CNI-toxicity (P<0.05), and ABMR (P=0.077), the strength of their association with transplant failure not being affected by cTMA history (P=0.38 for interaction).

Conclusions: Patients with cTMA have an increased risk of early transplant failure which vanishes with time elapsed since transplant when standard Banff diagnoses seem to take over cTMA history in determining transplant prognosis.

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

Underline represents presenting author.
at discharge. Multivariate Cox regression models adjusting for several donor, transplant and recipient factors were used to compare graft, death-censored graft failure (DCGF) and patient death in all KTR and further stratified by donor type.

Results: A total of 194307 and 5152 patients on Tac and Bela were identified. Compared to patients discharged on Tac, subjects discharged on Bela were more likely to be older (53.5y vs 52.1y), African American (35.2% vs 27.3%), and diabetic (36.6% vs.34.5%), had greater time on dialysis (974d vs 913d), and received higher HDPI kidneys (36 vs 23) (p<0.05). Results of all KTRs and further stratified by donor type are shown in Table 1. Outcomes were similar in living donor KTRs; in deceased donor KTRs, Bela was associated with increased risk of death and DCGF.

Conclusions: Based on demographic and clinical data, patients discharged on Bela as maintenance therapy had higher comorbid burden. Our study found increased DCGF and patient death in the Bela group, which might be related to increased comorbidity, risk of early rejections despite the reduced nephrotoxic effects, and possibly increased viral and fungal infections associated with Bela. Retrospective nature and selection bias are major limitations of database study. Randomized controlled trials comparing Bela vs Tac are awaited.

Outcomes of all, deceased and living donor kidney recipients based on immunosuppression maintenance at discharge

<table>
<thead>
<tr>
<th>All patients</th>
<th>Tac Death (n=146071), p</th>
<th>Adverse Overall Graft Failure (n=140231), p</th>
<th>Death Censored Graft Failure (n=136934), p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplant</td>
<td>0.10 (0.032 – 0.47), 0.009</td>
<td>0.15 (0.10 – 0.21), 0.007</td>
<td>0.05 (0.00 – 0.48), 0.04</td>
</tr>
<tr>
<td>Deceased Donor</td>
<td>0.07 (0.032 – 0.47), 0.009</td>
<td>0.15 (0.10 – 0.21), 0.007</td>
<td>0.05 (0.00 – 0.48), 0.04</td>
</tr>
<tr>
<td>Living Donor</td>
<td>0.23 (0.00 – 0.47), 0.009</td>
<td>0.35 (0.21 – 0.47), 0.003</td>
<td>0.22 (0.09 – 0.44), 0.003</td>
</tr>
</tbody>
</table>

Conclusions: Belatacept and low dose CNI/Sirolimus combination is scant. At our institution, patients were switched to this regimen if they had Slow/delayed graft function, complications related to CNIs or graft rejection while on these drugs.

Methods: It is a retrospective chart review study. We included all patients >18 years of age at Indiana University Hospital who had a Kidney transplant and were switched from Tacrolimus, Sirolimus or Cyclosporine to a combination of Belatacept and lower dose CNI/Sirolimus. ‘Response’ (to the addition of belatacept) was defined as >10% change in the eGFR per year from baseline (pre-belatacept values) over 2 years. Logistic regression models were performed.

Results: N=79 Mean Age=53 years. History of deceased donor kidney transplant= 64%. Response was observed in 54% of patients with improved eGFR by 6 months (p= 0.003) and sustained by 2 years eGFR of 49.1±19.5 vs 35.3±11.4 (p= 0.04). The mean duration of dialysis in responders vs. non responders was 33.2 months, respectively (p= 0.057) and there was no difference in tacrolimus levels post conversion. By univariate anaylises, non-response was significantly associated with retransplant (OR= 4.93) and higher level of proteinuria (OR= 1.51), and history of graft rejection before belatacept (OR= 3.45).

Conclusions: Belatacept in combination with low dose conventional immunosuppression appears to be a favorable option in patients with slow/delayed graft function or intolerance to conventional drugs at their therapeutic levels.

TH-PO831

Renal Allograft Function Outcomes After Conversion from Conventional Immunosuppression to Belatacept Plus Low-Dose Conventional Drug Regimen

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Background: Calcineurin Inhibitors (CNIs) and Sirolimus have been traditionally used as immunosuppressants to prevent rejection in kidney transplant recipients but they are often associated with undesirable renal and metabolic adverse effects. Belatacept which is a selective T-cell co-stimulation blocker does not have the undesirable AE's. Data on using Belatacept and low dose CNI/Sirolimus combination is scant. At our institution, patients were switched from Tacrolimus, Sirolimus or Cyclosporine to a combination of Belatacept and lower dose CNI/Sirolimus. ‘Response’ (to the addition of belatacept) was defined as >10% change in the eGFR per year from baseline (pre-belatacept values) over 2 years. Logistic regression models were performed.

Results: N=79 Mean Age=53 years. History of deceased donor kidney transplant= 64%. Response was observed in 54% of patients with improved eGFR by 6 months (p= 0.003) and sustained by 2 years eGFR of 49.1±19.5 vs 35.3±11.4 (p= 0.04). The mean duration of dialysis in responders vs. non responders was 33.2 months, respectively (p= 0.057) and there was no difference in tacrolimus levels post conversion. By univariate anaylises, non-response was significantly associated with retransplant (OR= 4.93) and higher level of proteinuria (OR= 1.51), and history of graft rejection before belatacept (OR= 3.45).

Conclusions: Belatacept in combination with low dose conventional immunosuppression appears to be a favorable option in patients with slow/delayed graft function or intolerance to conventional drugs at their therapeutic levels.

TH-PO832

Safety of Belatacept as a Maintenance Immunosuppressive Therapy in Kidney Transplantation: A Systematic Review and Meta-Analysis

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Background: Although calcineurin inhibitors (CNIs) are used as the standard maintenance immunosuppressive therapy after kidney transplantation, they are associated with nephrotoxicity and long-term renal allograft loss. Recent randomized controlled trials (RCTs) showed that using Belatacept (Bela) as an alternative to CNIs is associated with improves renal function. However, there has been conflicting data about the risk of adverse outcomes such as infections and malignancies.

Methods: A systematic search for RCTs assessing the safety and efficacy of Bela in adult kidney transplant recipients was conducted in multiple online databases including Google Scholar and PubMed. RSAdio was used for statistical analysis. Results are expressed as relative risk ratio (RR) and 95% confidence interval (CI).

Results: Five RCTs were included in our meta-analysis. The results showed no significant difference between the Bela and CNIs based-regimen in terms of renal allograft loss (RR= 0.77, 95% CI 0.52 – 1.09), cytomegalovirus (CMV) viremia (RR= 0.98, 95% CI 0.47 – 1.30), BK viremia (RR= 0.83, 95% CI 0.35 – 2.02), and malignancy (RR= 1.31, 95% CI 0.81 – 2.13). There was a significant increase in the risk of post-transplant lymphoproliferative disorder (PTLD) (RR= 3.87, 95% CI 1.08 – 13.82), but the majority of those patients were Epstein-Barr virus (EBV) seropositive.

Conclusions: Overall, the use of Bela as maintenance immunosuppressive therapy in kidney transplantation was generally safe and with no substantial increase in the risk of infection or malignancy. There was an increased risk of PTLD associated with this regimen in patients with EBV-negative serology. Avoiding Bela in EBV-negative patients may help lower this risk.
Expanded One-Year Experience of Bimonthly Belatacept

TH-PO833
Hyaemin Lee, TH-PO834
Background: Belatacept (bela) is a common immunosuppressive (IS) drug in kidney transplant (KT). We have over 300 KT patients on bela. Our initial cohort of expanded 2 monthly belatacept had favorable results so we expanded our cohort from 18 to 34 patients without complication until year 2.

Methods: 34 patients at high risk of infection were included who were beyond one year from transplant and had no donor specific antibody (DSA) or prior episodes of rejection. They had stable allograft function and maintenance IS included bela 5mg/kg monthly, with mycophenolate mofetil dosing of 1g daily and prednisone 5mg daily. We monitored donor derived cell free DNA (ddcDNA; Allosure), total IS graft level, and CD4 counts at baseline and then at 2, 4, and 12 months. Repeated measures ANOVA was used to assess statistical changes with multiple comparisons adjusted with Tukey-HSD.

Results: 20/34 (59%) patients were African American. The mean time on bela at initiation was 48.1 ± 30.0 months. The estimated glomerular filtration rate (eGFR; Mean ± SD) did not change significantly between initiation and month 12 (43.5 ± 3 ± 46.3 ± 6.6 ml/min). There was no significant change in ddcDNA between months 0 (0.23 ± 0.03%), 2, 4 and 6 (0.20±0.06%) months, though at month 12 there was an uptrend in mean ddcDNA in 10 patients that have achieved this interval (0.43±0.06%). There was no difference in absolute CD4 count; mean ± SE between month 0 and 12 (326 ± 33.9 vs 368 ± 72.5; p= 0.94) and similar results were noted for IgG levels (939.5 ± 57.2 vs 861 ± 124.2; p=0.72). 1 patient developed low grade DSA at 6 months which resolved spontaneously. 1 patient underwent biopsy for proteinuria which showed advanced diabetic nephropathy. One patient underwent biopsy for acute rise in ddcDNA with DSA, which showed antibody mediated rejection, which resolved after intensive therapy and return to monthly bela infusions. There were no graft losses.

Conclusions: This report evaluating q2m bela, in a carefully selected and monitored cohort, demonstrates low risk of rejection with change in dose interval. There was no significant change in DSA or ddcDNA or incidence of major opportunistic infections. Long term outcome monitoring is needed, and close interval assessment of ddcDNA and DSA is critical for management of these patients in order to reduce the risk of acute rejection.

Comparisons of Clinical Outcomes Between Hypertensive and Normotensive Living Kidney Donors: A Nationwide Prospective Cohort Study

TH-PO834
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Background: Living kidney donors with hypertension is potential candidates to solve the imbalance between supply and demand for renal transplantation. However, the safety of hypertensive donor is not sufficiently ensured after donor nephrectomy and there are limited studies, which compare the clinical outcomes between hypertensive and normotensive donors.

Methods: All data from this study were obtained from the Korean Organ Transplantation Registry. A total 642 hypertensive donors and 4,848 normotensive living kidney donors for the national KTF registry for the recruitment period from May 2014 to December 2020.

Results: Compared to normotensive donors, hypertensive donors had lower eGFR before nephrectomy and remained lower after kidney transplantation. However, the risk of eGFR below 60 ml/min/1.73 m² (adjusted HR, 0.87; 95% CI 0.70-1.09; P = 0.217) or below 45 ml/min/1.73 m² (adjusted HR, 1.52; 95% CI 0.70-2.94; P = 0.209) was not significantly increased in hypertensive donors after multiple adjustment. When comparing the rate of eGFR decline between the hypertensive and normotensive donors, there was no significant difference (adjusted unstandardized β, -0.19; -1.15 – 0.76, P = 0.691). The incidence of proteinuria occurrence in hypertensive donor was increased, and it tended to increase even after 4-5 years. Hypertensive donors were found to have significantly more proteinuria than normotensive donors (adjusted HR, 1.77; 95% CI 1.10-2.85; P = 0.020). Our study indicated that the risk of proteinuria after donation was increased in hypertensive donor, while it was not translated into significant decline in renal function. The careful monitoring for proteinuria should be required in hypertensive donor after nephrectomy.

Funding: Government Support - Non-U.S.

Anti-Thymocyte Globulin vs. Alemtuzumab Induction and Associated Complications in Kidney Transplantation: A 28-Year Multi-Center Experience

TH-PO836
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Background: Antibody-depleting immunosuppression such as anti-thymocyte globulin (ATG) and alemtuzumab are commonly-used induction therapies after kidney transplantation and may result in varying rates of associated complications including, but not limited to, acute or delayed allograft rejection, leukopenia, sepsis, allograft failure, CMV infection, BK virus nephropathy, or death.

Methods: We performed a retrospective multi-center cohort study using TrnInetX, a gloablized health research network, providing access to electronic medical records across large healthcare organizations [HCOs] grouped into Global Collaborative Network including 97 HCOs. We identified 4,920 propensity-matched kidney transplant recipients inducted with ATG (n=2460) or alemtuzumab (n=2480) between Jan 2003-2023 from 26 HCOs from 3 countries, compared for clinical outcomes with risk analysis and Kaplan-Meier survival analysis.

Results: Kidney allograft rejection occurred in 1,159(47.1%) patients with alemtuzumab induction as compared to 794(32.3%) patients in ATG cohort(OR=1.460;95%CI 1.36-1.57). Severe sepsis confirmed in 1606(6.5%) patients with alemtuzumab vs 797(2.72%) in ATG group(OR=0.894;95%CI 0.73-1.09). With alemtuzumab, 908(36.9%) patients developed leukopenia vs 741(30.1%) patients in ATG cohort(OR=1.225;95%CI 1.13-1.33), and 135(5.48%) died in alemtuzumab group compared to 176(7.15%) in ATG group(OR=0.77;95%CI 0.61-0.95). Kidney transplant failure (KTF) was confirmed in 1090(44.3%) patients in alemtuzumab group and 724(29.4%) patients in the ATG group (OR=1.506, 95% CI 1.36-1.624), with graft survival of 53.06% and 67.80% in alemtuzumab vs ATG cohorts, respectively(OR=1.68;95%CI 1.18-2.45; p=0.004). CMV disease confirmed in 860(34.9%) with alemtuzumab induction vs 693(28.8%) in ATG group(OR=1.241;95%CI 1.14-1.35). With alemtuzumab induction, BK virus nephropathy was diagnosed in 370(15.05%) vs 265(10.7%) in ATG group(OR=1.396;95%CI 1.21-1.74).

Conclusions: Kidney transplant patients with alemtuzumab induction had significantly increased risk of rejection, leukopenia, transplant failure, CMV infection, and BK virus nephropathy. Risk of death is significantly less in the alemtuzumab group as compared to ATG group. No significant difference in severe sepsis between alemtuzumab and ATG cohorts.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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Methods: 12 adults receiving a kidney transplant from either a living or deceased donor were enrolled. To be included in this study must be be seropositive for EBV, free of donor specific antibodies, have low panel reactive antibodies, and the organ cannot be from an extended criteria donor or have a prolonged cold ischemia time. All participants will receive rATG and a regimen consisting of tegrobarpit 20 mg/kg IV administered every 3 weeks after initial loading, mycophenolate and alemtuzumab. The primary endpoint is safety at one year. Secondary endpoints include characterizing the pharmacokinetic profile of tegrobarpit, the incidence of biopsy proven rejection (BPAR) and changes in estimated glomerular filtration rate (eGFR).

Results: As of the abstract submission deadline, May 2023, 5 participants have been transplanted, and 3 are ongoing. No participant has experienced rejection. One discontinued due to an SAE of BK viremia and another for mild alopecia and fatigue. BK viremia was the only SAE reported to date, and the drug appears safe and well tolerated. Participant information is summarized in Table 1, and mean eGFR is summarized in Figure 1.

Conclusions: Improved graft function may improve long term outcomes in kidney transplantation. It is postulated that tegrobarpit could be an alternative therapy for prevention of rejection in kidney transplant recipients. Data to date are encouraging, with no rejections, a good safety profile and excellent allograft function.

Funding: Commercial Support - Eledon Pharmaceuticals Inc
Incidence and Experience of Post-Transplant Lymphoproliferative Disorder After Kidney Transplantation: A 20-Year Multi-Center Study

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Background: Post-transplant lymphoproliferative disorder (PTLD) is a rare complication following solid-organ transplantation, involving a spectrum of lymphocytic and/or plasmacytic proliferations in immunosuppressed patients. While often associated with Epstein-Barr Virus (EBV) reactivation, the pathogenesis and risk factors of PTLD are not clearly understood; its clinical manifestations are diverse, and management is challenging with focus on immunosuppression reduction, chemoradiotherapy or surgical resection of localized lesions, while aiming to preserve graft function.

Methods: We performed a retrospective multi-center cohort study using TriNetX, a global federated health research network providing access to electronic medical records across large healthcare organizations (HCOs). We identified 163,826 post-kidney transplant patients from January 15 2003-2023 from 89 HCOs in 13 countries. Patients with confirmed diagnosis of PTLD (n=2181) and those without PTLD (n=161,645) post-revascularization were assessed for clinical outcomes including death and kidney transplant failure (KTF) with risk analysis and Kaplan-Meier survival analysis.

Results: Among 163,826 post-revascular transplant recipients, 2,181 (1.3%) were identified with confirmed diagnosis of PTLD and 161,645 (98.6%) did not develop PTLD. At the time of transplant, the PTLD group was younger (p<0.0006), more likely to have received a previous transplant (p<0.0001), and on an immunosuppressive agent (p<0.0001). Of those who developed PTLD, 524 (24.4%) died as compared to 23,924 (11.7%) in the non-PTLD group; survival rate was 55.87% in PTLD vs. 44.79% in non-PTLD cohort [HR=0.434, 95% CI 0.398-0.473, p<0.00], Risk difference for death in patients without PTLD vs. with PTLD was -0.097 [RR=0.602, 95% CI 0.516-0.697, p<0.00]. KTF was confirmed in 34,483 (21.4%) in non-PTLD vs 600 (27.5%) in PTLD group.

Conclusion: Younger age, previous transplant and being on an immunosuppressive agent at time of kidney transplant is associated with occurrence of PTLD. Additionally, PTLD is associated with increased risk of graft failure and death.

Histological Analysis of Protocol Biopsies and Outcomes in ABO-Incompatible Renal Transplants: A Single-Centre Prospective Study from West India

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Background: ABO Incompatible renal transplants (ABOiKtx) is known to provide a viable option to increase donor pool for ever increasing need. Outcomes are comparable to ABO compatible counterparts. Limited data exist regarding role of Protocol Biopsies and the impact of histological changes on the outcomes of ABO incompatible renal transplants.

Methods: We included all ABO incompatible renal transplant patients from April 2017 and have completed 6 months of follow up till March 2019. A Protocol biopsy was done when eligible at 3 and 12 months post transplant. All the patients were analyzed for outcomes. Methodology for Biopsy: Biopsy samples were processed at our hospital, 2 cores were taken for histology and IF, C4D done by IF. Protocol biopsies were assessed and deemed adequate for interpretation by pathologists and graded according to the revised Banff classification 2017.

Results: 34 patients who underwent ABOiKTX between April 2017 to March 2018 were included. 23/34 patients underwent biopsies at 3 months [17 protocol and 6 indication biopsy (5 didnot consent, 2 were on antipatelettes, and 4 grafts were lost)] and 20/23 at 12 months [7 protocol and 3 indication biopsy (2 grafts were lost and one was on antipatelettes)]. Protocol biopsies revealed no subclinical rejections. 3/17 and 8/17 at 3 months, 17 protocol and 3 indication biopsy (2 graft were lost and one was on antipatelettes). Protocol biopsies revealed no subclinical rejections. 3/17 and 8/17 at 12 months respectively. Presence of C4D positivity or Tubulo-interstitial inflammation at 3 months was not associated with reduced GFR or increased fibrosis at end of 1 year. Lack of subclinical rejections were encouraging. Those with normal biopsies at 3 months had better graft survival and patient survival.
Conclusions: Our study demonstrates that combination therapy with metformin and tacrolimus in KT recipients with PTDM is associated with a lower risk of acute rejection and graft failure.

Methods: Flow cytometric analysis of peripheral blood leukocytes and CD8+ T cell subpopulations was performed shortly before transplantation (timepoint V1) in 65 kidney transplant recipients. CMV viremia was defined as above 100 CMV copies/ml in at least one PCR during the first year of transplantation.

Results: CMV viremia (CMV+) was frequent (n=33, 50.8%) in our cohort. After one year, eGFR was worse in CMV+ compared to CMV- patients (1.66 vs. 1.25ml/min/1.73m2, p<0.001), underlining its detrimental effect on graft function. Overall, pre-transplant frequencies of CD3+CD8+ in lymphocytes (19.7% vs. 15.4%, p=0.05) and FoxP3+CD25+ in CD3+CD8+ T cells (1.45% vs. 0.74%, p=0.01) were significantly higher in CMV+. Absolute numbers of leukocytes (4145/µl vs. 5249/µl, p=0.001), granulocytes (2576/µl vs. 3317/µl, p=0.01) and monocytes (222/µl vs. 315/µl, p=0.01) were lower in CMV+. Although not generally regarded as risk factor, women were disproportionally affected by CMV in our cohort (16 CMV+ in 25 women, 64% vs. 17 CMV+ in 40 men, 42.5%). Although we are limited by a small sample size, we sought to explore potential sex-specific risk factors for CMV within the peripheral blood at V1: For men, CD3+CD8+ T cells were increased in those who later developed CMV viremia (21% vs. 15.2%, p=0.04). Foxp3+CD25+ in CD3+CD8+ T cells (1.19% vs. 0.71%, p=0.01), and monocytes (211/µl vs. 358/µl, p=0.02) were decreased in women, who became CMV+.

Conclusions: Pre-transplant predictors of CMV viremia within the peripheral leukocyte and CD8+ T cell pool may aid in selecting patients for antiviral prophylaxis. While CD8+ T cells are generally regarded as cytotoxic, expansion of regulatory subtypes like Foxp3+CD25+CD8+ T cells may render individuals susceptible to infections. Our findings further hint towards sex-specific differences in immune cell abundance and function, which ought to be confirmed in a larger cohort.

Funding: Commercial Support - Chesi, Government Support - Non-U.S.

TH-PO843
A National Retrospective Cohort Study of BK Viremia in Renal Transplant Recipients
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Background: BK nephropathy is an important cause of graft dysfunction and graft loss. Treatment options are limited and involve immunosuppression reduction. In Ireland, post-transplant BK DNA is checked monthly between months 1-6 and thereafter at month 9-12. We examine incidence, risk factors and effect of BK viremia on long-term graft survival.

Methods: A national retrospective cohort study of renal transplant recipients in the first 12 months post-transplant between 2011-2021 was performed using data from the National Renal Transplant Registry and the National Virus Reference Lab. Patients were followed up for a minimum of 3 months and BK viremia was defined as >5000 DNA copies per ml (CPM). A cox proportional hazards model was used to assess risks associated with BK viremia. Statistical analysis was performed using Stata 16 SE.

Results: Of 1319 transplanted patients, BK surveillance rates were high across all nephrology centres (96-99% of patients had results available as per monitoring protocol). 179 (14%) of recipients developed BK viremia with peak levels occurring at two months and levels falling to 1000 CPM by six months. Rates of BK viremia were higher in males than females, 145 per 1000 patients (95% CI 121-175) versus 103 per 1000 patients (95% CI 76- 141). Highest rates of BK viremia were seen in ages 49-59 (190 per 1000 patients, 95% CI 146-247). Higher rates of biopsy-proven rejection at one year (HR 1.65 95% CI 1.41-1.94, p=0.001) were associated with BK viremia. Statistical analysis was performed using Stata 16 SE.

Conclusions: No significant difference in graft survival was observed in those who developed BK viremia in the first 12 months post-transplant over a decade of transplantation in Ireland. The next step of this analysis is the examine the effect of immunosuppression changes on the development of donor specific antibodies.

TH-PO844
A Comparison of BK Polyomavirus Nephropathy Between Native and Allograft Kidneys
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Background: BK polyomavirus nephropathy (BKVNP) has emerged as an important but uncommon cause of renal dysfunction and loss in allograft kidney and native kidneys from hematopoietic stem cell transplant recipients (HSCTRs). Yet it is unclear whether there is difference between these two populations on the clinicopathological features and renal outcomes.

Methods: Patients diagnosed as BKVN by renal biopsy from 2019 to 2022 were collected for a retrospective cohort study. The patients were divided into native kidney group (including 7 HSCTRs) and allograft kidney group (including 50 KTRs).

Results: BKVN in the time of diagnosis, the median age of native kidney group was younger than that of allograft kidney group (median 14.4 vs. 35.3y, P<0.001). There was no difference in renal graft survival in those with BK viremia than without at 10 years (p-value 0.37).

Conclusions: No significant difference in graft survival was observed in those who developed BK viremia in the first 12 months post-transplant over a decade of transplantation in Ireland. The next step of this analysis is the examine the effect of immunosuppression changes on the development of donor specific antibodies.
Efficacy and Safety of Sodium-Glucose Cotransporter-2 Inhibitor in TH-PO846

Increased Incidence of Kaposi Sarcoma Among African and Hispanic Kidney Transplant Recipients

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Background: Post-transplant Kaposi’s sarcoma (PTKS) is a rare complication among transplant patients. However, the incidence of PTKS is 100-500 times higher than Kaposi’s sarcoma (KS) in the general population. There have been no retrospective analyses characterizing increased incidence of PTKS among racial minorities in the U.S.

Methods: We performed an IRB-approved retrospective analysis of all adult patients (18 years of age) diagnosed with KS at Montefiore Medical Center. We reviewed electronic medical records based on ICD-9/10 code between the dates of 01/01/2014 – 09/01/2022 and identified 80 patients with KS, 10 of which were diagnosed with PTKS. Nine patients with PTKS after kidney transplant were included and 1 patient with PTKS after bone marrow transplant was excluded.

Results: Of the 9 patients that received kidney transplants and subsequently developed PTKS, 3 were female and 6 were male. All patients were minorities, with 6 African American and 3 Hispanic patients. Median age at transplantation was 60 years (range 44-70). Average time elapsed between transplant and PTKS development was 832.3±384.97 days (range 125-2630). Anatomic locations of PTKS lesions in patients included lower extremities (n=5), upper extremities (n=3), lymph nodes (n=3), kidney (n=1), and lung (n=1). Immunosuppression included tacrolimus (n=9), mycophenolate (n=7), cyclosporine (n=1), and steroids (n=10). After PTKS diagnosis, 7 patients had immunosuppression switched to sirolimus. 1 patient had tacrolimus and mycophenolate reduced, and 1 patient expired before treatment modification. All patients continued steroids. Four patients required additional treatment including radiotherapy (n=2), excision (n=1), and immunomodulation (n=1). One patient experienced PTKS recurrence approximately 18 months after initial resolution. Mortality was high (44%), and 4 patients died at a median of 95 days (range 19-1760) after diagnosis.

Conclusions: This study demonstrates high mortality rate in PTKS patients in minority kidney transplant recipients.

Efficacy and Safety of Sodium-Glucose Cotransporter-2 Inhibitor in Diabetic Kidney Transplant Recipients: A Case-Control Study


Background: KDIGO guidelines recommend initiating sodium-glucose cotransporter 2 inhibitors (SGLT2i) in diabetic chronic kidney disease (CKD) patients for its cardiovascular and renal protective effects. However, up till now, there are no recommendations regarding its use in diabetic kidney transplant recipients (KTR). The aim of this study was to determine the efficacy and safety of SGLT2i in diabetic KTR.

Methods: This was a retrospective case-control study. Cases (diabetic KTR using SGLT2i) and controls (diabetic KTR not using SGLT2i) were matched for recipient age, gender, year of transplant, and donor type. This study has been approved by Hamad general hospital research center. MRC-01-23-077

Results: There were 78 cases and 78 controls. The mean follow-up period in cases and controls was 23.9 and 24.1 months, respectively. Both groups had similar baseline graft function and HbA1c. Compared to controls, cases had a statistically significant reduction of BMI (-1.1 vs. -0.23; P=0.001). There was also a trend for better graft function and diabetes control, but it did not reach statistical significance. Both groups had similar adverse events such as AKI, UTI, cardiovascular and cerebrovascular complications (figure 1).

Conclusions: SGLT2i use in diabetic KTR was associated with a significant reduction in BMI and a trend for better kidney function and diabetes control. Longer prospective randomized controlled trials are needed to confirm their safety and efficacy outcomes in KTR.

Funding: Government Support - Non-U.S.
TH-PO848

Transition of Care of Stable Kidney Transplant Patients to Referring Nephrologists: A National Survey of US Transplant Centers

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Background: Transition of care from transplant centers (TC) to referring nephrologists is critical for long-term care of kidney transplant (KTx) recipients. We conducted a national survey to assess opinions and experiences of TC staff related to care graduation processes.

Methods: After IRB approval, staff at U.S. adult kidney TC were surveyed using the Qualtrics survey platform (4/5-22–10/31/22). Respondents were invited via email and professional society list-servs. If >1 survey was submitted for a TC, a selection hierarchy was utilized (e.g. prioritizing nephrologists).

Results: Respondents represented 55% of YC (n=108) and 67% of national KTx volume. The majority of respondents (78%) were nephrologists. Full graduation to referring nephrologists was reported by 37% of TC, while 48% reported partial graduation with ongoing co-management. Rationales for graduation included patient travel distance (64%), maintenance of referral base (58%), continuity of care (58%), and TC burden (58%) (Fig. A). Common reasons cited by TC for post-graduation return of care included worsening renal function (80%), malignancy (66%), opportunistic infection (63%), local nephrololgist availability (58%), and pregnancy planning (57%) (Fig. B). Additional staff were cited by 78% of TC as needed to enable TC perpetual care, with 70% expressing need for more clinicians. Nearly 50% thought more physical space or telemedicine are needed to enable TC perpetual care, with 70% expressing need for more clinicians. Nearly 50% thought more physical space or telemedicine are needed to enable TC perpetual care.

Conclusions: Graduation of KTx patients is common, with half of TC using joint-care. With continued growth of the KTx population, expanded opportunities related to transplant care for the general nephrology community are essential.

Funding: Private Foundation Support

TH-PO849

Transition of Care of Successful Kidney Transplant Patients from the Transplant Center: A National Survey of Referring Nephrologists

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Background: We conducted a national survey of nephrologists to assess opinions and experiences related to the process of returning kidney transplant (KTx) patients from the transplant center (“graduating”) to referring nephrologist care.

Methods: After IRB and Renal Physicians of America (RPA) approval, RPA members were surveyed using the Qualtrics electronic survey platform during October, 2022.

Results: The majority of the 105 respondents self-identified as private practice general nephrologists (78%). While 40% of respondent practices were within 10 miles of a transplant center (TC), >30% were more than 50 miles from a TC (Fig. A). Post-graduation visits were most frequently reported as every 3 mos. (51%) or every 6 mos. (29%), with lab draw intervals more frequent (monthly 32%, every 2 mos. 11%, and every 3 mos. 33%). Practices that did not accept patients back when ready for graduation (n=15) most typically cited the inability to work closely with the TC (67%) or inadequate staffing/resources for immunosuppression monitoring (53%); time commitment (40%) and patient complexity (33%) were less frequent concerns. Clinicians reported referring KTx recipients back to TC for management after graft dysfunction (79%), cancer (51%), pregnancy planning (41%), or fever (21%) (Fig. B).

Conclusions: Despite many general nephrologists being relatively close to a TC, most care for KTx patients. As expected, allograft dysfunction often leads to referral back to the TC after graduation. Nephrologists who do not accept KTx patients have concerns about communication with the TC or lack of office resources--both of which TC can actively help develop.

Funding: Private Foundation Support

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

Underline represents presenting author.

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OUTCOMES OF LIVING RELATED KIDNEY DONORS IN A TERTIARY CARE KIDNEY TRANSPLANT FACILITY OF A DEVELOPING COUNTRY

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Background: The long-term effects of unilateral nephrectomy for the live kidney donors are a neglected area of study in the developing countries. In Western countries like US, there is extensive data on living donor outcome through National Health and Nutrition Examination Survey (NHANES III), while no such resource is available in Pakistan. The purpose of this study is to evaluate the outcome of kidney donors at a large public-sector Academic hospital, Pakistan Kidney and Liver Institute, Lahore.

Methods: One hundred and thirty-two successive donors with living donor nephrectomies (during March 2018 to Feb 2021) were enrolled in this prospective observational study. Of these, 100 donors were successfully followed up since every six months for total of six encounters in 3 years. Outcome included short and intermediate term effects of unilateral nephrectomy on donor physical parameters (blood pressure and BMI), kidney function (serum creatinine, eGFR) and glycemic status (HbA1c) by comparing pre and post donation data. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

Results: Out of 100 living donors followed, 51 were male. All donors were in age range of 18-69 years with mean age 30-49 years. Left donor nephrectomy was performed in 89 (89%) patients. Mean diastolic blood pressure was slightly decreased and mean HbA1c pre and post donation were not statistically significant. Mean eGFR value before nephrectomy was 106.1ml/min and it dropped by 38% (65.2ml/min) at 6 months. The eGFR then increased by 12% at 1year, 10% at 1.5 years, 16% at 2 years, 14% at 2.5 years and 18% (79.3ml/min) at 3 years post nephrectomy.

Conclusions: We hereby conclude that living kidney donation resulted in initial decline in the renal function because of loss of one kidney. Subsequently, taking post-donation value of eGFR at 6 months as baseline, it gradually increased by 18% at 3 years.

TH-PO850

PREVALENCE OF VASCULAR CALCIFICATION AND VASCULAR STIFFNESS IN KIDNEY TRANSPLANT PATIENTS

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Background: Mineral and bone disorders related with chronic kidney disease (CKD) increased risk of vascular health in both CKD and dialysis patients, leading causes of morbidity and mortality. Although, kidney transplantation (KT) is the best way to treat end stage kidney disease and some important risk factors might be improved after KT, the prevalence of vascular diseases seems to be persistently high in KT recipients. Early detection, prevention and optimal management is the key to attenuate vascular diseases in KT.

Methods: This cross-sectional study was conducted in 400 KT recipients who received KT for at least 1 year and followed up at King Chulalongkorn Memorial Hospital. Plain film of lateral abdomen was done to assess the presence of vascular calcification (Abdominal aortic calcification scores) while cardiac-ankle vascular index was performed to evaluate vascular stiffness. Severe vascular calcification was defined by using abdominal aortic calcification scores ≥5. Baseline characteristics, laboratory data, and medications were collected for evaluation of important risk factors by multivariable logistic regression analysis.

Results: 400 KT recipients were enrolled in this study. The prevalence of severe vascular calcification and vascular stiffness was 35.94% and 27.75%, respectively. By multivariable logistic regression, diabetes mellitus and post parathyroidectomy were correlated with severe vascular calcification (OR 2.299; 95%CI 1.036-5.100; 95%CI 2.928-20.082, respectively). Systolic blood pressure, mean arterial pressure and severe vascular calcification were 35.94% and 27.75%, respectively. By multivariable logistic regression, diabetes mellitus and post parathyroidectomy were correlated with severe vascular calcification (OR 2.299; 95%CI 1.036-5.100; 95%CI 2.928-20.082, respectively) while elderly was correlated both severe vascular calcification and vascular stiffness (OR 1.108; 95%CI 1.074-1.142, OR 1.094; 95%CI 1.057-1.133, respectively).

Conclusions: The prevalence of vascular calcification and vascular stiffness were still high in KT recipients. Optimal management of important risk factors including mineral bone disorders (CKD-MBD) before and after KT, diabetes and blood pressure control should be highlighted to attenuate cardiovascular diseases in KT recipients.

Funding: Private Foundation Support

TH-PO852

CALCIPHYLAXIS IN KIDNEY TRANSPLANT RECIPIENTS


Background: Calciphylaxis, also called calcific uremic arteriolopathy (CUA), is a rare vascular disorder of subcutaneous microcirculation calcification and thrombosis. CUA results in painful non-healing necrotic ulcers and often portends poor outcomes. Minimal data exist describing post-kidney transplant calciphylaxis’s incidence, management, and long-term outcomes. Herein we describe a series of calciphylaxis in kidney transplant recipients.

Methods: Single-center observational cohort study of patients who received kidney transplantation (KT) between 1/1/1994 and 1/1/2023 and who developed calciphylaxis at any time after transplant with a functional kidney allograft.

Results: During the 29-year study period, nine patients had biopsy-proven calciphylaxis (CUA). Six patients had kidney transplant (KT) alone, two had a simultaneous pancreas and KT, and one had simultaneous liver and KT. None of the patients had a preemptive KT; only one received a living donor transplant. The mean age at the time of KT was 41 ± 13.4 years, and the mean at the time of calciphylaxis diagnosis was 45 ± 16.5 years. All patients received lymphotoxic-depleting induction (anti-thymocyte globulin) at the time of transplant. The mean duration on dialysis before KT was 3.4 ± 2. The mean time from transplant to the diagnosis of CUA was 4 ± 6.4 years; six patients developed CUA within twelve months of KT. Only one patient had a history of calciphylaxis before the transplant. At the time of CUA diagnosis, the mean eGFR was 57 ± 23 mL/min/1.73 m2; the mean for calcium was 10 ± 0.7, phosphorous was 3.6 ± 1, and iPTH was 212 ± 284 pg/mL. Location of CUA was distal lower extremity in seven patients. Eight patients required debridement, and four patients received sodium thiosulphate. Six patients were concurrently on anticoagulation at time of CUA diagnosis. Before 2001, three of four patients received parathyroidectomy. After 2001, one of five patients had parathyroidectomy. The mean follow up after the calciphylaxis diagnosis was 3 ± 3.2 years. At the last follow-up, three patients lost their kidney allograft, and four died.

Conclusions: Post-transplant calciphylaxis is rare and associated with high mortality and allograft loss. More extensive studies are needed to examine this condition’s risk factors and management.

TH-PO853

HYPERCALCEMIA OF HUMORAL MALIGNANCY AFTER KIDNEY TRANSPLANT

Srinath Tripuraneni, Amer A. Belah, Rohan V. Mehta, Alfonso Santos. University of Florida College of Medicine, Gainesville, FL.

Introduction: Hypercalcemia of humoral malignancy (HHM) occurs due to a tumor-produced parathyroid hormone-related peptide (PTHrP) and is associated with increased morbidity and mortality. HHM typically presents with severe hypercalcemia (>13 mg/dL), decreased or normal parathyroid hormone (PTH), and elevated PTHrP with variable serum 25 hydroxy vitamin D levels. Although HHM has been associated with renal, bladder, breast, ovarian carcinomas and squamous cell carcinomas of the lung, head, and neck, it can very rarely can present with squamous cell carcinoma of the skin. We describe a case of HHM in a kidney transplant (KT) Recipient (KTR).

Case Description: A 41-year-old Black man with a history of KT in early 2019, ESRD from Hypertension and Dyslipidic Kidneys with a baseline serum creatinine of 1.8-2.2 mg/dL was admitted for a groin mass. Relevant medical history included failed KT (2005), tertiary hyperparathyroidism s/p two lobe parathyroidectomy in 2018 (on sensipar), with baseline serum calcium 9.0-10.0mg/dL and baseline PTH of 200-400 pg/mL. The patient noted a perineal mass about two months prior to admission, that developed into a purulent and bleeding ulcer. Home medications included monthly Belatacept infusions, Mycofenolate 750 mg BID, and prednisone 5 mg daily. Laboratory data included serum creatinine 2.6 mg/dL, serum calcium 11 mg/dL, 25-OH vitamin D 18.71 ng/mL, and PTH of 133 pg/mL. Intravenous fluids were initiated, and a punch biopsy was performed by Dermatology. On post-admission day 7 with serum Calcium of 14.1 mg/dL, ionized calcium of 2.1 mmol/L, calcitonin was administered and sensipar was increased to 60 mg BID. Punch biopsy reported a well-differentiated squamous cell carcinoma, which was excised 10 days after admission. Serum Calcium dropped to 11.9 mg/dL, 4 days after surgery. PTHrP obtained before excision returned elevated at 60.2 pg/mL, while serum creatinine remained baseline. Serum Calcium had normalized to 9.2 mg/dL, about 4 weeks after surgery.

Discussion: HHM has been associated with solid organ cancers but can occur with dermatologic malignancies. Clinicians should be aware of the possibility of HHM as a rare complication of squamous cell skin cancer. In patients with tertiary hyperparathyroidism, it can present with severe hypercalcemia, non-suppressed PTH, and an elevated PTHrP.
Hypercalcemia as a Rare Manifestation of Pneumocystis jirovecii Pneumonia

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Introduction: Pneumocystis Jirovecii pneumonia (PPJ) is a fungal infection which disproportionately affects immunocompromised individuals. We present two cases of PPJ associated with hypercalcemia and acute kidney injury (AKI) in renal transplant recipients (RTR).

Case Description: Case 1: A 40-year-old male RTR patient presented with one-week of fever, cough, and shortness of breath. CT Chest showed peripheral ground-glass opacities. Patient remained febrile, tachycardic, and hypoxic. Given the clinical presentation and Fungitell > 500 pg/mL, treatment for PPJ was started with Atovaquone and steroids. Hypercalcemia (ionized calcium 1.62 mmol/L) was reported with routine workup insignificant for pharmacological or alternate underlying conditions. PTH was suppressed at 6 pg/mL and 1,25 DiHydroxyvitamin D was elevated above 200 pg/mL. 25-Hydroxy Vitamin D levels were within normal limits. Due to lack of improvement in hypercalcemia with IV hydration, Denosumab was prescribed with improvement in serum calcium levels. Bisphosphonates were contraindicated with renal dysfunction. Case 2: A 63-year-old male RTR patient presented with a three-week history of fatigue, cough, and chills. Workup similarly revealed PJP, hypercalcemia, and AKI with an elevated 1,25 DiHydroxyvitamin D. Due to failed treatment with IV Saline, Miacalcin, and Ketoconazole, Denosumab was used with improvement in Hypercalcemia. Clinical improvement of PJP reported with Primamucin and Clindamycin.

Discussion: Two renal transplant patients, on immunosuppressive medications, presented with AKI, hypercalcemia, and PJP. This hypercalcemia is believed to be due to an alveolar macrophage mediated process, increasing 1-a-hydroxylase activity and elevating 1,25-DiHydroxyvitamin D. Both patients responded favorably to denosumab, a RANK-L inhibitor which prevents osteoclast activation. PJP was suspected based on bilateral peripheral ground-glass opacities on imaging, elevated fungitell, and presence of dry cough in an immunocompromised patient. LDH was not elevated in Case 1, as sensitivity of LDH elevation in non-HIV patients with PJP is as low as 63%. Clinical improvement noted with treatment of PJP. Hypercalcemia is a unique presentation of PJP in renal transplant recipients. Early intervention is recommended given the potential for continued acute kidney injury.

Conclusions: Under Etelcalcetide than Cinacalcet Greater Incidence of Severe Hyperparathyroidism Requiring Early Transplantation, 35, 75, and 262 patients were treated with etelcalcetide, cinacalcet or no calcimimetic, respectively. After a median follow-up of 1064 (IQR 367-1658) days, the incidence of parathyroidectomy in the etelcalcetide no calcimimetic, respectively. After a median follow-up of 1064 (IQR 367-1658) days, the incidence of parathyroidectomy in the etelcalcetide vs cinacalcet vs no calcimimetic groups was 29% (n=10) vs 12% (n=9) vs 1% (n=2), respectively (p<0.001). Etelcalcetide was associated with an increased incidence of parathyroidectomy after transplantation, both in unadjusted analyses and after adjustment for age, sex and hemodialysis vintage (HR 91.0, 95% CI 1.91-493.9, p<0.001). The incidence of parathyroidectomy was related to etelcalcetide dosage (6/11 [54.6%] in patients with ≥10 mg vs 2/42 [16.7%] in patients with < 10 mg/dialysis session, p= 0.02). Moreover, calcium levels were higher (2.81 [IQR 2.60-2.99] mmol/L vs 2.63 [IQR 2.58-2.72] mmol/L, p<0.001) and parathyroidectomy was performed earlier (median 80 vs 480 days, p<0.001) in the etelcalcetide compared with the cinacalcet group. Long-term graft function, graft loss and mortality were similar between groups.

Conclusions: Etelcalcetide use during maintenance HD is associated with an increased incidence of early parathyroidectomy after transplantation compared to cinacalcet or no calcimimetic.
Transplantation: Clinical - I

TH-PO858
Correlates of Bone Mineral Density and Fractures in Kidney Transplant Recipients
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Background: Although kidney transplant recipient are known to be at high risk for bone disease, the optimal timing of testing for bone health and risk factors for osteodystrophy remain unclear.

Methods: We conducted a retrospective analysis of 65 patients from the Veterans Affairs at Loma Linda, California who underwent at least one DEXA scan after receipt of kidney transplantation.

Results: The mean age of our cohort was 64.0±12.2 and was predominantly male. Most patients received a combination of calcineurin inhibitor, antimetabolite and steroids for immunosuppression. Thirty patients had normal DEXA scans, while 25 patients were osteopenic and 10 were osteoporotic by DEXA; and 11 had documented fracture(s). Many patients received calcium and vitamin D prophylaxis but few received bisphosphonates or calcimimetics post transplant. (Table 1) In a multivariate model, after adjusting for age, dialysis vintage and other characteristics, we found that female gender was correlated with higher risk of fractures. In the same model, there was also a trend towards diabetes and high PTH (>300) predicting higher risk of fractures although this relationship did not reach statistical significance.

Conclusions: Despite the prevalence of bone disease among kidney transplant recipients, we found that a significant portion of such patients may not be receiving optimal therapy. Further studies are needed to establish effective treatments and determine the optimal monitoring frequency of bone parameters.

<table>
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<th>Table 1: Cohort characteristics. legend: DDKT: deceased donor kidney transplant; LRKT: living related kidney transplant; LUKT: living unrelated kidney transplant. Values are reported as mean ± SD or N (%), as appropriate.</th>
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The trajectory of hemoglobin, total calcium, and free calcium in KTRs with and without persistent hypercalcemia.
Method: We analyzed all SPK transplant recipients at our center between 1998 to 2021. PTE was defined as least 2 consecutive hematocrit (Hct) levels of >5% within the first 2 years of transplant. Controls were selected at a ratio of 3:1 at the time of PTE occurrence using event density sampling. Risk factors for PTE and graft survival were examined.

Results: Of 887 SPK recipients, 108 (12%) developed PTE a median of 273 days (IQR: 159.5-393) after transplantation. The incidence rate of PTE was 7.5 per 100 person-years. Multivariable analysis found increased incidence associated with being on dialysis before transplant (HR: 3.15, 95% CI: 1.67-5.92, p<0.001), nonwhite donor (HR: 2.14, 95% CI: 1.25-3.66, p<0.006), female donor (HR: 1.50, 95% CI: 1.0-2.26, p=0.05), and male recipient (HR: 2.33, 95% CI: 1.43-3.70, p<0.001). The 108 cases of PTE were compared to 324 control recipients without PTE. PTE was not associated with pancreas graft failure (HR: 1.36, 95% CI: 0.51-3.68, p=0.53) or kidney graft failure (HR: 1.16, 95% CI: 0.40-3.42, p=0.78).

Conclusion: The likelihood of non-utilization of kidneys from active or resolved COVID-19+ donors declined over time. During 2020-2022, kidneys from COVID-19+ donors had a higher risk of non-utilization compared to kidneys from donors without COVID-19. In 2023, kidneys from active or resolved COVID-19+ donors were no longer associated with higher risk of non-utilization. No higher risk of graft failure was found in KT recipients receiving active COVID-19+ kidneys (adjusted hazard ratio [aHR], 1.03; 95% CI, 0.78-1.37) or resolved COVID-19+ kidneys (aHR, 1.10; 95% CI, 0.88-1.39). Donor COVID-19 positivity was not associated with all-cause death, longer LOS, higher risk of acute rejection, neither DGF.

Conclusions: This cohort study found that the non-utilization rate of kidneys from COVID-19+ donors declined over time and donor COVID-19+ positivity was not associated with inferior KT outcome within 2 years post-transplantation.
TH-PO864

A Rare Case of Malakoplakia in a Renal Transplant Patient
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Introduction: Malakoplakia is a rare condition that affects immunocompromised patients, typically resulting in chronic inflammation, infections, and increased risk of bleeding in the affected tissues due to impaired bacterial clearance. Here we present a case of malakoplakia in a renal transplant patient that was complicated by bleeding and ultimately resulted in renal graft loss.

Case Description: A 70 y/o man presented to the emergency room with abdominal pain, fullness, and an acute kidney injury. He had a medical history of end-stage renal disease due to obstructive uropathy, deceased-donor renal transplantation in 2022 with anti-thymoglobulin induction, and was currently on triple immunosuppression with tacrolimus, mycophenolate, and prednisone. Abdominal computed tomography showed a large irregular mass in the right pelvis involving the right ureter, bladder, and renal transplant. Biopsy showed malakoplakia with chronic and acute inflammation, and ultimately grew Bacillus species. A drain was placed, and the patient was discharged with four weeks of piperacillin/tazobactam. Four months later, the patient was admitted with hypotension and abdominal pain. Abdominal imaging showed a subcapsular hematoma in the native right kidney originating from the malakoplakia lesion and extending into the right ureter, which required interventional radiology embolization. Imaging showed malakoplakia was still present throughout the native urinary tract. Immunosuppression was further reduced on discharge and suppressive antibiotics were continued to allow for adequate clearance of the chronic infection. The patient was ultimately readmitted with worsening kidney disease and restarted on dialysis. Malakoplakia findings were still present and largely unchanged on imaging. Immunosuppression was completely stopped and antibiotics were continued. The patient is currently undergoing nutritional optimization and chronic suppressive antibiotic therapy with the aim of pursuing surgery to remove the native urorugal tract.

Discussion: Here we show a case of malakoplakia in a renal transplant patient that required reduction of immunosuppression and subsequently led to graft function loss. Malakoplakia must be considered when imaging findings consistent with post-transplant lymphoproliferative disorder are seen in the urorugal tract.

TH-PO865

Urothelial Tumor in Transplant Patient with BK Nephropathy
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Introduction: BK is a dDNA virus in polyomaviridae family. BK does not cause disease in immunocompetent hosts. However BK can get activated in immunocompromised & cause BK nephropathy, ureteric stenosis in renal TX, hemorrhagic cystitis in HSCT and rarely associated with urothelial carcinoma. We present a case of urothelial cancer in patient with persistent BK viremia, presenting with new onset microscopic hematuria.

Case Description: A 62 y/o WM with a history of LDKT in 2016, on Prograf, MMF, steroid. He developed BK viremia & nephritis 2 years post-TX. Appropriate reduction in IS was implemented, along with weak IVIG. His allograft function remained stable with CKD3b. BK viremia remained stable in the range of 40K -100K. He was found to have Microscopic Hematuria in 2022, cystoscopy revealed 2 Invasive Papillary bladder cancer which stained positive for BK by SV40 stain. The patient was ultimately readmitted 4 months later, the patient had a medical history of end-stage renal disease, presented with hypotension and abdominal pain. Abdominal imaging showed a subcapsular hematoma in the native right kidney originating from the malakoplakia lesion and extending into the right ureter, which required interventional radiology embolization. Imaging showed malakoplakia was still present throughout the native urinary tract. Immunosuppression was further reduced on discharge and suppressive antibiotics were continued to allow for adequate clearance of the chronic infection. The patient was ultimately readmitted with worsening kidney disease and restarted on dialysis. Malakoplakia findings were still present and largely unchanged on imaging. Immunosuppression was completely stopped and antibiotics were continued. The patient is currently undergoing nutritional optimization and chronic suppressive antibiotic therapy with the aim of pursuing surgery to remove the native urorugal tract.

Discussion: Here we show a case of malakoplakia in a renal transplant patient that required reduction of immunosuppression and subsequently led to graft function loss. Malakoplakia must be considered when imaging findings consistent with post-transplant lymphoproliferative disorder are seen in the urorugal tract.

TH-PO866

Mystery Lung Mass in a Kidney Transplant Recipient
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Introduction: The differential for lung masses in solid organ transplant recipients is broad. It includes infections particularly fungal and mycobacterial infections, malignancy, and recurrence of underlying systemic disease (e.g.GPA). The overlapping clinical and radiographic findings make diagnosis challenging.

Case Description: This is a 64-year-old female with ESKD due to hypertension who underwent a deceased donor kidney transplant with Alemtuzumab and methylprednisolone induction. She received sulfamethoxazole-trimethoprim for Pneumocystis prophylaxis. She was maintained on tacrolimus, mycophenolate mofetil, and prednisone. She had no prior episodes of rejection. She presented one-year post-transplant with 20-lb weight loss, fevers, generalized weakness, and productive cough. CT chest revealed a large right lung mass. Sputum and BAL cultures grew Nocardia nova. Transbronchial needle aspiration of the mass was negative for malignancy. She was treated with imipenem/cilastin and trimethoprim-sulfamethoxazole. Her mycophenolate mofetil was held. She subsequently improved clinically with marked improvement of radiographic findings.

Discussion: Nocardia is a low virulence organism found in soil and water. It is a rare life-threatening opportunistic infection that affects the lung, brain, and skin. It is more common in solid organ transplants recipients and usually presents 1-2 years post-transplant. Pulmonary nocardia presents with non-specific clinical symptoms. Imaging typically shows cavitary lesions. The risk of nocardiosis increases with net immunosuppression, rejection episodes, and time since transplantation. Prophylaxis with trimethoprim-sulfamethoxazole covers nocardia. This case demonstrates the importance of high index of suspicion for nocardia and a low threshold to send testing for sputum AFB/culture and to pursue early bronchoscopy/BAL. Timely diagnosis and initiation of treatment allow for a good clinical outcome such as what was achieved in this case.
TH-PO867

Complete Remission of Donor-Derived Metastatic Urothelial Carcinoma After Transplant Nephrectomy and Discontinuing Immunosuppression

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Introduction: De novo urothelial carcinoma is associated with kidney transplant and tends to present with advanced disease at diagnosis. We present a case of donor derived metastatic urothelial carcinoma with complete remission following transplant nephrectomy and withholding immunosuppression.

Case Description: A 55-year-old male with ESRD secondary to hypertensive nephropathy was on dialysis from 1992 -2005 and underwent deceased donor kidney transplant in 2005. Dual kidney transplant was performed due to donor’s smoking history and donor finding of > 10% glomerulosclerosis. He did well post-transplant, baseline creatinine, 1.3 mg/dL. He developed allograft dysfunction with biopsy showing BK Polyoma Nephropathy in 2006. In 2021, he presented with bilateral flank pain and gross hematuria for 1 week. Urine cytology was positive for urothelial carcinoma. Bladder and prostatic urethra biopsies and right native pelvis washings were negative for carcinoma. Cytology from superior transplant kidney demonstrated high-grade urothelial carcinoma. PET CT in June 2021 showed abdominopelvic retroperitoneal nodal metastatic disease extending cephad to the right retroperitoneal region with relative sparing of the pelvic nodal chains and focal hypermetabolism of the left adrenal gland, presumed to be metastatic. Both transplant kidneys were surgically removed in June 2021. Lymph node dissection and adrenalectomy were not performed due to position and proximity to the aorta. A 5 x 4 cm high grade urothelial carcinoma with lymphovascular invasion was present in the pelvis of the superior allograft. BK virus DNA was undetectable in 2021. Immunosuppressive therapy included CNI, mycophenolate, and low dose prednisone. Immunosuppression was discontinued after resuming hemodialysis. Patient did not receive chemotherapy. Subsequent PET CT scans as recently as March 2023 demonstrated complete remission of metastatic disease. Cell-free DNA was < 0.12%, below the threshold for detection, supporting the absence of tumor.

Discussion: We report a case of complete remission of donor derived metastatic urothelial carcinoma following transplant nephrectomy and immunosuppression withdrawal. Future research should explore the balance between innate immunity as a protective factor against malignancy and immunosuppression to prevent rejection.

TH-PO868

When the Diagnosis Is Skin Deep: A Case of Cutaneous Chromoblastomycosis in a Patient with Kidney Transplant

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Introduction: Chromoblastomycosis, caused by fungi from the Herpotrichiellaceae family, primarily affects skin and soft tissues. Although it’s prevalent in tropical and subtropical regions, U.S. cases have been reported. The disease presents various dermatologic lesions and can, in rare cases, affect lungs, bones, and brain. Treatment includes physical interventions, antifungal therapy, and is notoriously difficult due to frequent relapses and possible bacterial infections.

Case Description: A 43-year-old male kidney transplant recipient with a history of end-stage kidney disease from hypertension presented with a persistent, expanding skin lesion on his right anterior leg. Despite being non-pruritic, non-painful, and without any surrounding inflammation, his interest in gardening raised suspicion. A skin biopsy confirmed the diagnosis of chromoblastomycosis. The patient began itraconazole treatment, resulting in slow lesion improvement.

Discussion: Melanized fungal infections, such as chromoblastomycosis, are infrequent, particularly in temperate climates, making diagnosis challenging. This case illustrates the necessity of an early skin biopsy for accurate diagnosis. Immunocompromised patient, are at an elevated risk of disseminated disease. Thus, early diagnosis and treatment are critical to reduce potential morbidity and mortality.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO870

Impact of Area Deprivation Index on Early Stages in the Kidney Transplantation Process

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Background: Socioeconomic factors play major roles in kidney transplantation (KT) access and outcomes but are difficult to identify. Area Deprivation Index (ADI) is a measure of socioeconomic conditions at the census block group level. We hypothesized that ADI may be a useful tool to identify patients at risk for inequities in the KT process. We investigated whether ADI was associated with attendance at KT clinic and subsequent waitlisting (WL).

Methods: We performed a retrospective cohort study of adults referred for KT evaluation from 1/1/15 -12/31/21. We compared clinical and sociodemographic characteristics between patients who were 1) seen vs. not seen in KT clinic and 2) WL vs. not WL. Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables were used. Multivariable logistic regression analysis was performed to examine the association between ADI and WL.

Results: 2,284 patients were referred for KT evaluation during the study period. Patients from the most vulnerable neighborhoods (ADI 44-100) were less likely to be seen following referral (31% vs 26%; p=0.008). 1,691 (74.0%) patients attended KT evaluation, of these patients, 643 (38%) were waitlisted for KT. Residents in the highest ADI quartile (44-100) had a 38% less odds of being WL relative to the residents in the lowest ADI quartile (1-18) (OR 0.62, 95% CI 0.45-0.87, p=0.005).

Conclusions: Patients residing in higher ADI neighborhoods are at increased risk of not being seen in KT clinic and not being WL after KT evaluation. These findings suggest that ADI may be a useful marker to proactively identify patients at risk for early inequities in advancement through the KT process and could help guide early intervention efforts to ensure a more equitable evaluation process.

Funding: NIDDK Support

Table 1: Multivariable Logistic Regression for Being Waitlisted for Kidney Transplantation (If Seen in Clinic):

<table>
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<th>Variable</th>
<th>B</th>
<th>SE</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
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</tbody>
</table>

TH-PO871

Unraveling the Hemodialysis Patient Network: Results from the Social Network and Renal Education (SNARE) Transplant Intervention

Alec Gayner,1 Avrum Gillespie,2 Peter P. Reese,2 Crystal A. Gadgebeku,1 Hannah Calvelli,1 Heather M. Gardiner,1 Edward L. Fink,1 Lewis Katz School of Medicine at Temple University, Philadelphia, PA; 2Hospital of the University of Pennsylvania, Philadelphia, PA; 3Temple University, Philadelphia, PA.

Background: In-center Hemodialysis (HD) is a unique therapy occurring in a group setting, facilitating patient social network formation. Social networks are a key social determinant of health, amenable to intervention if influential members are identifiable. Two goals of our study are to determine whether patients who are more clustered (a network member whose alters are interconnected) vs. more central (a network member who has multiple alters who are not interconnected) within HD networks are more likely to disseminate the Communicating About Choices in Transplant (COACH) intervention. This intervention has been shown to improve knowledge, communication skills, and behaviors regarding living/deceased-donor kidney transplantation (KT).

Methods: For this pilot network intervention clinical trial (NCT03536858), in a North Philadelphia HD clinic, the Monday, Wednesday, Friday patients were stratified to contact spread and Tuesday, Thursday, Saturday to clustering spread. Outcomes including number of transplant evaluation steps completed, change in KT knowledge, self-reported KT conversation self-efficacy, and living donation requests were assessed using repeated questionnaire data and chart review prior to the intervention, at 3-months, and 9-months post-intervention. Data analysis was performed using t-tests, repeated measures ANOVA, and Fisher’s exact test.

Results: Twenty-eight transplant-eligible patients completed the study. Groups (centrality N=11; clustering N=17) did not differ significantly in demographic or clinical variables. The clustering group completed more KT evaluation steps (+0.79 ± 1.72 vs. -0.38 ± 1.3, p=0.02) and reported higher conversation self-efficacy scores than the centrality group (21 ± 2.6 vs.16 ± 1.4, p=0.03). The difference in living KT requests was not significant (3 vs 1, p=0.5). No differences were observed in knowledge outcomes.

Conclusions: Selection of patients with the highest clustering yielded more efficient dissemination of the COACH intervention. Notably, this network intervention improved transplant behaviors but not knowledge, indicating a peer-network imitation effect on behaviors without changing knowledge. Further research is indicated to assess these effects in a larger population and with expanded network targeting strategies.

Funding: NIDDK Support
**TH-PO873**

Effect of Kidney Allocation System (KAS) Policy on Renal Transplantation in Elderly Recipients


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**Background:** Prior to 2015 KAS policy creation and implementation, there were inordinate number of kidneys being allocated to recipients who were not matched appropriately to enhance the longevity of the transplanted organ. Our aim was to analyze the impact of KAS policy on patient mortality.

**Methods:** This study includes retrospective analysis of primary DDRT patients aged ≥ 65 years reported to UNOS/OPTN and performed between 2010 and 2022. Patients were divided into preKAS and KAS group by dialysis status. Comprehensive univariate and multivariable analyses were performed.

**Results:** There were 347,171 patients analyzed. Fig 1 shows the changes in factors over time. The number of transplants increased significantly as well as the number of preemptive transplants. The wait time decreased significantly and the number of Black and Hispanic recipients increased significantly. Fig 1 shows patient and graft survival at 3 years. During the KAS era outcomes declined. The analysis showed an increased Relative Risk for transplants during KAS (RR: 1.39, 1.32-1.46) while the outcome for preemptive transplants is significantly lower (RR: 0.68, 0.64-0.73).

**Conclusions:** The number of kidney transplants in the elderly transplant group increased over time which offers an increased life expectancy. While overall the mortality risk could not be reduced, a shorter waitlist time was noted, which is important. This analysis also shows the importance of early transplantation in this age group to reduce mortality.

**Fig 1**

**TH-PO874**

Geographic Proximity to Donor Care Units Among Deceased Organ Donors After Brain Death

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**Background:** The National Academies recommend that all United States (US) organ procurement organizations (OPOs) operate deceased donor care units (DCU) but adoption is incomplete. Donors in hospitals at greater distances from DCUs may be less likely to transfer. We sought to characterize the geographic proximity of donors in hospitals to operating DCUs as a proxy for nationwide DCU access.

**Methods:** Retrospective analysis of all adult deceased donors after brain death with recovery dates Jan 2010 - Jun 2022 in Organ Procurement and Transplantation Network data. Driving times and distances between donor hospitals and DCUs were measured using ArcGIS road network software. We defined geographic proximity to a DCU by estimated driving times; primary outcome was drive time <2 hours (feasible for ground transport). We estimated the number of donors who would gain access to DCUs if OPO donor service area boundaries were ignored.

**Results:** Among 92,085 donors in 2,574 hospitals, 42,302 (42.0%) were managed in one of 25 OPOs with DCUs. Among donors in those areas, a majority (86.7%, 36,687 donors in 999 hospitals) were within 2 hours’ driving distance of a DCU. Rates of DCU proximity varied by OPO (median 43.5% (IQR 0-67.8%) of donors per OPO). When OPO area boundaries were ignored, 8164 additional donors in 229 hospitals were within 2 hours’ distance of at least one DCU (Fig 1). Donor characteristics were similar between groups.

**Conclusions:** Less than half of donors were within 2 hours drive of a DCU. Proximity rates varied across donor service areas. A substantial number of donors were in hospitals proximate to an existing DCU in a neighboring area. OPOs may consider collaborating to transfer donors from hospitals in nearby areas or opening additional DCUs. Future work is needed to understand whether, and how, optimally located DCUs may improve kidney donation and transplantation outcomes.

**Funding:** Private Foundation Support

**Fig 2**

**TH-PO875**

Using Machine Learning to Identify People Considering Living Kidney Donation on Reddit

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**Background:** Machine learning (ML) strategies may help to identify potential kidney recipients and living kidney donors on online digital platforms, who are considering living kidney donation (LKD), to target helpful information to them. Our study’s aims were to: (1) Identify people sharing their personal LKD experiences on the digital platform Reddit, (2) Determine whether ML models could distinguish between simplified or more nuanced labels.

**Methods:** A multidisciplinary team of engineers and transplant experts created and piloted a user labeling system to code 3,292 posts created by Reddit users from 2010-2023 using 3 simplified labels and 6 nuanced labels (Table). To validate the system, four team members independently labeled the same 100 posts manually, and definitions were refined until reaching unity. The remaining 3,192 posts were manually labeled using refined definitions. We explored the ability to automate this classification process using an ML model known as Bidirectional Encoder Representations from Transformers (BERT). Two models were trained to predict simplified and nuanced labels, respectively. Exploratory work using ChatGPT was also included for automatic classification.

**Results:** The BERT model accurately classified the simplified labels with 87% accuracy, but when trained to classify all six nuanced labels, was only able to perform with 67.1% accuracy. Preliminary experiments using ChatGPT showed poorer alignment with automated user labeling than ML models (69% and 45.3% for simplified and nuanced labels, respectively).

**Funding:** Private Foundation Support
Conclusions: Using expert defined classification criteria combined with ML methods, it is possible to identify those who may be interested in living donation on digital platforms. Current methods perform better on more simplified classifications, but improvements can be made and advances in ML may increase the predictive power of future models. Future work will explore ways to enhance the BERT method using integration with ChatGPT.

TH-P0876

Sociodemographic Barriers to Interest and Pursuit of Living Donation Among ESKD Patients

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Background: Living donor kidney transplants result in better patient and graft survival compared to deceased donor kidney transplants. Despite these benefits, only 23% of all kidney transplants in 2022 were from a living donor. To provide insight of potential barriers to living donation, we quantified the associations of interest in, and pursuit of, living donor transplantation with sociographic, demographic, and socioeconomic factors among end-stage kidney disease (ESKD) patients.

Methods: This was a retrospective study of 151,656 adult ESKD patients on dialysis for whom preferences and potential pursuit of transplant status were documented. Publicly available data sources were used for classification of sociographic status. Outcomes considered were interest in living donation and separately, pursuit of a living donor transplant with geographic, demographic, and socioeconomic factors among end-stage kidney disease (ESKD) patients.

Results: For the 59,893 patients in whom interest was recorded, 11,675 (19.5%) were interested in living donor transplant. Among those interested, 7,376 (63.2%) reported having pursued a living donation. The following factors were associated with interest in living donation: age at dialysis start, race/ethnicity, sex, diabetes status, insurance type at dialysis start, kidney education attendance, and poverty level. The following factors were associated with pursuit of a living donor transplant: age at dialysis start, race/ethnicity, and insurance type at dialysis start. Both interest and pursuit of living donation varied by state, but no obvious regional trends were observed.

Conclusions: Our results identify subgroups of patients who could potentially benefit from additional education regarding living donor transplantation.

TH-P0877

Experiences of Ethnically Diverse Living Kidney Donors

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Background: Living kidney donors enter the donation process in good health but are often ill-prepared to face any negative outcomes following donation. Adverse post-donation outcomes are more prevalent among ethnic minorities. We aimed to provide an in-depth description of ethnically diverse donors’ positive and negative outcomes to inform development of an online module of lived experiences.

Methods: We used the DIPEx (database of individual patient experiences) method to conduct in-depth individual interviews with a diverse sample of donors. This method combines in-depth patient interviews with rigorous systematic, purposeful sampling and qualitative analysis. All interviews were conducted by a primary and secondary interviewer and analyzed by a qualitative research team.

Results: Fourteen donors (9 women; 8 White, 5 Hispanic, 1 Native American) completed narrative interviews. Findings highlight the critical role of social support in validating the decision to donate and aiding post-donation recovery. Participants felt compelled to donate to prevent dialysis use or death for their recipient. Although familial duties seemed to motivate donation for Hispanic and Native American women, a call to action as a healthy individual was a greater motivator among the White donors. Most (n = 13) felt well-supported by healthcare providers throughout the entire pre-donation period, though three participants reported erroneously being told they had developed kidney disease in primary care due to a lack of clarity regarding post-donation clinical care. Among directed donations (n = 12), most reported either no change or improvement in the relationship to the recipient. Many donors (n = 11) experienced unanticipated outcomes post-donation, including minor complications (e.g., constipation, fatigue, pain), moderate complications (e.g., hernia, gout), or emotional distress (e.g., depression, mourning loss of kidney). Despite these adverse outcomes, all participants were enthusiastic about donation and reported no regrets.

Conclusions: Adverse outcomes post-donation did not preclude living donors’ enthusiasm and support of donation; therefore, greater transparency about post-donation outcomes is warranted. An online DIPEx module presenting these diverse experiences may enhance awareness and understanding of the donation process for future living kidney donors.

Funding: Other NIH Support - National Center for Advancing Translational Services - UL1TR001449

TH-P0878

Healthcare System Intervention Changed Negative Perceptions of Healthcare in Kidney Transplant Candidates

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Background: The kidney transplant (KT) evaluation process is lengthy for patients but even longer for Black patients. One potential reason for these longer times is past negative experiences with healthcare contributing to mistrust toward healthcare systems. We examined whether engaging in a streamlined evaluation process at a transplant center reduced negative perceptions of the healthcare system among Black patients.

Methods: We recruited patients undergoing KT evaluation, and the intervention occurred during the evaluation period. We collected survey responses at T1 (before evaluation initiation) and T2 (following KT evaluation completion). Surveys assessed experience of discrimination in healthcare, perceived racism in healthcare, medical mistrust, and trust in physician. Regression analyses adjusted for baseline characteristics. We examined whether negative perceptions of healthcare changed from T1 to T2 among White and Black participants.

Results: The final sample included 883 participants (658 White, 225 Black). White participants consistently had lower scores for discrimination, racism, and mistrust but higher scores for trust in physician, compared to Black participants, across both time points (all p < .001). Interaction effects indicate that White participants experienced a significant reduction in discrimination, racism, and mistrust scores at T2, and Black participants experienced a significant reduction in discrimination, mistrust, and trust in physician scores at T2 (all p < .05). The difference in change-in-perception scores between Whites and Blacks was statistically significant for trust in physician (p = .012).

Conclusions: A coordinated healthcare system intervention reduced perceptions of discrimination, racism, and mistrust in patients undergoing KT evaluation, but results varied by race. Future work will ascertain whether perceptions of discrimination, racism, and mistrust are associated with faster time to KT waitlisting, treatment adherence, and quality of post-transplant.

Funding: NIDDK Support
TH-PO879
Disparities in Phase Progression in Kidney Transplant Evaluation

Background: Inequity in access to kidney transplantation by race/ethnicity is a significant challenge. In this study, we evaluate the association between race and progression to subsequent phases of transplant in patients being evaluated for a kidney transplant.

Methods: We conducted a retrospective cohort study of patients undergoing kidney transplant evaluation at our center from 2020-2023. Using time-to-event analyses, we examined the time to reaching the next phase of transplant by self-identified patient racial group. Patients determined to be ineligible for listing were censored at committee review date while remaining patients were censored at the end of the study period. We then created a multivariate Cox proportional hazards model to assess the association between race and phase progression while controlling for age, gender, employment status, cause of end-stage renal disease, and insurance type.

Results: We identified 957 patients who were evaluated for kidney transplant with a documented race. Of these, 9% were Asian, 26% were Black/African American, 28% were Hispanic/Latino and 35% were White. Median progression time from evaluation to listing was 181 days and listing to transplant was 264 days. The unadjusted probability of progressing from evaluation to listing was significantly different between all racial groups (p<0.0001), but there was no difference in progressing from listing to transplant (p=0.12) (Figure). In adjusted models, Black/African American patients had 37% lower rate of progressing from evaluation to listing (p=0.00001) and 35% lower rate of progressing from listing to transplant (p=0.01) compared to White patients, and Hispanic/Latino patients had 34% lower rate of progressing from evaluation to listing (p=0.0005) compared to White patients.

Conclusions: Disparities in progression from evaluation to waitlisting contribute to racial disparities in kidney transplant access.

Figure: Kaplan-Meier failure curves displaying progression from evaluation to listing and listing to transplant, stratified by race

TH-PO880
Public Survey of Financial Incentives for Kidney Donation
Amgad E. El Agroudy. Arabian Gulf University, Manama, Bahrain.

Background: With the increasing prevalence of end-stage kidney disease in Bahrain, kidney donation is of vital importance. In this study we want to assess how financial incentives will influence peoples' views and decisions regarding kidney donation. The aim is to establish strategies to increase the number of kidneys for transplantation in Bahrain.

Methods: We adapted a previously established questionnaire on financial incentives for living kidney donations. The questionnaire assessed the public opinion in Bahrain on how kidney donation can be influenced by two different financial incentives, namely 10,000 BHD and life-long health insurance. We collected a convenient sample of 446 participants by distributing an electronic version of the questionnaire. SPSS-23 software was used for data entry and analysis.

Results: Of the total participants 39% were male and 61% were female. Eighty-percent of the participants believed that their chances for kidney donation will not increase in turn of receiving a financial compensation, while 20% of them believed that it will increase. Our study found that generally married participants (70%) find it a preferable incentives' system for kidney donation.

Conclusions: Although financial incentives for kidney donation might encourage a minority of the population, the majority may not be influenced by implanting a financial incentives’ system for kidney donation.

TH-PO881
Neighborhood Deprivation and Access to Living Donor Kidney Transplantation: Reducing Health Care Disparities
Byoungjun Kim, Gayathri Menon, Yiting Li, Maya N. Clark-Cutain, Dorry L. Segev, Mara McAdams-DeMarco. NYU Langone Center for Surgical & Transplant Applied Research. New York University Grossman School of Medicine, New York, NY; New York University Rory Meyers College of Nursing, New York, NY.

Background: Living donor kidney transplantation (LDKT) offers better health outcomes for individuals with end-stage kidney disease (ESKD). Deprived neighborhoods have low socioeconomic status, limited social cohesion, and reduced access to health care. However, the role of neighborhood deprivation on access to LDKT is understudied.

Methods: We used SRTR data to identify 510,674 non-Hispanic (NH) White, NH Black, NH Asian, and Hispanic KT candidates (age ≥18) who were listed for first KT from 1995-2015. The National Cancer Institute’s Neighborhood Deprivation Index (NDI) was averaged at the ZIP code level using population weights from the American Community Survey. Proportional hazards models were used to determine the likelihood of LDKT across tertiles of NDI, adjusting for clinical and neighborhood-level factors.

Results: Candidates residing in high-deprivation (HD) neighborhoods had a lower access to LDKT than those in low-deprivation (LD) neighborhoods (adjusted hazard ratio (aHR)=0.90, 95% confidence interval (CI): 0.79-0.92), notably, Black candidates living in HD neighborhoods had 37% lower access to LDKT than those in LD neighborhoods (aHR=0.63, CI: 0.60-0.67). Similarly, Asian and Hispanic candidates living in HD neighborhoods had 22% (aHR: 0.78, CI: 0.70-0.88) and 21% (aHR: 0.79, CI: 0.75-0.83) lower access to LDKT, respectively, relative to White candidates.

Conclusions: Neighborhood deprivation is associated with decreased access to LDKT, particularly among Black candidates. Identification of structural factors impacting healthcare access in disadvantaged neighborhoods can be used by policymakers and healthcare providers to develop interventions to address barriers and disparities in LDKT access.

Table 1. Neighborhood Deprivation Levels and access to LDKT (N=510,674).

<table>
<thead>
<tr>
<th>Neighborhood Deprivation Levels</th>
<th>Low Deprivation (32%)</th>
<th>Medium Deprivation (31%)</th>
<th>High Deprivation (37%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted Hazard Ratio (aHR)</td>
<td></td>
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<tr>
<td>Medium HD</td>
<td>0.96 (0.94-0.98)</td>
<td>1.00 (0.98-1.02)</td>
<td>1.00 (0.98-1.02)</td>
</tr>
<tr>
<td>High HD</td>
<td>0.94 (0.92-0.97)</td>
<td>1.00 (0.98-1.02)</td>
<td>1.00 (0.98-1.02)</td>
</tr>
</tbody>
</table>

Funding: Other NIH Support - NIA

TH-PO882
Ongoing Sex Disparities in Living Kidney Transplantation: A UNOS Analysis
Fausto R. Cabezas, Sandeep R. Sasisiharan, Mohammad W. Abushawer, Tahir A. Jatoi, Moro O. Salifu, Angelika C. Gruessel, Subodh J. Saggi. SUNY Downstate Nephrology Division. SUNY Downstate Health Sciences University, New York City, NY.

Background: In the United States, the prevalence of chronic kidney disease (CKD) is higher in females (16.2%) than in males (13.4%). Studies in Asia and Mexico have shown that females comprised 62% to 69% donors and were LDKT recipients in only 20% of cases. Disparities are not fully explained by socio-cultural or biological factors. Outdated U.S. data showed a lower rate of LDKT in females. We aim to explore current trend of LDKT in the US.

Methods: We queried the UNOS database for all adult primary single organ LDKTs from 2011 to 2022. We excluded deceased donor recipients which has been previously described. Comprehensive univariate and multivariate analyses were performed to describe changes and risk factors.

Results: There were 60,865 LDKTs, 36% were female recipients and 63.5% were donors (Table 1). The likelihood to receive a LDKTA decreased with increasing age. Black females were more likely to be donorsreceive a LD KTA when compared to white females (OR 1.4 [1.3-1.5] <0.001). Female donors recipients were less likely to be Black females (OR 1.4 [1.3-1.5] <0.001). Female donors recipients were less likely to be biological related to male recipients to receive a nonbiologically related KTA (OR 0.89 [0.86-0.93] <0.001). Furthermore, female recipients were longer on the transplant waiting list and were more likely to have a higher a cPRA (OR 6.2 [6.2-7.3] <0.001). Female to Male donors accounted for 40.6% of donors, this trend remained stable throughout the study period.

Conclusions: Females are more likely to be donors than LDKTA recipients and face longer times in the transplant waiting list. Black females were more likely to be donors and less likely to be recipients when compared to white females. The sex disparities in KT
listing and LKDT remains. However, socio-cultural factors, as well as biological factors influencing such disparities are yet to be elucidated. Data informed policy is warranted to bridge the sex disparities in LKDT.

<table>
<thead>
<tr>
<th>Table 1. Donor and Recipient Characteristics.</th>
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<tbody>
<tr>
<td><strong>Variable</strong></td>
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<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>African American (%)</td>
</tr>
<tr>
<td>Cold ischemic time, h</td>
</tr>
<tr>
<td>EPTS (%)</td>
</tr>
<tr>
<td>cPRA &gt;80%</td>
</tr>
<tr>
<td>Length of stay, d</td>
</tr>
<tr>
<td><strong>All recipients</strong></td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Female (%)</td>
</tr>
<tr>
<td>African American (%)</td>
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<tr>
<td>Cold ischemic time, h</td>
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<tr>
<td>EPTS (%)</td>
</tr>
<tr>
<td>cPRA &gt;80%</td>
</tr>
<tr>
<td>Length of stay, d</td>
</tr>
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</table>

Conclusions: In keeping with the KAS, organs from donors with KDPI >80% were more likely to be allocated to younger highly sensitized recipients. Mortality and graft failure at 1-year post-transplant did not differ between recipients with KDPI >80% vs. <80% kidneys despite the older age of the high KDPI recipients. The high DGF rate in our low KDPI group was likely to be due to the acceptance of allografts from donors with acute kidney injury in an effort to transplant recipients who were ranked lower. Our results suggest that high KDPI kidneys should be utilized although the early transplant period requires a strong multidisciplinary transplant team to guarantee good outcomes in underserved communities with low rates of DDKT such as ours.

TH-PO884
Living Kidney Donation in the United States from 2017 to 2022
Fawaz Al Ammary,1 Hayden R. Truitt,2 Deidra C. Crews,2 Abinereki Muzaaie,2 University of California Irvine, Irvine, CA; Johns Hopkins University, Baltimore, MD.

Background: Living kidney donation has not recovered to pre-pandemic rates. To inform the national efforts for increasing living kidney donation rates in the United States, we sought to characterize post-pandemic trends to guide future interventions.

Methods: We studied a US national registry (SRTR) of 35,511 living kidney donors from 2017 to 2022 (median age [IQR], 44 years [34-54], 64% female, 71.8% White, 15.2% Hispanic, 8.4% Black, 4.6% Asian donors). We used Poisson regression models to describe changes in the number of donors in 2020-2022 vs. 2017-2019 by donor-recipient relationship and race/ethnicity.

Results: Among biologically related donors aged <34, 35-49 and ≥50 years the number of White donors aged <34, 35-49 and ≥50 decreased by 13%, 13% and 19%, and Black donors aged <34, 35-49 years decreased by 27% and 22. Among unrelated donors <35, 35-49, ≥50 White donors decreased by 13% across age groups and Black donors <34 decreased by 49%. Among spousal donors aged 35-49 and ≥50 White donors decreased by 21% and 23% and Black donors decreased by 44% and 38% Among kidney-paired donors White donors ≥50 increased by 18%, and Hispanic donors aged <34 and ≥50 increased by 31% and 65%. No significant changes were observed for Asian donors across these described subgroups.

Conclusions: The decline in living kidney donation in the wake of the pandemic was driven by White and Black donor subgroups, warranting targeted efforts to uncover what new barriers may be responsible for these observations.

Funding: NIDDK Support, Other NIH Support - NIA

TH-PO885
Living Kidney Donors’ Perspectives of Telemedicine Video Visits for Donor Evaluation: A Qualitative Study
Fawaz Al Ammary,1 Ellie Kim,2 Transplant Quality Collaborative.1 University of California Irvine, Irvine, CA; Johns Hopkins University, Baltimore, MD.

Background: Living kidney donor evaluation is a complex multiphase process that takes approximately one year. It requires in-person visits where access to a transplant center becomes a barrier for willing candidates. Telemedicine via synchronous video enhances care coordination of donors. We conducted a qualitative study to understand donors/donor candidates’ perceptions of telemedicine in donor evaluation.

Methods: We conducted in-depth, semi-structured interviews between 11/23/2021 and 03/17/2022. We interviewed 20 donors/donor candidates who completed their evaluation via telemedicine or in-person visits at a tertiary transplant center in Baltimore, Maryland. Interviews were analyzed using thematic analysis.

Results: Participants reported the following: 1) Telemedicine reduces travel time and travel-related expenses. 2) Telemedicine requires less time commitment compared to in-person, which allowed for more flexibility with scheduling their visit and made it easier to take less time off work. 3) Telemedicine reduced the burden of arranging for child and family care. 4) Interest in having introductory information provided prior to their visit. 5) Some concerns about telemedicine visit privacy and security. 6) Suggestions for using visual aids to facilitate the information shared during their visit. 7) Preferences in telemedicine versus in-person based on the providers’ roles, specifically noting that they would prefer to meet the surgeon in-person. 8) Differences in levels of personal connectedness and communication. 9) Advantage of telemedicine allowing family and significant others to attend their visits.

Conclusions: Our findings provide information about donors/donor candidates’ experiences and attitudes toward using telemedicine for donor evaluation. The reported views help inform a care coordination model in the donor evaluation process to enhance engagement of donor candidates and support completion of their evaluation.

Funding: NIDDK Support
TH-PO886

Automated 3D Cortical Thickness Measurements from CT Images: A Novel Predictor of Low Kidney Function in Living Kidney Donors

Timothy L. Kling, Adriana Gregory, Panagiotis Korfliats, Andrew D. Rule, Aleksandar Denic. Mayo Foundation for Medical Education and Research, Rochester, MN.

Background: The kidney cortex volume can be quantified on contrast-enhanced CT and is prognostic for chronic kidney disease (CKD) outcomes. Reduced cortical thickness is routinely reported from kidney ultrasound, however, cortical thickness is highly variable throughout the cortex and can be difficult to estimate from 2D images. Additionally, the relative contributions of cortical thickness and cortical volume to CKD risk are unclear.

Methods: This study examined a cohort of 1,132 living kidney donors with robust cortico-medullary differentiation on contrast-enhanced CT of the kidneys. AI techniques first separately segmented the cortex and medulla. Automated post-processing was employed to measure kidney length and volume of cortex. Then a distance map-based method was used to calculate average, maximal, and summed cortical thickness of the retained kidney. Cox proportional hazards models assessed the risk of measured kidney length and volume of cortex. At the same level of cortex volume, a donor with lower total cortex thickness is at a higher risk for lower kidney function. Decreased total cortical thickness relative to total cortical volume may better detect loss of nephrons from nephrosclerosis than does cortical volume alone.

Results: Higher levels of all five AI-derived kidney cortex measures correlated with higher pre-donation mGFR (r=0.13-0.33, p<0.001). In unadjusted analyses, lower levels of all cortex measures associated with onset of a mGFR<60ml/min/1.73m2 at a median 4 months post-donation. After adjusting for cortex volume, lower sum of cortex thickness and higher mean cortical thickness associated with onset of a mGFR<60ml/min/1.73m2.

Conclusions: At the same level of cortex volume, a donor with lower total cortex thickness is at a higher risk for lower kidney function. Decreased total cortical thickness relative to total cortical volume may better detect loss of nephrons from nephrosclerosis than does cortical volume alone.

Funding: NIDDK Support

TH-PO887

Beliefs and Intention to Organ Donation

Sami A. Aljboaidi: University of Jeddah, Jeddah, Saudi Arabia.

Background: Efforts to increase organ donation globally have not been successful, as seen in the low donor rates in Middle Eastern countries like Saudi Arabia, despite advanced healthcare systems and supportive government policies. Multiple factors, including psychosocial, cultural, religious, and structural elements, influence organ donation rates, some of which are unique to Saudi Arabia. The theory of planned behavior (TPB) is used to study how attitudes, beliefs, and norms affect organ donation intention and practice. This study explores normative, behavioral, and control beliefs among Saudi Arabian residents.

Methods: This was an online survey conducted from June to December 2021 using a Google form questionnaire among residents of Saudi Arabia. The survey covered demographic factors and explored normative, behavioral, and control beliefs related to organ donation.

Results: This study received 1245 valid responses. Among the study participants, only 19.6% were willing to register as an organ/tissue donor. The intention for organ donation showed a statistically significant positive association with beliefs that organ donation is a good thing (123.51, df: 4, p<0.001), could save somebody’s life (61.38, df: 4, p<0.001), could have a positive impact on life after death (114, df: 4, p<0.001), and that the provision of better social support to the family of the deceased can increase organ donation (68.43, df: 4, p<0.001). Knowledge about family objections (190.76, df: 4, p<0.001), transplantation process (179.35, df: 4, p<0.001), religion’s view of medical autopsies (120.345, df: 4, p<0.001), and registration facilities (241.64, df: 4, p<0.001) increased willingness to donate organs. Worry about receiving less care (OR=4.25, 95% CI 1.17-15.51), belief in better social support increasing the risk of organ donation (OR=10.49, 95% CI 1.56-70.43), and concern for family emotions during donation (OR=4.37, CI 1.57-12.23) strongly predict intention to donate organs.

Conclusions: The study shows positive correlations between normative, behavioral, and control beliefs and definite intention for organ donation in the Saudi population. Control beliefs show a negative correlation. Promoting awareness about the organ donation process, including religious permissibility, is needed to increase donation rates.

TH-PO888

Procurement Retardation Improves Organ Recovery

Chloé Samson,1,2 Sarah Douin,2,3 David Boeb,3,1 Juliette Hadchouel,1,2 Pierre Galichon,1,2 Mécanismes de l’insuffisance rénale aigue et réparation.

1INSERM U1155, Paris, France; 2Sorbonne Universite, Paris, France; 3Assistance Publique - Hopitaux de Paris, Paris, France.

Background: The conditioning of the donor is crucial to avoid delayed graft function (DGF), which occurs in nearly 30% of cases and is associated with graft loss. A third of brain-dead donors have a recovered cardiac arrest (RCA), thus leading to a first episode of renal ischemia before procurement. Even if ischemia is known to be deleterious, studies conducted so far did not find an association between the donor’s RCA and DGF. We hypothesize that the time interval (TRCA) between the RCA (1st ischemia) and the graft’s procurement (2nd ischemia) could influence the function and survival of the graft.

Methods: To mimic the situation of a donor with RCA, we performed two renal ischemias separated by either 2 or 5 days, using a vascular occluder we recently developed. We evaluated the Glomerular Filtration rate (GFR) 24h after each ischemia by measuring the transcutaneous excretion kinetics of FITC-sinistrin (MediBeacon®). The histological analysis was carried out 24h after the 2nd ischemia by evaluating (i) the tubular injury and (ii) the cellular response using markers of proliferation (BrdU) and cell death (TUNEL).

Results: Comparably to the human data, the GFR following an early 2nd ischemia is lower than after a late 2nd ischemia. There was also a trend towards increased tubular lesions in the early group compared to the late one. Our future goal is to examine the effects of inhibiting proliferation after an early 2nd ischemia on the function and structure of the kidney (short & long-term after ischemias).

Conclusions: We hypothesize that the time interval (TRCA) between the RCA (1st ischemia) and the graft’s procurement (2nd ischemia) could influence the function and survival of the graft. The conditioning of the donor is crucial to avoid delayed graft function (DGF), which occurs in nearly 30% of cases and is associated with graft loss. A third of brain-dead donors have a recovered cardiac arrest (RCA), thus leading to a first episode of renal ischemia before procurement. Even if ischemia is known to be deleterious, studies conducted so far did not find an association between the donor’s RCA and DGF. We hypothesize that the time interval (TRCA) between the RCA (1st ischemia) and the graft’s procurement (2nd ischemia) could influence the function and survival of the graft.

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

TH-PO889

Health-Related Quality of Life in Altruistic vs. Directed Kidney Donors

Tamar Hod,1 Assaf Vital,1 Eronsh M. Askansays,2 Ronen Ghinea,3 Eytan Mor,3 Tel Aviv University, Tel Aviv, Israel; Ariel University, Ariel, Israel; Sheba Medical Center, Tel Hashomer, Israel.

Background: Despite the significant increase in the rate of living kidney donation, there has been a lack of sufficient investigation into the post-donation health related quality of life (HRQol) of altruistic donors (ADs) in comparison to directed donors (DDs).

Results: This study received 1245 valid responses. Among the study participants, only 19.6% were willing to register as an organ/tissue donor. The intention for organ donation showed a statistically significant positive association with beliefs that organ donation is a good thing (123.51, df: 4, p<0.001), could save somebody’s life (61.38, df: 4, p<0.001), could have a positive impact on life after death (114, df: 4, p<0.001), and that the provision of better social support to the family of the deceased can increase organ donation (68.43, df: 4, p<0.001). Knowledge about family objections (190.76, df: 4, p<0.001), transplantation process (179.35, df: 4, p<0.001), religion’s view of medical autopsies (120.345, df: 4, p<0.001), and registration facilities (241.64, df: 4, p<0.001) increased willingness to donate organs. Worry about receiving less care (OR=4.25, 95% CI 1.17-15.51), belief in better social support increasing the risk of organ donation (OR=10.49, 95% CI 1.56-70.43), and concern for family emotions during donation (OR=4.37, CI 1.57-12.23) strongly predict intention to donate organs.

Conclusions: The study shows positive correlations between normative, behavioral, and control beliefs and definite intention for organ donation in the Saudi population. Control beliefs show a negative correlation. Promoting awareness about the organ donation process, including religious permissibility, is needed to increase donation rates.

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

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**Methods:** We analyzed 112 living kidney donors (82 ADs and 30 DDs) who completed a SF-12 questionnaire and four supplementary questions. We compared the PCS and MCS scores between the two groups and examined secondary outcomes such as admission length of stay (LOS), time to return to normal activity and to physical activity, pre- and post-donation exercise rates, and physical activity continuation post-donation.

**Results:** Living kidney donors had higher mean PCS-12 and MCS-12 scores compared to the general population, with significantly higher scores in ADs than DDs (p<0.001). ADs returned to physical activity sooner than DDs (45 vs. 60 days), exercised more before and after donation, and continued post-donation. ADs had shorter admission LOS (3.4 vs. 4.4 days, p<0.001). Multivariable regression analyses revealed donation type and WBC count predicted PCS-12 score (altruistic vs. DDs: +2.69 (1.02), p<0.01) and donation type predicted MCS-12 score (altruistic vs. DDs: +4.43 (1.53), p<0.005). Altruistic donation type predicted a shorter LOS (by 0.78 days, p<0.001) and the odds of having PCS-12 and MCS-12 scores above 50 were almost 10 and 16 times higher in ADs, respectively (p<0.05).

**Conclusions:** ADs exhibit significantly higher physical and mental HRQoL compared to DDs post-donation, indicating the safety and potential benefits of promoting altruistic donation. However, it is essential to maintain a careful selection process to prevent any harm and ensure that donors’ genuine desire to help others is not exploited.

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**TH-PO891**

**Sex Disparity and Kidney Function in Living Kidney Donors**

Ekamol Tantisattano,W1,2 Voramol Rochanaroon,2 Wanprapit Norcut,1 Ben Thiravetyan,3 Thanathip Suengnataiphorn,1 Uraiwit Chuenchaemb,6 Narathorn Kualhamrongsi,1 Thitiphan Srikulmontri,1 Chanokorn Puchongmart,5 Pengpich Naamsri,1 Passawat Vutikrativit,2 Manaswee Tananayakul,6 Thirast Leesatipornchai,10 Jathamron Kittrakulratt,1 Satisorn Kunapakpan,1,2 Phuawadith Wattanachayakul1,4 University of California Irvine School of Medicine, Irvine, CA; 1Tibor Rubin Veterans Affairs Medical Center, Veterans Affairs Long Beach Healthcare System, Long Beach, CA; 2Rayong Hospital, Rayong, Thailand; 3Police General Hospital, Bangkok, Thailand; 4Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; 5Bhumrungrad International Hospital, Bangkok, Thailand; 6Siriraj Health Science Education Excellence Center, Mahidol University Faculty of Medicine Siriraj Hospital, Bangkok, Thailand; 7Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; 8Phraoongkkitklao College of Medicine, Mahidol University, Bangkok, Thailand; 9University of Hawaii John A. Burns School of Medicine, Honolulu, HI; 10Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; 11Ramathibodi Excellent Center for Organ Transplantation, Bangkok, Thailand.

**Background:** While a sex disparity in chronic kidney disease exists, it remains unclear if there is a disproportionate difference in kidney function following kidney donation.

**Methods:** A retrospective cohort study using OPTN/SRTR includes adult living kidney donors (LKD) undergoing donation between June 1972 and September 2022. The time-to-event of >35% rise in post-donation serum creatinine (SCr) from pre-donation SCr between female and male LKD was investigated by multiple Cox proportional hazard regression.

**Results:** In a cohort of 136,814 living kidney donors, meansSD age was 42±12 years and 61% were female. Out of 103,938 LKD with post-donation SCr data at 6, 12, or 24 months, 75,343 (72%) experienced the event within a median time to follow-up of 6.3 months (IQR 4.1, 8.7). The incidence rate of the event was 0.09 person-months. The mean and median pre-donation SCr was 0.85±0.19 and 0.80 mg/dL, respectively with notably female and male mean pre-donation SCr were 0.77±0.14 and 0.99±0.17 mg/dL, respectively (mean difference of 22%, 95%CI 0.22, 0.22; P<0.001). Compared to female LKD, male LKD had a 12% significantly higher risk of experiencing an increased post-donation SCr >35% (HR 1.12; 95%CI 1.10, 1.13; P<0.001). After adjusting for age, race/ethnicity, U.S. citizenship, education level, history of pre-donation hypertension, pre-donation BMI, SBP, DBP, post-donation proteinuria, and the interaction term between sex and pre-donation SCr (>0.8 or >0.8), male LKD remained at a significantly higher risk for the event (HR 1.42; 95%CI 1.36, 1.47; P<0.001). Furthermore, pre-donation SCr was identified as an effect modifier with an increased risk of rising SCr >35% observed in male LKD with pre-donation SCr >0.8 mg/dL (P<0.001).

**Conclusions:** Male LKD with pre-donation SCr >0.8 mg/dL are at a higher risk of experiencing an increased post-donation SCr >35% compared to female LKD regardless of other pre- and post-donation factors. Despite women contributing as LKD more than men, addressing the underlying causes of sex disparity may provide the opportunity to increase donations while taking precaution for high-risk population.

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**TH-PO890**

**Comorbidity and Multimorbidity Burden in Living Kidney Donors**

Nyan Lam, University of Calgary Cumming School of Medicine, Calgary, AB, Canada.

**Background:** After donation, living donors may develop one or more risk factors that increase the likelihood of subsequent cardiac and kidney adverse events.

**Methods:** We conducted a cross-sectional, population-based cohort study using linked healthcare databases to study 979 living kidney donors who had donated between 1994 and 2019 in Alberta, Canada. The primary outcome was the presence or history of cardiac and kidney comorbidities, as of March 31, 2020. Cardiac comorbidities included hypertension, diabetes, or major cardiovascular events (myocardial infarction, stroke, or transient ischemic attack). Kidney comorbidities included sustained low eGFR (<45 mL/min/1.73 m²), moderate-severe proteinuria, or kidney stones. Secondary analyses included the presence of other comorbidities, such as cancer, depression, and chronic pain.

**Results:** The median time since donation was 13 years (IQR 7–19). Of the cardiac comorbidities, hypertension was the most common (31%), followed by diabetes (7%), then major cardiovascular events (5%). Both hypertension and diabetes were present in 5% of donors. For the kidney comorbidities, a history of kidney stones was the most common (12%), while low eGFR (5%) and proteinuria (4%) were uncommon. For the other comorbidities, chronic pain (40%) was most common, followed by depression (36%). Overall, approximately three-quarters of donors had at least 1 comorbidity with the proportion of donors with multimorbidity (≥2 comorbidities) rising with increasing age.

**Conclusions:** Comorbidity and multimorbidity in the living kidney donor population rise with increasing age. The results of this study may inform long-term follow-up care of donors by identifying those who may benefit most from periodic health reviews.

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

Underline represents presenting author.
TH-P0892
Changes in Sex Lives Pre- and Post-Kidney Transplantation
Natascha Gupta, Yi Liu, Mara McAdams-DeMarco, New York University Grossman School of Medicine, New York, NY.

Background: Sexual dysfunction among patients with kidney disease (KD) is common. Although studies have demonstrated improvements in sexual function after kidney transplantation (KT), the impact of KD on patients’ sex lives pre- and post-KT is unknown.

Methods: We leveraged a prospective cohort of 497 adult KT recipients who responded to the Kidney Disease Quality of Life questionnaire from 2014 to 2022 at Johns Hopkins. Adjusted logistic regression models were used to estimate characteristics associated with self-reported sexual bother due to KD pre-KT versus 22.8% (14.8% of females and 26.9% of males) 3 years post-KT (p=0.001). Pre-KT participants who were male (adjusted odds ratio [aOR]=3.08 [95% CI:2.02-4.69]), non-Black (aOR=1.65 [95% CI:1.09-2.51]), partnered (aOR=1.93 [95% CI:1.27-2.93]), or prior current smokers (aOR=1.65 [95% CI:1.10-2.47]) had significantly more sexual bother. Estimated sexual bother due to KD improved significantly over time across all subgroups. The increase was only statistically significant among male participants.

Conclusions: Sexual bother due to KD is common and improves significantly after KT for patients across varying subgroups. The impact of KD on patients’ sex lives can be improved by KT.

Funding: Other NIH Support - National Institute on Aging, National Center for Advancing Translational Sciences (KL2TR001446).

TH-P0893
Care Considerations and Management of Transgender Individuals After Kidney Transplantation: A Single Institution Experience and Literature Review
Pragati Basera,1 Manish Anand,2 Amit Govil,3 Shikha Jaiswal.2 King George’s Medical University, Lucknow, India; 1University of Cincinnati, Cincinnati, OH.

Introduction: It is estimated that there are 0.04% to 0.06% transgender people in the United States. More than 4000 of them are affected by End Stage Kidney Disease (ESKD). There are limited studies on transgender patients undergoing kidney transplantation, and their post-transplant experiences. This study aims to describe 2 cases at our center highlighting this and review available literature.

Case Description: Case # 1: 48-year-old Trans-female, with past medical history of ESKD secondary to IgA nephropathy and major depressive disorder (MDD), underwent deceased Deceased Donor Kidney Transplant (DDKT) in 2018. The patient was on concomitant psychotropic medications for depression and anxiety during the transplantation period. The patient was a non-smoker and she was on no medications requiring dose adjustments prior to transplantation.

Case # 2: 57-year-old Trans-male with ESKD secondary to polycystic kidney disease, underwent DDKT in 2016. The patient was on concomitant psychotropic medications for depression and anxiety during the transplantation period. The patient was a non-smoker and he was on no medications requiring dose adjustments prior to transplantation.

Discussion: Transitioning through gender-affirming care can be stressful for a Transgender person. In the early peri-transplant phase, estrogen may lead to venous thromboembolic events and allograft loss. When used with calcineurin inhibitors (CNI) or with azathioprine, estrogen may increase hyperkalemia risk. Estrogen may cause urological complications. Regular screening for osteoporosis and sexually transmitted infections, as well as psychosocial support, is necessary. As hormone therapy can affect muscle mass and body composition, it is recommended to use a non-sex-dependent estimation of GFR using cystatin C.

TH-P0894
Kidney Allograft Outcomes Are Similar in Recipients with Living Donors and Those with Hematopoietic Stem Cell Transplant Donors
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Background: The impact of hematopoietic stem cell transplantation on the risk of allograft failure has been previously described; however, the study of its impact on kidney allograft outcomes has not been extensively studied.

Methods: We conducted a retrospective analysis of all adult patients who received a kidney allograft from an HCT donor at our institution between 1/1/2000 and 6/30/2020. The primary endpoint was graft function at 1 year post-transplantation. Comparison of overall survival, patient survival, and allograft survival was performed using Kaplan-Meier survival analysis.

Results: We identified 40 patients who received a kidney allograft from an HCT donor. The median follow-up time was 3.5 years (range: 0.2-13.2 years). The 1-year patient survival rate was 95% (38/40), and the 1-year allograft survival rate was 92% (36/40). There were no significant differences in patient or allograft survival between the transplant donor groups.

Conclusions: Kidney allograft outcomes are similar in recipients with living donors and those with hematopoietic stem cell transplant donors.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Pre-Transplant Biomarkers of Cellular Senescence Are Associated With Death With Function After Kidney Transplantation

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Background: Cellular senescence has associated with aging and medical risk in non-transplant populations. The goal of this study was to examine the relationship between pre-transplant biomarkers of cellular senescence and death with function after kidney transplantation.

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

Underlying represents presenting author.
Methods: We conducted a prospective, observational cohort study involving consecutive adult patients who received a kidney transplant at Mayo Clinic in Minnesota between 1/2006 and 12/2018. We measured biomarkers of cellular senescence in pre-transplant serum. Cox analyses, Kaplan Meier survival analyses, and gradient boosting machine modeling were used to examine the relationship between biomarkers and death with functioning kidney transplantation.

Results: Our cohort consisted of 1,595 kidney transplant recipients, of whom 62.9% were male and 38.3% were non-Hispanic white. Over a mean follow-up time of 7.4 ± 3.9 years, 19.7% of patients (n=315) experienced death with function. Higher levels of growth differentiation factor-15 (GDF-15), interleukin-6 (IL-6), monokine induced by gamma interferon (MIG), and soluble tumor necrosis factor receptor-1 (sTNFR1) were associated with death with function. Adding these biomarkers to a clinical Cox model improved the C-statistic for death with function from 0.732 to 0.750, while using a gradient boosting machine modeling approach instead improved the C-statistic from 0.715 to 0.754.

Conclusions: Pre-transplant biomarkers of cellular senescence predict death with function after kidney transplantation. Measuring serum concentrations of GDF-15, IL-6, MIG, and sTNFR1 may help risk stratify kidney transplant candidates.

Funding: NIDDK Support

TH-PO900

Graft Outcomes in Spousal Donor Kidney Transplantation: Impact of Donor-Recipient Sex Mismatch

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Background: Despite increasing demand for kidney transplantation (KT) due to aging populations, the shortage of available kidneys remains a significant obstacle. Spousal donor kidney transplantation (LDKT) in modern nuclear families. Given that patients' sex is a biological characteristic, the mismatch between the donor and recipient's sex can potentially affect the survival and function of the transplanted kidney. Moreover, female donors are exposed to donor HLA antigens during pregnancy, which increases immunological risk. We aim to investigate the impact of donor-recipient sex mismatch on the outcomes of spousal donor kidney transplantation.

Methods: We analyzed 456 spousal donor kidney transplantation (SDKT) recipients at Mayo Clinic in Minnesota from 1986 to 2022. Recipients were categorized based on immunological risk determined by Panel Reactive Antibody. Among the 367 standard-risk SDKT recipients, 75 were husband-to-wife (H2W) and 292 were wife-to-husband (W2H). In the high-risk group of 89 SDKT recipients, 55 were H2W and 34 were W2H. We assessed graft survival and allograft rejection based on donor-recipient sex mismatch.

Results: Long-term graft survival and the incidence of biopsy-proven acute rejection (BPAR) with 1 year after KT were comparable between H2W and W2H recipients in standard-risk group (10-year survival rate: 90.7% vs. 87.6%, p-value = 0.428; incidence of BPAR: 3% vs. 7%, p-value = 0.178). In the high-risk group, long-term graft survival was similar between H2W and W2H recipients (83.6% vs. 91.2%, p-value=0.593), while H2W recipients showed a higher incidence of BPAR within 1 year after KT compared to W2H recipients (5% vs. 17% p-value = 0.044), mainly due to acute antibody-mediated rejection (AAMR).

Conclusions: Our findings indicate that donor-recipient sex mismatch does not have a significant impact on graft survival. However, among high-risk SDKT recipients, H2W SDKT recipients exhibited a higher risk of AAMR compared to W2H SDKT recipients, who faced a slightly higher immunological risk. H2W SDKT recipients with a high immunological risk should receive careful management through personalized desensitization protocols and tailored immunosuppressant strategies to reduce the incidence of AAMR following KT.

TH-PO901

Risk of Symptomatic Kidney Stones After Kidney Donor Evaluation in Stone Formers

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Background: There are limited data on outcomes of kidney donor candidates with nephrolithiasis. We sought to identify risk factors for the development of kidney stone events after donor evaluation.

Methods: A survey was sent in 2022 to 446 adults with self-reported history or CT imaging evidence of nephrolithiasis at the time of kidney donor evaluation at Mayo Clinic (3 sites) between 2000 and 2016. The survey queried post-evaluation symptomatic (renal colic or gross hematuria) kidney stone events, complications, and management. Analyses assessed differences in stone burden between approved and denied donors and risk factors associated with symptomatic stone events.

Results: Surveys were completed by 161 (36%) of 446 kidney donor candidates with nephrolithiasis. Of 161, 74 were approved and 48 were denied for donation. 26 (16%) experienced a symptomatic stone event after donor evaluation and this occurred more frequently in denied vs approved donors (27% vs 12%, p=0.019), in the first 4 years after evaluation (19% vs 1%, p<0.001). Factors associated with denial for donation included presence of medullary sponge kidney, a2 stones on CT imaging, presence of bilateral kidney stones, and diameter of largest stone ≥3mm. [Table 1] There was no difference in medical management, surgical/procedural management, or reported development of chronic kidney disease between the two groups. Risk factors for symptomatic stone events after evaluation can include bilateral kidney stones (p=0.001), kidney stone diameter≥3mm (p=0.019), younger age (p=0.008), and a2 stones on CT imaging (p=0.003).

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

Underline represents presenting author.
Conclusions: For low KDPI (~50%) kidneys, impact of prolonged DWIT (~60 minutes) on graft survival is minimal, likely reflecting the resilience of higher quality renal allografts to ischemic insult over time. Caution should be taken in considering KT of high KDPI (~50%) kidneys with prolonged DWIT given overall lack of confidence in the existing dataset.

TH-PO904
Association of Pre-Donation Kidney Length with Estimated Glomerular Filtration Rate in Living Kidney Donors
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Background: The compensatory mechanism increases estimated glomerular filtration rate (eGFR) after unilateral native nephrectomy. Predicting post-living donation eGFR may depend on pre-donation factors, including kidney length. We aimed to examine the association between kidney length and post-donation eGFR.

Methods: A single-center cross-sectional study included adult living kidney donors (LKD) between February 2015 and January 2023. The association between the pre-donation kidney length (by CT scan)/height ratio (LHR) of the remaining kidney and post-donation eGFR was examined by multiple linear regression analyses.

Results: Of 136 LKD, the mean±SD age was 47±12 years and 59% were female. The median (IQR) of LHR was 0.63±0.07 cm/m. Mean pre-donation creatinine clearance (CcrCl)= 130±9.2 ml/min, followed-up (FU) eGFR at 1 wk, 6-, 12-, and 24-mos post-donation were 67.8±16.2, 71.3±16.3, 73.6±16.3 ml/min/1.73 m2, respectively. The eGFR increased from quartile 1 to 4 of LHR for all FU periods (P<0.001, 0.004, 0.004, and 0.003; Figure 1A). Each 0.1 cm/m increase in LHR was associated with 0.9–1.2 ml/min/1.73 m2 greater eGFR of all post-donation FU periods with the lowest and highest eGFR at 12 and 24 mos, respectively (β(95%CI)= 11.8 (6.1, 17.5); β12mo= 11.3 (4.7, 17.9); β24mo= 12.0 (4.8, 19.2); Figure 1B–1D). After adjusting for age, sex, race, pre-donation BMI, CcrCl, urinary microalbuminuria, creatinine ratio, systolic and diastolic blood pressures, the magnitude and direction of the LHR–eGFR association remains (β12mo= 11.2 (5.8, 16.7); β24mo= 12.1 (6.5, 17.8); β24mo= 10.5 (4.6, 16.3); β24mo= 15.1 (7.7, 22.5)). There was no effect modification observed in all major covariates for the LHR–eGFR association.

Conclusions: Pre-donation LHR is positively associated with post-donation eGFR during 24 mos FU, suggesting its relevance in selecting potential LKD with low eGFR.

TH-PO905
Males Show Greater eGFR Recovery than Females Following Kidney Donation
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Background: Living donor kidney transplantation is the optimal treatment for end-stage kidney disease and requires donor risk assessment. More data is needed to understand kidney function recovery after donation. We aimed to assess the impact of BMI, age, and sex on post-donation estimated glomerular filtration rate (eGFR) in kidney donors over 2 years.

Methods: We analyzed data from 178 kidney donors who underwent living donor nephrectomy at a single medical center between Nov. 2017 and Jan. 2022. Follow-up visits occurred at approximate 1-month, 6-month, 12-month, and 24-month intervals. eGFR was calculated using the CKD-EPI equation (2021) at each timepoint. We utilized Friedman’s test to identify variations in eGFR over the follow-up periods. Relationships between post-donation eGFR and BMI, age, and sex were explored using a generalized least squares model with AR1 error structure. The resulting relationships were plotted using model-estimated eGFR values.

Results: The study included 57 male and 121 female kidney donors. Median pre-donation eGFR was similar for males and females (98.85 vs 94.59, p=0.184). Pre-donation eGFR, BMI, and age did not significantly affect eGFR trajectories (p=0.89, p=0.37, and p=0.17, respectively). However, sex appears to significantly affect eGFR trajectories. As seen in Figure 1, despite the initially lower eGFR (59.13 vs. 65.21, p=0.001), males showed a significantly greater eGFR recovery than females through 24-month follow-up (p=0.003).

Conclusions: Our study suggests that male kidney donors recover kidney function to a greater degree than females after donation. These findings may have implications for donor evaluation, pre-operative patient counseling, and sex-specific monitoring. Further studies are needed to investigate underlying mechanisms and potential interventions to enhance eGFR recovery in both male and female kidney donors.
Safety of Low-Dose ACE Inhibition in Living Kidney Donors
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Background: ACE inhibitor (ACEi) medications have positive effects on vascular function separate from their anti-hypertensive effects. We evaluated the safety of low dose ACEi, (Ramipril 1.25mg) in kidney donors and impact on flow mediated dilatation (FMD) at 6 months post donation.

Methods: In an open label, randomized control trial, all prospective living renal donors, 18-60 years, with no hypertension or allergy to ACEi were enrolled. Baseline eGFR and FMD were recorded, and subjects were randomized (1:1) at the time of discharge to receive either daily dose of 1.25 mg of Ramipril or no medication. Repeat measurement of FMD and eGFR was done at 6 months after kidney donation. Subjects were withdrawn from the study during follow up if serum creatinine increased by ≥25% as compared to baseline, or serum potassium rose to >5.5 mEq/L, or systolic blood pressure (SBP) fell to <90 mm Hg or fell by ≥25% as compared to baseline.

Results: Total 59 subjects were enrolled and randomized. 29 and 30 participants were allocated to the Ramipril and Control arm respectively. At 6 month, 19 subjects in the intervention arm and 23 subjects in the control arm completed follow up (Figure 1). One participant in intervention arm developed side effect (increase in serum creatinine >25% from baseline). In the control arm, 2 subjects had a rise in serum creatinine. Mean difference in eGFR was 25.4±16.3ml/min/1.73m2 in intervention arm while 26.0±17.1ml/min/1.73m2 in the control arm (p=0.909). The mean difference in FMD at 6 months vs baseline in intervention arm was 3.63±10.76% while in control arm was -2.62±10.28% (p=0.098).

Conclusions: Use of ramipril in dose of 1.25 mg once every day in living kidney donors was safe. A trend in improvement in vascular function (increase in FMD) was noted in intervention arm suggesting further study the effect of ACEi on vascular function in post kidney donation with adequate sample size.

Funding: Government Support - Non-U.S.

Figure 1: Patient flow

Patient flow

Vertebral Fracture Risk Is Increased Among Living Kidney Donors 25 Years After Donation: Survey-Based Study
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Background: Living kidney donors may have an increased risk of fractures due to reductions in renal mass, low concentration of 1,25-dihydroxyvitamin D, secondary increases in parathyroid hormone and bone turnover markers. We compared the long-term risk of fractures among living kidney donors with matched controls from the general population.

Methods: Surviving kidney donors from 3 transplant centers completed a survey about bone health and history of fractures. Age, sex, and race-matched non-donor controls without a history of comorbidities that would have precluded kidney donation were identified from population-based resources and completed the survey. The proportion of persons reporting fractures was compared using standardized incidence ratios (SIR).

Results: A total of 1,930 donors and 1,615 controls responded to the survey. Average time between donation/index date and survey date was 24.8 years for donors and 27.3 years for controls. At the time of the survey, donors were 1.1 years younger than the controls (67.4 vs 68.5 years). Although the overall rate of fractures in donors was significantly less than in controls (SIR 0.91; 95% CI 0.82-0.99), there were significantly more vertebral fractures in donors than in controls (SIR 1.43; 95% CI 1.06-1.86) and more hip fractures in women donors compared to controls (SIR 1.90; 95% CI 1.01-3.26).

Conclusions: Our findings suggest excess vertebral fractures in both men and women and excess hip fractures in women among living kidney donors compared to controls after 25 years of follow-up.

Funding: NIDDK Support

Age-, sex-, and time after index-standardized incidence ratios (SIRs) for fracture risk in donors vs. controls

High Coronary Artery Calcium Score Is Associated With an Increased Risk of Death in Patients Evaluated for Kidney Transplant
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Background: Coronary artery calcification (CAC) is a marker of coronary artery disease which is related to increased risks of cardiovascular complication in kidney transplant recipients. Over the past 5 years, our transplant center has utilized CAC score for cardiac risk stratification in pre-evaluation of kidney transplant. This is a single center, retrospective observational study to evaluate the association between CAC score and death from any cause among kidney transplant (KT) evaluations.

Methods: Retrospective observational study including adults, > 40 years evaluated for a KT between January 1, 2018, and December 31, 2022. All-cause mortality was ascertained through electronic medical records and the Ohio death index. CAC scores were grouped into low (0-100), medium (100-400), and high (>400). Cox proportional hazard models were used to explore the relationship between CAC score and the mortality.

Results: Of the 570 subjects included, 345 (60%) were male, 272 (48%) were of white race, and 245 (43%) were black. The mean age was 57.8 years. CAC scores were: 247 (43%) low, 91(16%) medium, and 232 (41%) high. The median follow-up for the entire cohort was 22.4 months (IQR 21.4 months). During the study period, 71(12.4%) received kidney transplants, and 67(11.7%) died. Multivariante Cox model showed high CAC score (>400) was associated with a high hazard of death (HR 3.29, 95% CI: 1.71-6.32).

Conclusions: High CAC scores are independent risk factors for mortality from any cause in patients evaluated for a kidney transplant. Transplant centers should consider closely monitoring patients with high CAC scores to ensure better performance in the Organ Procurement and Transplant Network metric of waitlist mortality.

Funding: None

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

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Impact of Recipient Hepatitis C Virus (HCV) Sero-Status on the Outcomes Following Kidney Transplantation from HCV Viremic Donors in the Era of Directly Acting Anti-HCV Agent Use

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Background: Kidneys from hepatitis C virus (HCV) infected donors were historically utilized for transplantation into HCV seropositive recipients and in recent years with the availability of highly effective directly acting anti-HCV (DAAs) agents into HCV-naive recipients. We aimed to look at the trend in the use of kidney from HCV infected donors by stratified by recipient HCV sero-status and compared transplant outcomes with respect to recipient HCV sero-status.

Methods: OPTN/UNOS files were used to identify all HCV viremic donors for whom each kidney was transplanted into a first-time kidney-only recipient with known HCV sero-status from 01/2015 to 12/2022. Length of stay (LOS), delayed graft function (DGF), time to death and graft failure were assessed. Marginal models with robust sandwich estimators were used to account for clustering by donor, allowing odds ratio (OR) for DGF and hazard ratios (HR) for graft failure, death-censored graft failure and death to be calculated within a wake-male kidney frame work. Models were adjusted for multiple recipient and transplant related variables.

Results: Median study follow up was 22 (10-35) months. There were 3524 recipients of matched HCV+ donor kidneys and 80.5% of recipients were HCV+. There was an increase in HCV+ donor kidney availability over time from 116 in 2015 to 614 in 2022. HCV+ to HCV+ transplantation increased from 6% of all kidneys in 2015 to 95% in 2022. LOS was similar for HCV+ [5 days (4-6)] vs. HCV- [4 days (3-6)] recipients (p=0.7). Transplant outcomes for HCV+ (n=668) vs. HCV- (n=2836) recipients are shown in the table.

Conclusions: Our analysis showed increasing utilization of HCV+ (viremic) kidneys over time with preferential use in HCV+ recipients more recently. Similar graft and patient outcomes of HCV+ kidney transplantation into HCV+ vs. HCV- recipients likely reflect availability of DAA agent. Our study demonstrates reduced accessibility of HCV+ kidneys for HCV+ recipients in recent years despite equivalent outcomes.

TH-PO9012

Social Support and Diet Behaviors Among Adults with ESKD and Obesity

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Background: End stage kidney disease (ESKD) patients with obesity (~40% of the dialysis population) have unique challenges with weight management and diet. Few studies have explored the role of different types of social support in achieving optimal outcomes for the ESKD and renal diet adherence.

Methods: We conducted semi-structured, 60-90-minute phone interviews in 2020-21 with 40 adults with ESKD and obesity (body mass index, BMI, ≥30 kg/m²). Participants were recruited from dialysis centers and patient networks in 22 states, using purposive sampling for geographic and demographic diversity. Interviews were audio recorded and transcribed verbatim. A coding framework was developed by an interdisciplinary team including a nephrologist, a nutrition scientist, and a social scientist. By memoing patient narratives on the role of social support in dietary behaviors, codes were finalized to include sources of social support (family, friends, community members, fellow patients) and types of social support (emotional, appraisal, instrumental, informational). Patient typologies based on social support levels were identified to explain patterns of dietary behaviors.

Results: Mean age of participants was 55 years; average BMI was 39.5kg/m², 58% of patients were female, 35% were Black/African American, 60% had diabetes. Participants reported receiving the most varied types of social support from family members in their household, while also accessing emotional support from fellow patients, and informational and appraisal support from online communities. Qualitative data analyses identify patient typologies based on social support levels to explain patterns of dietary behaviors. Using behavior change theory and study data, the included figure illustrates how social support influences diet adherence.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: Social support buffers the negative health consequences of adverse life events and helps patients with self-management, with implications for renal diet adherence and promoting healthy diets among patients with ESKD and obesity.

Funding: NIDDK Support

TH-PO913

Comparing the Value of Periodic Assessment of Three Objective Nutrition Scores on the Prognosis of Hemodialysis Patients: A Multicenter Longitudinal Study

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Background: The prognostic value of objective nutrition scoring tools for longitudinally assessing the relationship between nutritional status and prognosis in hemodialysis patients remains unclear. In this multicenter retrospective cohort study, the prognostic nutritional index (PNI), correcting nutritional states scores (CONUT), and geriatric nutritional risk index (GNRI) were used to longitudinally evaluate nutritional status, and their predictive values for all-cause and cardiovascular mortality were compared.

Methods: Hemodialysis patients from four hospitals were included in the study, and laboratory data and nutrition scores were collected at the start of dialysis, 6 months, 12 months, and 18 months of dialysis. A joint model was used to analyze the relationship between changes in the three nutritional scores and patient prognosis, and area under the curve (AUC) was used to compare their predictive values.

Results: Of the 863 patients included in the study with a median follow-up of 37 months, 23.8% died during follow-up, with 14% being cardiovascular deaths. Malnourished patients had a higher risk for all-cause and cardiovascular mortality. Dynamic changes in PNI and GNRI scores were significantly associated with a reduced risk of all-cause and cardiovascular mortality. Longitudinal increases in PNI and GNRI scores were associated with a 4% and 3% reduction in all-cause (PNI: hazard ratio [HR], 0.96; 95% confidence interval [CI], 0.95-0.97; GNRI: HR, 0.97; 95% CI, 0.96-0.98) and cardiovascular mortality risk (PNI: HR, 0.96; 95% CI, 0.94-0.98; GNRI: HR, 0.97; 95% CI, 0.95-0.98) respectively, with increasing dialysis duration. CONUT score changes were not significantly associated with all-cause death and cardiovascular mortality. The AUC of three joint models showed that GNRI (0.8925) score showed higher predictive accuracy for all-cause than PNI (0.8315) and CONUT (0.8522). Similar results were found for the three scores regarding cardiovascular mortality.

Conclusions: GNRI is strongly associated with increased all-cause and cardiovascular mortality in hemodialysis patients. Regular assessment of nutritional status using GNRI has higher predictive accuracy than CONUT score and PNI score for all-cause and cardiovascular mortality in patients with MHD.

TH-PO914

Effect of Geriatric Nutritional Risk Index (GNRI)-Based Stratified Diet Intervention on Nutritional Status and Self-Efficacy of Elderly Patients with Maintenance Hemodialysis

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Background: To explore the effect of stratified dietary intervention based on geriatric nutritional risk index (GNRI) on nutritional status and self-efficacy in elderly patients with continuous hemodialysis (MHD).

Methods: A total of 60 elderly patients with MHD from the Second Affiliated Hospital of Nanjing Medical University from January 2020 to January 2021 were randomly selected and divided into an intervention group and a control group by random number table method, with 30 cases in each group. The control group used the general intervention measures, and the intervention group implemented GNRI stratified dietary intervention based on conventional intervention measures. The nutritional status of the two groups before and after 3 months of intervention, including the score of the subjective global assessment (scored patient-generated subjective global assessment, PG-SGA), body mass index (body mass index, BMI), and triceps skinfold thickness were measured.

Results: After 3 months of intervention, the intervention group PG-SGA score, BMI, and triceps skinfold thickness were significantly improved compared to the control group. The body mass index of the control group was lower than that of the intervention group (p < 0.05). The intervention group had better outcomes compared to the control group.

Conclusions: GNRI stratified dietary intervention can improve the nutritional status of elderly MHD patients, help to enhance their self-efficacy, improve Diet therapy attitude, improve the quality of life, and has high clinical application value.

Funding: Government Support - Non-U.S.

TH-PO915

Veteran Diet Patterns and Quality of Life in West African Veterans with Chronic Kidney Disease

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Background: Over 500,000 Veterans have chronic kidney disease (CKD) with higher incidence (16-36%) than the general population. Most CKD is caused by diabetes and associated with hypertension and cardiovascular disease. Dietary changes may potentially delay, or maybe prevent, hypertension, diabetes, and CKD. Poor dietary quality and low adherence to recommended diets is common in CKD. The purpose of this study was to describe diet quality and cross-sectional associations of plant-based diet components with vascular function measures in Veterans with CKD.

Methods: We conducted a secondary analysis of baseline data from the Phosphate Lowering in CKD Trial (NCT02290636) that recruited 66 Veterans with CKD stage 3b-4. Primary study outcomes were vascular function measures, carotid-femoral pulse-wave velocity (PWV) and flow mediated dilation (FMD). We calculated plant-based diet components from 3-day dietary records by linking the Food and Nutrient Database for Diet and Nutrition Studies with food composition data provided by the USDA Nutrient Database for Standard Reference. We classified food and nutrient degree of processing by the NOVA diet classification system. Analysis included basic descriptive statistics and paired T-tests to compare nutrient intake above/below the median with PWV and FMD.

Results: Mean±SD ultra-processed calories was 64.3±15.1% of total intake and animal protein was 52.3±19.6% of total protein intake. Mean a SD combined processed/ultra-processed nutrients intake was 72.4±17.8% of total sodium (2,358g), 56.2±14.9% of total calcium (1,191g), 64.1±6.5% of total phosphorous (743g). No participants were Dietary Approaches to Stop Hypertension (DASH) diet adherer (1.3±0.9 points of 9) and the Healthy Eating Index score was 48.9±1.17 of 100. Individuals with unprocessed plant protein above the median intake had lower PWV (99.6±2.373 1/m/s) than those below the median intake (122.5±0.91 1/m/s, p=0.04). Those with unprocessed plant phosphorus above the median intake also had lower PWV (97.9±2.233.8 1/m/s) than those below the median intake (124.1±8.399 1/m/s, p=0.02).

Conclusions: Veterans in the Phosphate Lowering in CKD Trial had low dietary quality, however, those who consumed more unprocessed plant protein and phosphorus had better vascular function at baseline. These results indicate opportunities for nutritional intervention and future research.

Funding: Veterans Affairs Support

TH-PO916

Dietary Patterns and Kidney Function in West Africans with Chronic Kidney Disease

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Background: There is little known about the impact of dietary patterns on chronic kidney disease (CKD) in West Africa. Our study describes associations of dietary patterns with estimated glomerular filtration rate (eGFR) and is the first study to do so in a well-phenotyped West African CKD cohort.

Methods: We analyzed participants in the Diet, Apolipoprotein L1 and CKD (DCA) study with dietary patterns in West Africa. We used participants with estimated GFR above 39 mL/min/1.73m² and associated with hypertension and cardiovascular disease. Dietary changes may potentially delay, or maybe prevent, hypertension, diabetes, and CKD. Poor dietary quality and low adherence to recommended diets is common in CKD. The purpose of this study was to describe diet quality and cross-sectional associations of plant-based diet components with vascular function measures in Veterans with CKD.

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Funding: NIDDK Support

*Underline represents presenting author.
TH-PO917
Dietary Sodium and Potassium Intake Estimations in Different Stages of CKD by Multiplex 24-Hour Urine Collections

Background: Dietary sodium (Na) and potassium (K) intake in chronic kidney disease (CKD) patients can be calculated most accurately by multiple 24-hour urine samples. While Na intake targets are known, optimal K intake according to different stages of CKD is not known. We aimed to examine how much Na intake met the guideline recommendations and the effect of K on serum K values in CKD patients.

Methods: This retrospective cohort study was based on 253 stable patients (who collected 5 or more 24h between 2012-2022) at different stages of CKD. Clinical data was obtained through database of Hacettepe University Hospitals. 24hNa (24hU) and potassium (24hUK), serum Na, K and creatinine (Scre) values were analyzed. Generalized linear model for analysis of parametric variables was used.

Results: There was a total of 3493 urinary K values from a mean of 13 collections in 253 patients. Mean 24hU was 13.4±70.5 mmol/d. Only 32.7% (n=1142) were below the recommended target of 100 mmol/d. There was a total of 1959 urinary K values from a mean of 14 collections in 135 patients. Mean 24hUK was 58.3±22 mmol/d. 24hU and 24hUK excretion according to the CKD stages was shown in Figure. There was no correlation between CKD stages and 24hU and 24hUK excretion. Scre values and 24hU Na values were inversely proportional, with beta=-0.001 and p=0.04. Scre values and 24hUK values showed an inverse correlation, with beta=-0.007 and p=0.00. When serum K values and 24hUK values were analyzed, beta is negligible, p=0.884. No statistically significant correlation was found between serum K values and 24hUK values.

Conclusions: 24hU Na levels with recommended Na targets is present only in one third of the samples. The lack of relation with serum K and 24hUK values needs further studies to define an optimal K intake in different stages of CKD.

TH-PO918
Effects of Dietary Salt on Immune and Microbiome Composition: Results from a Randomized Clinical Trial
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Background: Increased dietary salt intake ranks among the most prominent nutritional risk factors worldwide and has been tied to arterial hypertension and all-cause mortality. The mechanisms responsible are incompletely understood and have recently been extended to include inflammatory and microbiome-associated mechanisms. Building on our preliminary data, the present study investigates whether a moderate increase in salt intake in healthy subjects primes host physiology to a more transient unstable state, potentially leading to changes in the microbiome-immune axis.

Methods: We conducted a prospective, randomized, double-blinded trial to evaluate the effect of high dietary salt in healthy participants (NCT03024567), where the intervention group (n = 19) was given 6g of salt (NaCl) in addition to their daily normal salt intake (match double-blindly to the recommended salt intake) against a paired control group (n=19) for 14 days. Clinical parameters, stool, and PBMC were collected at baseline and day 14. Shotgun metagenomic sequencing, metabolomics (stool and serum), and single-cell sequencing (Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITEseq)) of whole PBMC and CD4+ T cells (~150k single cells) was performed.

Results: Our results confirm previously established findings showing an increase in the dissimilarity of the microbiome composition (Jensen-Shannon Divergence) under a high salt diet. Differential abundance of the microbiome’s functional space, as quantified by functional gene-specific modules, picked up a salt-specific module (sodium extrusion) two-component regulatory system in the salt intake group. A short-chain fatty acid-specific module (MF0128, Propionate conversion to succinate) was reduced in the salt arm. CITEseq revealed a significant amount of differently expressed genes in healthy donors only in the salt group. We found 692 DEG in naive conventional T cells (Tcon) and 202 DEGs in non-naïve Tcon, e.g. belonging to NF-κB and T cell receptor signaling pathways.

Conclusions: Our placebo-controlled study is the first to utilize different omics techniques to investigate and identify high-salt-induced changes in the microbiome and immune in healthy individuals that may be relevant to the development of pathological conditions in the long term.

TH-PO919
High-Salt and Low-Salt Diets Can Modulate Kidney Immune Cells and Endothelial Cells
Kyungho Lee,1 Jenseok Jeon,1 Hojin Jeon,1 Jinho Ko,2 Jung eun Lee,1 Woo seong Huh,3 Yoon-Goo Kim,1 Hye Ryun Jang,1 1Samsung Medical Center, Cell and Gene Therapy Institute, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 2Gachon University, Seongnam-si, Gyeonggi-do, Republic of Korea.

Background: Kidney immune cells and endothelial cells mediate kidney ischemia-reperfusion injury and can affect kidney transplant outcomes. We aimed to study the effect of changes in dietary salt intake on kidney immune cells and endothelial cells in experimental models and kidney transplants.

Methods: We treated C57BL/6 mice with normal diet, low-salt diet, or high-salt diet and obtained kidneys after 6 weeks of allocated diets. Kidney sections were stained for CD45, to compare intrarenal sodium buffer, glycosaminoglycan (GAG) concentration was measured with kidney protein extracts. Lymphocytes isolated from kidneys were analyzed by flow cytometry. Human kidney transplant tissues obtained at 2 weeks after kidney transplantation by a protocol biopsy were stained with CD45 and CD31 and analyzed by T cells, monocytes’ pro-inflammatory T cells, and CD11b+ monocytes’ sodium levels. Induction of different cell-derived endothelial cells (ipSC-ECs) from healthy individuals and end-stage kidney disease (ESKD) patients were treated with additional sodium, and proliferation was assessed.

Results: Mice kidneys from high-salt diet group had higher kidney leukocytes (CD45+), than those from normal diet group (1.9±0.3% vs 0.9±0.1%, P=0.043). Kidney GAG level was lower in high-salt diet group than in low-salt group (41.0±3.1 vs 48.3±1.3 mg/g, P=0.004). Both low-salt and high-salt diets increased effector-memory CD4+ T cells (normal 44.2±2.6%, low-salt 57.1±3.5%, P=0.029; high-salt 62.1±2.5% of CD4+ T cells, P=0.002) and mature B cells (70.0±1.5%, 79±1.14%, P=0.001; 76.7±1.6% of CD19+ cells, P=0.015), whereas decreased naïve CD4+ T cells (45.9±2.1%, 32.7±3.2%, P=0.016; 27.8±3.1% of CD4+ T cells, P=0.001) in kidneys. Human kidney transplants from donors under low-salt diet exhibited lower leukocytes (CD45+; 0.3±0.1% vs 9±0.3%, P=0.019) and higher capillary density (CD31; 29.0±2.2% vs 16.1±1.8%, P=0.009) than those from donors under high-salt diet. The proliferation of iPSC-ECs from healthy individuals and ESKD patients after hypoxia was suppressed under higher sodium concentrations.

Conclusions: High-salt and low-salt diets seem to exert adverse effects on kidney immune cell numbers and phenotypes as well as endothelial cells. Modulation of kidney microenvironment by modifying dietary salt intake could be a potential strategy to improve kidney transplant outcomes.

TH-PO920
Dietary Potassium and Fiber Intake and Health-Related Quality of Life in a Multicenter Prospective Hemodialysis Cohort
Yuki Narasaki,1 Kamyrant Kalantar-Zadeh,2 Seung Hyock Han,1 Tae Ik Chung,4 Diana S. Kalantar,1 Tracy Nakata,1 Danh V. Nguyen,1 Connie Rheu,1 1University of California Irvine School of Medicine, Irvine, CA; 2Harbor-UCLA Medical Center, Torrance, CA; 3Yonsei University, Seoul, Seoul, Republic of Korea; 4National Health Insurance Service, Wonju, Gangwon-do, Republic of Korea.

Background: Guidelines recommend dietary potassium (K) restriction in ESKD patients due to concerns about hyperkalemic CV events. However, K-rich foods tend to be from heart-healthy sources with high fiber content. We examined the relationship of dietary K and fiber intake with health-related quality of life (HRQOL) in a prospective HD cohort.

Methods: Among 583 HD patients from the multicenter NH MADRAD cohort recruited across 16 outpatient dialysis clinics, information regarding dietary K intake was obtained (using a protocoalized Food Frequency Questionnaires (FFQs)) and HRQOL was assessed using Short Form 36 surveys administered over 10/2011-9/2022. We examined associations of dietary K intake categorized as tertiles with HRQOL using linear mixed models.
**Effect of Dietary K on eGFR in Middle-Aged and Older Community-Dwelling Japanese Adults**

**Methods:** Baseline data from a Japanese community-based cohort (age 40–97 years) were identified by physical examination and/or results from fasting laboratory samples. Participants without diabetes were further categorized according to 4 metabolically unhealthy phenotypes in males [adjusted odds ratio: MUNO 1.94 (1.41-2.68) and MUO 1.83 (1.40-2.38)], but only with MUNO [1.50 (1.12-1.99)] among females.

**Conclusions:** These findings suggest different associations between MetS and CKD between males and females. Understanding how sex-specific differences, such as sex hormones, modulate the interaction between obesity/metabolic phenotypes and CKD may provide additional avenues for prevention and treatment.

**Funding:** NIDDK Support

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**Diet and the Discrepancy Between Cystatin C- and Creatinine-Based eGFR in Middle-Aged and Older Community-Dwelling Japanese Adults**

**Background:** Discrepancy between creatinine-based eGFR (eGFR_creat) and cystatin C-based eGFR (eGFR_cys) is associated with kidney health and frailty. Dietary factors may affect serum creatinine concentration, but little is known about the association between diet and eGFR discrepancy.

**Methods:** Baseline data from a Japanese community-based cohort (age 40–97 years) comprising 3,029 men and 3,115 women were analyzed. We cross-sectionally assessed nutrients and food groups derived from a food frequency questionnaire adjusted by

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

Underline represents presenting author.

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**Table: Multivariable logistic regression analysis of diet and eGFR discrepancy by sex.**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein</td>
<td>1.10</td>
<td>1.08</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>1.12</td>
<td>1.06</td>
</tr>
<tr>
<td>Potassium</td>
<td>1.17</td>
<td>1.03</td>
</tr>
<tr>
<td>Fiber</td>
<td>1.07</td>
<td>1.02</td>
</tr>
</tbody>
</table>

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**Figure B:** In adjusted analyses of pairings of dietary K/fiber intake in the absolute (Fig C) and relative (Fig D) models, the second tertile of dietary K intake was associated with better trajectory of physical functioning and physical component scores (PCS) over time (ref: lowest tertile): Estimates (95%CI) (95%CI)

<table>
<thead>
<tr>
<th>Dietary K Intake</th>
<th>PCS (ref: lowest tertile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low K/low fiber</td>
<td>(β: -0.37, 95% CI: -0.49, -0.24)</td>
</tr>
<tr>
<td>Low K/high fiber</td>
<td>(β: -0.19, 95% CI: -0.30, -0.07)</td>
</tr>
<tr>
<td>High K/low fiber</td>
<td>(β: 0.04, 95% CI: 0.01, 0.08)</td>
</tr>
<tr>
<td>High K/high fiber</td>
<td>(β: 0.16, 95% CI: 0.09, 0.25)</td>
</tr>
</tbody>
</table>

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**Results:** In adjusted analyses of pairings of dietary K/fiber intake in the absolute (Fig C) and relative (Fig D) models, the second tertile of dietary K intake was associated with better trajectory of physical functioning and physical component scores (PCS) vs. those with low K/fiber intake.

**Conclusions:** In a prospective HD cohort, higher dietary K and fiber intake were associated with better HRQOL, particularly related to physical function domains. Further studies are needed to determine the causal mechanisms linking dietary intake and physical function in this population.

**Funding:** NIDDK Support

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**Different Effects of Dietary Selenium on All-Cause Mortality According to the Baseline Characteristics Based on the Nationwide Population Study: Results from the NHANES, 1999-2016**

**Background:** As an antioxidant, selenium has a beneficial role in human health including metabolism and thyroid function. Based on the metabolism process, kidney function status has a potential role in the bioavailability of dietary selenium. Herein, we aimed to evaluate the impact of dietary selenium on all-cause mortality in different baseline characteristics including kidney function status.

**Methods:** We used data from the US National Health and Nutrition Examination Survey 1999-2016. Based on a 1-day 24-hr dietary intake, the intake of selenium was divided by quintile; the third quintile was regarded as a reference. Baseline characteristics included kidney function, body mass index, and alcohol consumption status. We used a multivariate Cox proportional hazard model to identify the impact of selenium on all-cause mortality.

**Results:** A total of 41,423 subjects were included in the study. The risk for all-cause mortality was significantly increased in subjects included in the 1st quintile (adjusted hazard ratio [AHR] 1.12, 95% confidence interval [CI] 1.03-1.21) after adjustment with age, gender, ethnicity, income, comorbidities (hypertension, diabetes), BMI, total calorie intake, laboratory results (hemoglobin, serum albumin, total cholesterol, serum glucose, and estimated glomerular filtration rate). In subgroup analysis, lower intake of selenium increased mortality in subjects with eGFR ≥60 mL/min/1.73 m2 (AHR 1.14, 95% CI 1.03-1.27), BMI 25-30 kg/m2 (AHR 1.24, 95% CI 1.08-1.43), and moderate to heavy drinker (AHR 1.27, 95% CI 1.11-1.44). Selenium intake and blood level of selenium showed a positive correlation, and it was prominent in subjects with eGFR ≥60, BMI 25-30, and non-drinkers. The impact of the blood level of selenium on all-cause mortality was the same as the results in selenium intake.

**Conclusions:** Deficiency in selenium intake and lower levels of blood selenium significantly increased all-cause mortality, especially in subjects with preserved kidney function, overweight, and moderate to heavy drinkers.

**TH-PO923**

**Association of Obesity, Metabolic Syndrome, and Diabetes with CKD in Men and Women: National Health and Nutrition Examination Survey (NHANES), 2003-2020**

**Methods:** Data were analyzed for 8,586 male and 8,420 non-pregnant female adults (≥20 years), from the 2003-2020 cycles of the NHANES. CKD (defined as albuminuria and/or eGFR<60mL/min), MetS (defined as ≥3 of the following: hypertension, prediabetes, hypertriglyceridemia, low HDL cholesterol, and/or central obesity), and obesity (BMI≥30) were identified by physical examination and/or results from fasting laboratory samples. Diabetes was identified by self-report, prior diagnosis, and/or high fasting glucose or hemoglobin A1C. Participants without diabetes were further categorized according to 4 obesity/metabolic phenotypes: metabolically healthy non-obese (MUNO), metabolically unhealthy non-obese (MUO), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO). Multivariable-adjusted logistic regression models were used to examine the relationship of CKD with obesity/metabolic phenotypes using appropriate sampling weights.

**Results:** The prevalence (95% CI) of CKD for male and female diabetics was 36.7% (33.6-39.8) and 35.9% (32.2-39.9), respectively. The prevalence of CKD for male and female MUNO was 13.2% (10.6-16.5) and 21.0% (18.0-24.3), respectively; for MUO 10.9% (9.1-13.1) and 14.8% (12.9-16.9); for MHO 5.6% (4.9-6.5) and 9.6% (8.5-10.9); and for MUNO 4.6% (3.4-6.2) and 8.4% (6.6-10.7). CKD was associated with the metabolically unhealthy phenotypes in males [adjusted odds ratio: MUNO 1.94 (1.41-2.68) and MUO 1.83 (1.40-2.38)], but only with MUNO [1.50 (1.12-1.99)] among females.

**Conclusions:** These findings suggest different associations between MetS and CKD between males and females. Understanding how sex-specific differences, such as sex hormones, modulate the interaction between obesity/metabolic phenotypes and CKD may provide additional avenues for prevention and treatment.

**Funding:** Government Support - Non-U.S.
**TH-PO924**

**Ketogenic Diet Mitigates Renal Fibrosis and Partially Preserves Kidney Function in Nephotropic Serum Nephrin**


**Background:** Ketogenic diet (KD) has garnered medical interest due to its potential in treating diseases including a significant regulatory impact on inflammatory processes. Our study examined the effects of a KD on an experimental mouse model of immune-complex-mediated glomerulonephritis (GN).

**Methods:** Male C57BL/6 mice were put on a KD or continued with standard chow (SC). KD was initiated three days after the induction of nephrotropic serum nephritis (NTS). Mice were observed for 21 days post-induction. Key parameters like the albumin-to-creatinine ratio (ACR) in spot urine and kidney histology were evaluated. Further, we transitioned mice back to SC on day 21 and observed them for an additional 5 weeks. During this period, kidney function was monitored using transdermal glomerular filtration rate measurement devices. Kidney fibrosis was assessed using Sirius Red staining. To thoroughly examine the molecular mechanisms associated with a ketogenic diet, we employed a multifaceted approach incorporating comprehensive immunophenotyping of blood and lymphatic tissues via flow cytometry and immunohistochemistry, renal NMR spectroscopy (metabolomics), and renal RNA-seq sequencing.

**Results:** KD significantly reduced levels of albuminuria. We noticed fewer crescents and lower PAS scores, indicating an improved glomerular phenotype in the KD group, but a trend toward increased tubular injury and tubular fat deposition. Mice switched back to SC after the initial KD phase demonstrated a reduction in kidney fibrosis and preserved kidney function with regression of the tubular fat deposits. KD mice showed major systemic immunological and metabolic adaptations like a reduction in blood leukocyte numbers and an increase in the concentration of renal ketone bodies. We further observed an increase of renal neutrophil infiltrates and changes in bulk inflammatory signatures including a decrease in Mpo expression. Notably, transcriptomics analysis revealed a decrease in extracellular matrix production.

**Conclusions:** A therapeutic KD was protective in a mouse model of GN, leading to a reduction in albuminuria, preserved kidney function, and reduced renal fibrosis. Further research is needed to fully understand these protective mechanisms.

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

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**TH-PO925**

**Dietary Acid Reduction with Either Fruits and Vegetables or Oral NaHCO3, Adjuvant to Angiotensin-Converting Enzyme Inhibition, Slows Progression of Macroalbuminuric Stage G1 CKD**

Nimirrt Goraya, 1 Jan Simoni, 2 Maninder Kahlon, 3 Nakaz Aksan, 4 Donald E. Wesson, 5 1 Baylor Scott and White Central Texas, Temple, TX; 2 Texas Tech University System, Lubbock, TX; 3 The University of Texas at Austin, Austin, TX; 4the University of Texas at Austin Dell Medical School, Austin, TX.

**Background:** Patients with macroalbuminuric (urine albumin-to-creatinine ratio > 200 mg/g creatinine) chronic kidney disease (CKD) are at increased progression risk despite angiotensin converting enzyme inhibition (ACEI). As high-acid-producing diets are associated with risk for CKD progression, we tested the hypothesis that dietary acid reduction with either base-producing fruits and vegetables (F+V) or oral NaHCO3 (HCO3) slows progression in macroalbuminuric CKD with initially normal eGFR (> 90 ml/min/1.73 m2 or stage G1).

**Methods:** One hundred fifty-three macroalbuminuric, non-diabetic G1 participants on SC were randomized to receive either F+V diet load 50%, oral NaHCO3 (HCO3, n=51) 0.4 meq/Kg bw/day, or no additional intervention (Usual Care, n=51). They were followed annually for 5 years, measuring eGFR and these urine parameters per g creatinine: albumin (Ualb), N-acetyl-D-glucosaminidase (UNAG, indicator of tubulointerstitial injury), angiotensinogen (ANGT; index of kidney angiotensin II), and isoprostane 8-isoprostaglandin F2α (8-iso, index of systemic oxidative stress). Mixed linear regressions with random intercepts tested differential group trajectories, p-values from the relevant interaction terms are included below.

**Results:** We highlight group differences at year-5 for brevity and provide p-values from the full model. For F+V and HCO3 relative to UC, 5-year eGFR was higher ([mean difference](https://www.ncbi.nlm.nih.gov/pubmed/35040294)) vs. UC [1.27 (0.03)], HCO3 [2.5 (0.05)], UC [2.8 (0.06)], U/g, p<0.001). Additionaly, 5-year UAGT and U8-iso were lower in F+V and HCO3 than UC (UAGT, F+V [20.9 (0.32)], HCO3 [20.6 (0.35)], UC [23.1 (0.40), p<0.001; 8-iso, F+V [1.08 (0.02)], HCO3 [1.06 (0.02)] vs. UC [1.27 (0.03)], p<0.001).

**Conclusions:** Dietary acid reduction with either F+V or NaHCO3, adjunctive to ACEI, yielded better eGFR preservation than UC in macroalbuminuric G1 CKD, associated with reductions of indicators of kidney angiogenesis II and systemic oxidative stress, each potential mediators of CKD progression.

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**TH-PO926**

**The Relevance of a Personalized Low-Normal Protein High-Calorie Diet in Nephotropic Patients for Renal Cell Carcinoma (RCC): Myth or Reality?**

Francesco Trevisani, 1 Matteo Paccagnella, 2 Francesco Fiorio, 3 Fabiana Laurenti, 1 Riccardo Vago, 1 Federico Di Marco, 1 Matteo Floris, 1 Umberto Capitanio, 1 Michele Ghidini, 1 Ornella Garrone, 1 Andrea Salonia, 1 Francesco Montorsi, 1 Arianna Bettiga. 1 IRCCS Ospedale San Raffaele, Milano, Italy; 2 Fondazione ARCO, Cuneo, Italy; 3 Università degli Studi dell’Aquila - Polo Capotosto, L’Aquila, Italy; 4 Azienda Ospedaliera Brotzu, Cagliari, Italy; 5 Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano, Italy.

**Background:** Nutritional therapy (NT) based on a controlled protein intake represents a cornerstone in the management of CKD. However, if a CKD patient is at the same time affected by cancer, oncologists suggest a diet based on high protein intake to avoid malnutrition. International guidelines are not dirnent in this asset of patients. In particular, no clear nutritional management is established in the radical nephrectomy (RN) patients for RCC. The aim of our study was to investigate the efficacy of a Low-Normal Protein High Calorie (LNPHC) diet in a consecutive RN cohort of RCC pts using an integrated nephrologist and nutritionist approach.

**Methods:** A consecutive cohort of 40 nephrectomized pts for RCC was enrolled in a tertiary institution between 2020-2022. Inclusion criteria: Age >18 years old, eGFR=60 ml/min/1.73,RN for. An initial nutritional and pathological evaluations were performed and then a conventional CKD LNPHC diet integrated with aromatic foods (0.7-1.0 g/Kg/die; calories: 30-35 kcal per kg body weight/die) for a period of 6 months (+/- 2 months). MST, Body Mass Index (BMI), Phase Angle (PA), Fast Mass percentage (FM%), Fat-Free Mass Index (FFMI), body cell mass index (BCM), extracellular/intracellular water ratio (ECW/ICW), waist/hip circumference ratio (WHC), lab test exams and clinical variables were examined at baseline and after 6 months. Statistical analysis: Kruskal-Wallis rank sum test; Data analysis: R programming language and RStudio integrated development environment.

**Results:** Descriptive analysis is showed in Table 1. Our results clearly highlighted that LNPHC was able to generate a significant improvement in several nutritional parameters (Tables 2 and 3). Moreover, LNPHC was responsible for a significant decrease of urea.

**Conclusions:** LNPHC represents a new important therapeutic strategy to apply in the onco-nephrological patients with solitary kidney due to renal cancer.
of amino acids was 1.19 (0.85, 1.35) g/kg/day. The average pH of the TPN solution was 5.3 ± 0.36. The mean eGFR of FTAL was 71.43 (48.35, 85.05) ml/min/kg without statistical correlation with CKD when normalized by body weight.

Conclusions: The prevalence of CKD in the HPN was higher than in the general population, with a high rate of eGFR decline. The study showed no statistical correlation between FTAL and CKD in those patients. A prospective study with different eGFR measurements should be conducted for the accuracy of eGFR and to demonstrate risk factors for the deterioration of renal function.

Funding: Government Support - Non-U.S.

TH-PO928
Do Protein Intake, Serum Bicarbonate, and Inflammatory Markers Explain the Associations of Advanced CKD with Muscle Wasting?
Farahnaz Akrami, Ravinder Singh, Robert E. Boucher, Guo Wei, Augustine Takyi, Azeem M. Mohammed, Amara Sarwal, Sydney E. HartSELL, George Bissada, Srinivasan Beddhu. University of Utah Health, Salt Lake City, UT.

Background: Muscle wasting is a significant concern in individuals with chronic kidney disease (CKD) as it adversely affects their overall well-being and increases the risk of mortality. Low protein intake, metabolic acidosis and systemic inflammation are considered to be some of the main drivers of muscle wasting in CKD. Therefore, we examined in the Chronic Renal Insufficiency Cohort (CRIC), whether these factors explain muscle wasting in CKD.

Methods: We included 3040 eligible CRIC participants. Baseline protein intake was determined from dietary protein intake. Serum bicarbonate was used as marker of acid-base status. Serum hsCRP, IL6, fibrinogen, TNFalpha and IL1beta were used to derive a previously published CRIC inflammatory score. Muscle wasting was defined as gender specific lowest quartile of fat-free mass estimated from bioelectrical impedance analysis (BIA) at month 24 visit. We investigated the association between low fat-free mass (FFM) and eGFR groups using logistic regression, with covariate adjustment for age, gender, race, site, comorbidities, SBP, DBP, and medications. With additional adjustment for baseline protein intake, serum bicarbonate, and inflammatory score, we examined whether the associations of CKD stages with low FFM at month 24 were attenuated.

Results: Mean baseline age was 58 ± 11 years, 56% were male, 40% were black, and mean eGFR was 45 ± 15. Mean weight was 91 ± 23 kg and mean FFM was 61 ± 16 kg. n multivariate logistic regression model, more advanced CKD was associated with significantly higher risk of low FFM (Figure 1 Panel A). These associations persisted after adjusting for baseline protein intake, serum bicarbonate, and inflammatory score (Figure 1 Panel B).

Conclusions: More advanced CKD is a strong predictor of muscle wasting. These associations are not fully explained by protein intake, serum bicarbonate and inflammatory markers. Further studies are needed to unravel the mechanisms of muscle wasting in CKD.

Funding: NIDDK Support

TH-PO929
Evaluation of Protein Malnutrition in CKD Patients on Low-Protein Diet
Arianna Bologna,1,2 Nadia Edvige Foligno,1,2 Giuseppe Vezzoli.1,2 IRCCS Ospedale San Raffaele, Milano, Italy; 1Università Vita Salute San Raffaele, Milano, Italy.

Background: Low-protein diet is considered crucial to slow down kidney function deterioration in patients with chronic kidney disease and control metabolic variables such as serum phosphate, urea and bicarbonate. However, low-protein diet may result in malnutrition if patients do not respect nutritional prescription. Thus, the present study examined the risk of protein malnutrition in CKD patients who started a low-protein diet.

Methods: Anthropometric variables, blood variables, nutrient intake and body composition were measured in 40 patients with CKD stage 4-5 (MF: 25/17, age 70±15 years; body weight 70±17 kg) before and after 3-months of a low-protein diet (0.6 g/kg; energy intake 30 Kcal/kg). Nutrient intake was estimated from a food frequency questionnaire; body fat mass (FM), free-fat mass (FFM) and skeletal muscle mass normalized to height2 (SMI) were assessed using biocompartmental analysis.

Results: In the whole sample, after a 3-month diet protein intake decreased from 0.8±0.24 to 0.7±0.20 g/kg (p<0.001) without a decrease in calory intake (22.3±5.9 and 21.5±4.9 kcal/kg). The diet induced a decrease in body weight (70±17 to 69±16 kg; p<0.001), BMI (26.5±6.4 to 25.9±6.2 kg/m²; p=0.001), FM (21±10 to 20±10 kg; p=0.003), serum phosphorus (10.6±48 to 13±4±43 mg/dl; p=0.001). Eight patients (20%; 4 diabetes) had a protein intake lower than 0.6 g/kg after 3-months of diet. Compared with patients having a higher protein intake, these patients showed lower protein intake at baseline (0.7±0.21 vs 0.89±24 g/kg; p=0.05) and serum albumin (36.3±2.7 vs 40.5±3.2 g/l; p=0.012). Their protein intake after the diet was significantly lower than that at baseline (0.5±3±0.2 vs 0.7±0.21 g/kg; p=0.016). They also showed a significant decrease in BMI (9.5±1.9 to 8.5±1.3; p=0.003). Conversely, the other 32 patients did not change BMI (9.2±2 to 9.2±2 kg/m²), but significantly decreased FM (23±11 to 21±11 kg; p=0.002) and increased phase angle (4.2±0.9 to 4.6±0.9; p=0.017).

Conclusions: Protein malnutrition may occur during a low-protein diet in CKD patients with a low consumption of proteins before starting this diet. Nutritional analysis is necessary to identify CKD patients at risk of protein malnutrition and to adequately follow-up CKD patients on low protein diet.

TH-PO930
Phosphorus Balance Calculator, an Individualized Tool for Treatment of Hyperphosphatemia in Hemodialysis Patients: A Randomized Clinical Trial
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Background: Lack of evaluations of the dietary phosphorus and dialysis phosphorus removal in daily clinical practice are the common obstacle to assess phosphorus balance and control phosphorus in hemodialysis patients. We aimed to investigate whether the individualized therapy using phosphorus balance calculator improves phosphorus control.

Methods: A randomized, open-label, multicenter, 4-week clinical trial was conducted. 119 patients aged 18 to 85 years old and with serum phosphorus level higher than 1.45mmol/l from 3 university teaching hospitals in Shanghai were enrolled and randomized in a 1:1 ratio to individualized (n=60) or conventional therapy (n=59). The primary outcome was the serum phosphorus concentration after 4-week treatment.

Results: Among 119 randomized participants (mean age, 62 years; 68 males(57%)), 116 completed the trial. By using the phosphorus balance calculator, the individualized group achieved a better phosphorus equilibrium state, significantly reduced the serum phosphorus (1.6±0.45mmol/l versus 1.85±0.45 mmol/l, P=0.006), increased the proportions of patients achieving target serum phosphorus range (41% versus 18%, P=0.006), and had greater adjusted mean difference in change in serum phosphorus over the 4 weeks (-0.47 versus -0.23mmol/l, P=0.010) when compared to conventional therapy.

Conclusions: Phosphorus balance calculator was proved to improve serum phosphorus control in patients undergoing maintenance hemodialysis, offering a new tool for managing refractory hyperphosphatemia.

Funding: Government Support - Non-U.S.

Figure 1. Changes in serum phosphorus, calcium and PTH over 4 weeks in response to individualized and conventional treatment in hemodialysis patients

Figure 2. Percentage of in target of serum phosphorus, calcium and PTH during the study period in two groups

TH-PO931
Exposure Estimates of Both Inorganic and Organic Phosphate-Containing Food Additives in US Grocery Household Food Sales in 2022 Validates Need for Labeling Phosphorus Content
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Background: A new paradigm based on the degree of food processing to assess the health of dietary patterns has replaced the traditional approach based on the nutrient content of the foods consumed. Dietary patterns where ultraprocessed foods (UPF) dominate are linked to adverse health conditions including CKD, CVD and mortality. Industrial use of food additives is a hallmark of UPF with 60% of foods purchased by Industrial use of food additives is a hallmark of UPF with 60% of foods purchased by

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Since no databases exist to estimate phosphate additive intake from processed foods, our objective was to use 2 proxy methods to estimate exposure to all commonly used P-containing food additives, both inorganic and less studied organic PO₄ additives (e.g., lecithins, phosphated modified starches). We used household grocery product food label information from USDA's Branded Food Product Database (BFPD) to estimate the number of foods being sold to American consumers that contain inorganic and organic PO₄ additives in foods (Table). Sales data from Euromonitor International were then used to identify products sold by the top 25 food and beverage manufacturers in the US. The proportion of products from these top 25 manufacturers that contained PO₄ additives was used to determine the total number of food products containing PO₄ additives, we show the % of foods that contained PO₄ additives in the 6 categories food categories. USDA identifies 6 food categories contributing the majority of total P intake (81%); however, this is thought to be mostly natural P as additive contribution is significantly underestimated (8%).

Conclusions: Using category-level sales data as a proxy for actual intake of foods with PO₄ additives, we show the % of foods that contained PO₄ additives in the 6 categories (Figure). More than 50% of bread, processed meats and ready meals contained PO₄ additives. USDA survey intakes of total P are thought to significantly underestimate total P intake (81%); however, this is thought to be mostly natural P as additive contribution is rarely included.

Results: These findings justify the need for P content labeling of foods to accurately link the health consequences of excessive P intakes in CKD and the general public.

TH-PO932
Inorganic Phosphate Additives in US Household 2022 Product Sales from the Top 25 Grocery Store Food Manufacturers: An Existential, Pervasive Risk Factor for CKD
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Background: Restricting dietary phosphorus (P) intake is critical to managing CKD uremia. Inorganic and organic phosphate additives also determine the progression of kidney failure, hyperphosphatemia and cardiovascular disease. Limiting dietary P intake is not a simple task of consuming less natural food sources rich in P (red meats, dairy) since the use of inorganic phosphate (PO₄) additives to process a variety of foods can contribute significant P hidden in processed food. Additives present a unique problem different from natural organic protein and lipid bound P in foods. PO₄ additive salts are rapidly dissociated in stomach acidity, absorbed quickly and can acutely disrupt serum P homeostasis and hormonal dysregulation linked to cardiovascular disease and mortality. Control of P intake is further complicated by the unknown extent of exposure to these PO₄ additives from packaged food and beverage products.

Methods: To estimate exposure to PO₄ additives, we examined ingredient labels of US household packaged products from the top 25 food and beverage manufacturers to identify the total number of food products containing PO₄ additives across USDA's 23 food categories. USDA identifies 6 food categories contributing the majority of total P intake (81%); however, this is thought to be mostly natural P as additive contribution is rarely included.

Results: These findings justify the need for P content labeling of foods to accurately link the health consequences of excessive P intakes in CKD and the general public.

TH-PO933
Calcium- and Iron-Based Phosphate Binders Impact the Gut Microbiome in Rats with CKD
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Background: Limited studies suggest that phosphate binders may impact the gut microbiota. Our objective was to examine the effects of a calcium-based binder and an iron-based binder on the cecal microbiota and gut-derived uremic toxins in a rat model of progressive CKD.

Methods: Rats with normal kidney function (NL) were compared to rats with CKD (Cy+/+ male rats): 1) control (CKD), 2) 2% ferric citrate (CKD + FC), 3) 2% calcium gluconate in water (CKD +Ca). Rats consumed the treatments for 10 weeks (18 to 28 weeks of age; mild to moderate/advanced CKD, respectively). The V4 region of the 16S rRNA gene was sequenced on cecal digesta and analyzed by Qiime2. Serum gut-derived uremic toxins were quantified using ultra-performance liquid chromatography-tandem mass spectrometry.

Results: Richness of the microbiota (alpha-diversity) was similar between groups, but overall microbial composition (beta-diversity) was different from each other. At the phylum-level, all CKD rats had lower relative abundance of Firmicutes, and CKD+Ca had higher Bacteroidetes. At the genus-level, CKD+FC had a higher relative abundance of Akkermansia, unclassified Desulfovibrioaceae, and Clostridium, and a lower relative abundance of Allobaculum, Bifidobacterium, and Lactobacillus. CKD+Ca had higher relative abundance of unclassified Lachnospiraceae and Blautia. Indoxyl sulfate and p-cresyl sulfate were elevated in CKD but were not affected by phosphate binders. However, phenyl sulfate and phenyl glucuronide were lower in CKD+Ca.

Conclusions: Calcium- and iron-based phosphate binders altered the gut microbiota, but only the calcium-based binder impacted phenyl-derived uremic toxins.

Funding: NIDDK Support, Other NIH Support - NAIMS T32, Commercial Support - Keryx pharmaceuticals for parent study.

TH-PO934
Effects of Curcuma longa L. and Green Propolis Extract-Loaded Microcapsules Supplementation on Inflammation in Hemodialysis Patients
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Background: Nutritional interventions with food that contains bioactive compounds such as Curcuma longa L. and propolis can mitigate inflammation in patients with CKD on hemodialysis (HD). Although broadly available, there are limitations in using these bioactive compounds when ingested in their traditional forms. In this way, the microencapsulation process of these natural compounds can be a good alternative. This longitudinal, double-blind, placebo-controlled study aims to evaluate the effects of Curcuma longa L. and green propolis extract-loaded microcapsules supplementation on inflammatory markers in HD patients.

Methods: Patients were randomized into two groups: Intervention (137mg/d of Curcuma longa L. and 500mg/d of concentrated and standardized green propolis extract EPP-AF®, Aapis Flora, Brazil) as microcapsules administered hard vegetable capsules or placebo for eight weeks. The levels of inflammatory biomarkers (IL-5, GM-CSF, TNF-α, IL-1β, IL-13, IL-4, MCP-1, IL-8, MIP-1, IL-10, G-CSF, IL-7, IL-12 and IL-17) were analyzed by multiplex assay (Bio-Plex MagPix®). C-reactive protein (CRP) was analyzed using a Bioclin device. All analyses were adjusted according to age, sex, BMI and time on HD.

Results: 38 patients completed the study; 18 patients in the intervention group (49 ± 16.6 yr.; BMI 21.6 ± 5.2Kg/m²; 8 men) and 20 in the placebo group (49 ± 16.2 yr.; BMI 24.4 ± 3.4Kg/m²; 10 men). After supplementation, MIP-1 and CRP plasma levels were significantly reduced (Fig 1).

Conclusions: Supplementation with 137mg/d of Curcuma longa L. and 500mg of microencapsulated EPP-AF® green propolis extract in hemodialysis patients for eight weeks significantly reduced MIP-1 and CRP values, evidencing the potential anti-inflammatory effects of the supplement.

Funding: Government Support - Non-U.S.
Recent trials have investigated the effects of urate-lowering agents, with conflicting results. However, these trials did not include severe chronic kidney disease patients, leaving uncertainty regarding febuxostat’s efficacy in this population. Moreover, high prevalence of hyperuricemia in severe chronic kidney disease patients, we aimed to assess febuxostat’s impact on cardiovascular events and deaths in this population.

Methods: We conducted an observational study using Japanese nationwide administrative claims data. Patients (n = 3,783; median age 74 years; 2,479 [65.5%] men; 1,453 [38.5%] with diabetes; median eGFR 28.8 ml/min/1.73 m²; median urate 8.3 mg/dl or allopurinol group (n = 396, median age 75 years; 246 [71.5%] men; 185 [31%] with diabetes; median eGFR 28.5 ml/min/1.73 m²; median urate 7.3 mg/dl) with respect to cardiovascular events and deaths, febuxostat (1032 patients [0.035 events per 100 patient-years]) was superior to allopurinol (227 patients [0.042 events per 100 patient-years], adjusted HR 0.861 [95% CI 0.747–1.001]).

Results: A total of 4,793 patients were enrolled: febuxostat group (n = 3,783; median age 74 years; 2,479 [65.5%] men; 1,453 [38.5%] with diabetes; median eGFR 28.8 ml/min/1.73 m²; median urate 8.3 mg/dl) versus allopurinol group (n = 396, median age 75 years; 246 [71.5%] men; 185 [31%] with diabetes; median eGFR 28.5 ml/min/1.73 m²; median urate 7.3 mg/dl). We did intention-to-treat analysis, in which we ignored switching of drugs, using Cox proportional hazard regression models.

Conclusions: This analysis using Japanese nationwide data suggested that febuxostat seemed to decrease cardiovascular events and deaths compared to allopurinol in chronic kidney disease patients.

Tao et al. (2023) characterized the metabolic response of zebrafish to a high-calorie diet. They found that overfed zebrafish were heavier and had larger kidneys. Kidney metabolomes differed significantly (Figure 1A), and 235 metabolites were significantly different between groups (125 upregulated in high calorie diet, 110 downregulated) (Figure 1B). Analysis of specific metabolites suggested alterations in tryptophan metabolism.

TH-PO937
Antioxidative Effects of Molybdenum and Its Association with Reduced Prevalence of Hyperuricemia in the Adult Population

Background: Obesity is an epidemic risk factor for the development of chronic kidney disease. Obesity induces systemic changes in metabolism; its effect on kidney metabolism specifically is not known.

Methods: Urinary molybdenum’s epidemiological relationship to hyperuricemia and kidney-related disease outcomes was assessed in 15,370 adult participants in the National Health and Nutrition Examination Survey (NHANES) collected between 1999 and 2016. Individuals’ urinary molybdenum levels were corrected to their urinary creatinine concentrations. The association between urinary molybdenum and kidney-related disease outcomes were assessed by multivariable linear and logistic regression analyses, adjusting for covariates including age, sex, ethnicity, diabetes mellitus, hypertension, body mass index, and estimated glomerular filtration rate. Antimyosin and tungsten were used as control trace metals. Experimentally, HK-2 cell was used to assess molybdenum’s antioxidative properties. HK-2 cells were challenged with H2O2-induced oxidative stress. Oxidative stress was measured using a fluorescent microplate assay for reactive oxygen species (ROS) and antioxidation levels were assessed by measuring the expression of manganese superoxide dismutase.

Results: In the adult NHANES population, urinary molybdenum-tocreatinine ratio was significantly associated with decreased serum uric acid (β, -0.119; 95% CI, -0.148 to -0.090) concentrations, and decreased prevalence of hyperuricemia (OR, 0.73; 95% CI, 0.64-0.83) and gout (OR, 0.71; 95% CI, 0.52-0.94). Higher urinary molybdenum levels were associated with lower levels of systemic oxidative stress (gamma-glutamyltransferase activity; β, -0.052; 95% CI, -0.067 to -0.037) and inflammation (C-reactive protein levels; β, -0.184; 95% CI, 0.220 to -0.148). In HK-2 cells under H2O2-induced oxidative stress, molybdenum upregulated manganese superoxide dismutase expression and decreased oxidative stress.

Conclusions: Urinary molybdenum levels are associated with decreased prevalence of hyperuricemia and gout in adult population. Molybdenum’s antioxidative properties might have acted as an important mechanism for the reduction of systemic inflammation, ROS, and uric acid levels.

TH-PO938
Characterizing the Metabolic Response of the Zebrafish Kidney to a High-Calorie Diet

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Background: Obesity is an epidemic risk factor for the development of chronic kidney disease. Obesity induces systemic changes in metabolism; its effect on kidney metabolism specifically is not known.

Methods: We treated zebrafish for 8 weeks with a control (ND) and a high calorie (HC) diet. We performed an untargeted metabolomic analysis on the kidneys of fish using ultra-high performance liquid chromatography coupled mass spectrometry. We used murinechoc and gene set enrichment analysis to uncover differentially affected metabolic pathways.

Results: Overfed zebrafish were heavier and had larger kidneys. Kidney metabolomes differed significantly (Figure 1A), and 235 metabolites were significantly different between groups (125 upregulated in high calorie diet, 110 downregulated) (Figure 1B). Analysis of specific metabolites suggested alterations in tryptophan metabolism.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Diet Significantly Influences the Induction of Endoplasmic Reticulum Stress (ERS) in the Kidneys of Male C57Bl/6 Mice

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Background: Previous studies have associated ERS with different forms of kidney disease, but it is unclear whether ERS influences renal physiology in normal, non-diseased states. Previous work has suggested an interaction exists between diet and ERS in other organs. Therefore, this study aimed to determine if diet alters the severity of tunicamycin (TUN) in kidneys.

Methods: Weanling male C57Bl/6 mice were randomly assigned to receive one of three diets: chow, commercially available Western Diet (WD), or a novel Americanized diet (AD) formulated to match 50% percentile nutrient intake in humans. After 6 weeks, mice were injected with TUN (1 mg/kg, IP), or saline, to induce ERS. 24 hours later, mice were euthanized, and plasma and kidneys were collected. Plasma BUN and creatinine were quantified using commercially available assays and mRNA expression of ERS-related genes was quantified using commercially available PCR arrays. All data were analyzed using GLM procedures and significance identified with P<0.05.

Results: Mice fed the WD had the greatest body weight and adiposity (P<0.002). TUN alone did not influence either measure, but a significant diet×TUN interaction was observed where only mice fed WD had a 20% reduction in body weight and adiposity (P<0.01) with TUN. TUN reduced (P=0.001) BUN (20.6±0.7 mg/dL) as compared to control mice (28.0±0.8), and a diet×TUN interaction was observed with mice fed AD having lower (P=0.001) BUN with TUN. Diet alone had no effect on BUN (P=0.5), but plasma creatinine was higher in mice fed AD regardless of TUN (0.65±0.04 mg/dL, P=0.005). Neither diet or TUN influenced renal inflammation by CD45 mRNA expression. Diet alone significantly (P<0.05) influenced the expression of 30% (26 of 84) of the quantified ERS-related genes, and a significant diet×TUN interaction was observed for 14 genes. Generally, mice fed the AD had greater change in ERS-related genes with TUN.

Conclusions: These data highlight an interaction between diet and ERS on renal function in a non-disease setting. Our data suggest that diet, formulated to model typical American intakes, modulates the expression of ERS-related genes. Further studies are needed to validate these findings and understand their physiological significance.
Conclusions: Our data demonstrate that 1) in cultured primary RPTECs, the tryptophan-kynurenine pathway loses its function for de novo NAD+ synthesis, 2) the downregulation of a key enzyme gene KMO disrupts the conversion of KYN to 3HK in the pathway.

Funding: Commercial Support - NJI

TH-PO942

Glucocorticoid Treatment Induces Lymphatic Dysfunction via ATP-Sensitive Potassium Channel

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Background: Previously, we showed proteomic changes impair lymphatic vessel function. Glucocorticoid (GC) therapy is a cornerstone treatment of proteomic diseases but can cause GC induced adiposity. Since lymphatics are the principal conduit for transport of lipoprotein particles and clearance of excess lipids, adiposity has been proposed as an indicator of impaired lymphatic function. We investigated whether glucocorticoids directly disrupt lymphatic integrity and function.

Methods: We exposed cultured lymphatic endothelial cells (LECs) to dexamethasone (DXMS) or control medium and assessed relevant parameters including proliferation, migration, and expression of tight junction protein-1 (TJP1), vascular endothelial growth factor receptor 3 (VEGFR3 or Flt4), and caspase 2/3/9 (casp2/3/9) genes. Ex vivo microscopy studies evaluated DXMS effects on dynamics by exposing isolated rat mesenteric lymphatic vessels to increasing concentrations of DXMS. We also studied mesenteric lymphatic dynamics in vessels harvested from rats receiving daily DXMS or vehicle x 2 weeks. Finally, we evaluated effects of chronic DXMS exposure on response to vasoactive agents: L-NNAME, PGE2, furosemide, and pinacidil, an ATP-sensitive potassium channel (KATP) agonist.

Results: Our findings revealed that DXMS significantly reduces proliferation, migration, and TJP1 gene expression in LECs, while enhancing Flt4 gene expression. DXMS did not alter apoptosis of LECs. In mesenteric lymphatic vessels isolated from normal rats, DXMS increased frequency and end-systolic diameter (ESD), along with decreased amplitude of contraction (AMP) and ejection fraction (EF) with little effects on end-diastolic diameter (EDD). Similarly, vessels from DXSM-treated rats had decreased AMP and EF vs vehicle-treated rats. Moreover, chronic exposure to DXMS dramatically diminished responsiveness to pinacidil when compared to vessels of control rats, suggesting that DXMS can alter lymphatic function via modulation of KATP channels.

Conclusions: Our data suggest the novel observations that glucocorticoids are powerful modulators of lymphatic vessel function, lymphatic endothelial cell integrity and function, and can alter the mechanism of circadian disruption in the context of proteomic kidney disease.

Funding: Other NIH Support - NHLBI

TH-PO943

Environmental Circadian Disruption Accelerates 5/6 Nephrectomy-Induced Chronic Kidney Injury in Mice

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Background: Circadian disruption such as shift work, jet lag, has gradually become a global health issue and is closely associated with many metabolic disorders. The effect and mechanism of circadian disruption on renal injury and chronic kidney disease (CKD) remains poorly understood. Here, we evaluate the effect of environmental light/dark shifting on the progression of chronic renal injury in CKD mice.

Methods: Mice were subjected to 5/6 nephrectomy and then exposed to either a standard 12h light/12h dark cycle or weekly light-dark cycles reverse (LDDL) or weekly 6h phase advance (6h adv) for 3 months. Plasma and kidney tissues were harvested for renal function and histological examination. RNA-seq and untargeted metabolomics were performed for mechanistic investigation.

Results: The results showed that 3-month light interference by weekly LDDL significantly exacerbated renal dysfunction, accelerated renal injury, and promoted renal fibrosis in mice with 5/6 nephrectomy, while light interference by weekly 6h phase advance failed to worsen renal function and kidney injury. RNA-seq and untargeted metabolomics results revealed significant upregulation of genes related to inflammatory response and immune cell chemotaxis, while obvious downregulation of genes and metabolites related to energy metabolism was indicated in the LDDL-conditioned Kidney kidneys. Consistently, the renal content of AMP was decreased and ROS production was increased in the renal kidney tissues of the LDDL-challenged CKD mice.

Conclusions: We concluded that circadian disruption by environmental light interference may aggravate chronic kidney injury by facilitating inflammatory response and suppressing energy metabolism in the CKD kidneys. Targeting the circadian machinery and keeping routine light-dark cycles may represent promising approaches for the prevention and treatment of CKD.
TH-PO946
Case Report on Successful Treatment of Life-Threatening Anemia in ESRD Patient on Maintenance Hemodialysis Who Is a Jehovah Witness and Refusing Blood Transfusion
Omar N. Elhawary,1,2 Sandeep R. Sasidharan,1,2 Syeda S. Bukhari,1,2 Ishu Puri,1,2 Mary C. Mallapalli.1,3 Kings County Team. 1SUNY Downstate Health Sciences University, Brooklyn, NY; 2Kings County Hospital Center, Brooklyn, NY.

Introduction: Anemia is prevalent in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) who undergo regular hemodialysis. This is primarily attributed to reduced production of erythropoietin by the kidneys. Existing guidelines recommend managing anemia when the hemoglobin (Hgb) is below 11 g/dL by administering intravenous iron and erythropoietin injections. In cases where patients have severe anemia with hemoglobin levels below 7.8 g/dL and experience symptoms, blood transfusion is typically recommended. Blood transfusions help in correcting anemia, alleviating symptoms, and enhancing tissue oxygenation. However, providing appropriate treatment for anemia becomes challenging when patients refuse blood transfusion due to religious beliefs, such as our patient. In our case report, we present a successful treatment approach for severe anemia in an ESRD patient without utilizing blood transfusions.

Case Description: 60-year-old woman with history of Hypertension, ESRD on hemodialysis (HD) due to Systemic lupus erythematosus with failed kidney transplant presented with altered mentation. She was found hemodynamically unstable, in atrial-flutter requiring ablation and cardiac monitoring on admission. She had a long hospitalization with Hgb at presentation 9. It gradually went down to 4.8 over 3 weeks. Due to her religious beliefs as a Jehovah’s witness, she declined blood transfusion. To treat her anemia, we initiated a daily treatment regimen consisting of short-acting erythropoietin alfa at a dose of 40,000 Units for seven days, along with daily intravenous iron sucrose at 100 mg. After one week of this treatment, the patient’s hemoglobin level improved to 11.5 g/dL and felt markedly better.

Discussion: For Jehovah Witness patients undergoing HD, who have severe anemia and decline blood transfusions, we suggest initiating a daily, short-term treatment of erythropoietin alfa at a dosage of 40,000 U, along with intravenous iron, for a duration of one week. If the patient is already receiving long-acting darbepoetin alfa, it is advised to transition to short-acting erythropoietin alfa. This approach may also be applied for preventing and managing anemia, regardless of whether the patients are receiving renal replacement therapy or not.

TH-PO947
SGLT2-Induced Erythrocytosis Unveiling Heterozygous Hereditary Hemochromatosis (HH) Gene Mutation in an Individual with CKD
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Introduction: SGLT2 were shown to increase hemoglobin (Hb) levels in clinical trials. We report a case of symptomatic erythrocytosis in an individual treated with SGLT2 empagliflozin who was later found to have a HH gene mutation.

Case Description: This was a 72-ya-old male with CKD and baseline serum creatinine (SCr) of 2.1mg/dL (eGFR 33mL/min/1.73m2), controlled type 2 diabetes (AIC 6.9%) and hypertension. Empagliflozin 12.5mg daily was initiated due to persistent grade A3 proteinuria (aACR ~1.55g/g) despite daily combination of losartan 100mg and spironolactone 25mg. Hb and hematocrit (Hct) were 16.8g/dL (normal 13.5-17) and 49.5% (normal 38-50) at the time of SGLT2 start. The patient had no history of obstructive sleep apnea. There was a remote history (>30 years ago) of smoking. Over the years, he had intermittent mild Hb elevation in 17-17.5g/dL range. At that time, erythropoietin initiation, Hb (Hct) gradually rose to 20g/dL (59.3%) despite advice to maintain adequate hydration. The patient reported worsening fatigue and diffuse myalgias. Physical examination and vital signs were normal. Transferrin saturation (Tsat) was 30%. Ferritin was 145ng/mL. SCr rose to 2.6mg/dL (eGRF 25 mL/min/1.73m2). Screening for HH in the nephrology clinic revealed H63D heterozygosity in the HFE (Hemochromatosis Iron regulator gene and negative C282Y gene mutation. Two serial platelet counts were performed and lead to the normalization of Hb (Hct) to 16.5g/dL (48%), resolution of symptoms, and an improvement in Scr to 2.0mg/dL (eGRF 35 mL/min/1.73m2). Tsat and ferritin remained normal. Empagliflozin was continued for renoprotection. Monthly platelet counts was continued to maintain adequate Hb.

Discussion: SGLT2 induces erythrocytosis in patients with CKD. Their use may also be associated with erythrocytosis. The presence of underlying heterozygous HH gene mutation was likely predisposing risk factor of SGLT2-induced erythrocytosis. This case suggests that periodic monitoring of Hb level should be considered. Additionally, screening for HH could be offered to patients with SGLT2-induced erythrocytosis to implement phlebotomy if a HFE gene mutation is detected. Stopping SGLT2 will likely lower Hb to baseline, but it will also remove their cardio renal benefits.

TH-PO948
Successful Treatment of Anemia with Roxadustat in a Hemodialysis Patient Following Erythropoietin-Induced Pure Red Cell Aplasia
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Introduction: Erythropoietin (EPO) antibody (Ab)-induced Pure Red Cell Aplasia (PRCA) is a rare condition. Treatment usually requires immediate withdrawal of EPO and treatment with immunosuppression or renal transplantation. Here, we present the successful treatment of a case of EPO Ab-Induced PRCA with cyclosporin (CyA) and Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI).

Case Description: A 58-year-old man developed kidney failure as a result of diabetes mellitus. In July 2021, shortly before he began dialysis, he was commenced rhHuEPO (Jimaxin, epoetin-α, KexingBio, Shandong, China) subcutaneously 5000 IU twice a week. He began hemodialysis (HD) in November 2021. He was switched to intravenous rhHuEPO (6000 IU) (Yupindg, epoetin-α, NCPC GenetechBio, Hebei, China) once a week. His Hb increased to 116 g/L in the first 3 months but fell to 75 g/L 6 months into HD. 3½ weeks later, he presented with a pneumonia and a Hb of 48 g/L. He was treated with antibiotics and was transfused. His EPO was stopped. He was started on Roxadustat. 18 days later, his Hb fell to 38 g/l, his reticulocytes was 2900/μL. A bone marrow (BM) biopsy showed a proliferative active BM but reduced erythropoiesis and an erythroid precursor of 7.2%. A diagnosis of EPO Ab-induced PRCA was suspected. However, an anti-EPO Ab ELISA test later turned out negative. Some likely causes of PRCA such as lymphoproliferative disorder, parvovirus B19 infection, thrombotic and systemic autoimmune disease were excluded. The Roxadustat was discontinued. A second BM biopsy showed a erythroid precursors of 5.2%. The suspicion of a EPO Ab-induced PRCA was maintained. The patient was commenced CyA 3mg/kg/day and was given 25 more units of rhHuEPO. The reticulocyte counts took 3 months to recover to normal. The patient was recommenced on Roxadustat 100 mg TIW and his Hb stabilized.

Discussion: Even though the anti-EPO Ab was negative by ELISA assay in our case, the clinical course, with markedly reduced reticulocyte count <10000/μL, a BM biopsy revealing reduced erythroblasts only, and its subsequent response to CyA, were in keeping with EPO Ab-induced PRCA. Anti EPO Ab assay is not always positive in EPO Ab-induced PRCA. Our case illustrates that treatment with Cyclosporin and a switch to Roxadustat are useful in treating EPO Ab-induced PRCA.

TH-PO949
Risk Factors Involved in Erythropoietin Resistance in Patients with CKD in a Hemodialysis Unit
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Background: Recombinant human erythropoietin is administered to patients with end-stage chronic kidney disease for the treatment of anemia. However, there are different factors that generate resistance to this treatment. This paper seeks to evaluate the impact of a structured team approach for the management of anemia in erythropoietin-resistant hemodialysis patients.

Methods: Prospective study of 18 months. A total of 27 patients in a hemodialysis unit of a reference center, where erythropoietin resistance was defined as those patients who had erythropoietin >300 units/kg/week. Hemoglobin, iron indices, parathyroid hormone, folate, vitamin B12, and reticulocyte counts were determined at baseline. Some previous parameters were followed every 6, 12 and 18 months. The target hemoglobin was 10-12 g/dL. All factors potentially contributing to erythropoietin resistance were evaluated and, if possible, treated every 4 weeks by a specialized nephrology team. Downward erythropoietin dose adjustments of 12.5 to 25% to the nearest 1000 units were considered if the underlying causes of resistance could not be identified or reversed, or if hemoglobin exceeded the target level.

Results: Parathormone levels and iron deficiency were the predominant treatable factors associated with erythropoietin resistance. At 4 months, mean erythropoietin dose decreased significantly from 469 to 319 units/kg/week (p < 0.001) and mean hemoglobin increased significantly from 10.6 to 11.6 g/dL (p = 0.023), At 8 months, the patients had erythropoietin doses of less than 300 units/kg/week, reaching target hemoglobin levels.

Conclusions: A structured team approach of nephrologists and a monthly adaptation of individualized management of the patient managed to significantly reduce the dose of erythropoietin with an improvement in serum hemoglobin reaching the objectives set in the international guidelines, identifying and solving the factors involved.
3-Cardio-4-Methyl-5-Propyl-2-Furanpropionate (CMFP), an Endogenous Protein-Bound Uremic Solute, Renders Erythrocyte Osmotically More Fragile, Possibly Through a Piezo1 Pathway

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Background: Shortened red blood cell (RBC) life span contributes to renal anemia and may be caused by uremia-induced premature RBC death (eryptosis). Recently, it was hypothesized that the uremic solute CMFP interacts with the Piezo1 mechanoreceptor on the RBC surface due to CMFP’s structural similarity with Jedi1, a well-characterized synthetic Piezo1 agonist (Kotanko et al., 2022). In this study, we compared the effects of Jedi1 and CMFP on RBC osmotic fragility.

Methods: RBC from 5 healthy subjects were incubated for 30 min with CMFP or Jedi1 (both at concentrations of 87 µM) in phosphate-buffered saline with 4% human serum albumin. RBC incubated without CMFP or Jedi1 were negative controls. Subsequently, RBC suspensions were incubated in NaCl solutions of increasing osmolality (NaCl 3 to 9 g/L). Free hemoglobin was measured in the supernatant by spectrophotometry at 540 nm. The data were fitted to a 4-parameter logistic regression curve to obtain the osmotic fragility index (IC50). IC50 is defined as the NaCl concentration that causes 50% hemolysis.

Results: RBC incubation with CMFP or Jedi1 increased IC50 (i.e., increased osmotic fragility) when compared to the negative control (Table 1). The IC50 increase was most pronounced in RBC incubated with CMFP.

Conclusions: Our findings suggest that CMFP − an endogenous metabolite and uremic solute − may increase RBC osmotic fragility, possibly through a Piezo1 pathway. Understanding the molecular mechanisms involved may aid the developing new therapeutic approaches to renal anemia.

Table 1 – RBC osmotic fragility index (IC50) under different experimental conditions

<table>
<thead>
<tr>
<th>Experimental condition</th>
<th>IC50 mean (SD)</th>
<th>IC50 difference (IC50 control)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative control</td>
<td>4.57 ± 0.13</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Jedi1 (µM)</td>
<td>5.02 ± 0.86</td>
<td>0.45 (0.05–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>CMFP (µM)</td>
<td>5.57 ± 3.19</td>
<td>1.00 (0.31–2.50)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

TH-P0951

A Retrospective View of the Relationship of Soluble Fas with Anemia and Outcomes in CKD

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Background: Anemia is common in chronic kidney disease (CKD) and is related to serum levels of soluble Fas (sFas), which are associated with resistance to erythropoietin (EPO). The study objectives to compare clinical data and serum levels of sFas, EPO, and pro-inflammatory markers between non-dialytic CKD patients and healthy individuals. To assess the relationship of serum EPO and sFas between these patients with and without anemia.

Methods: Retrospective study of 58 CKD patients under conservative treatment and 20 healthy individuals. Complete blood count, renal function, serum EPO, sFas, and pro-inflammatory markers (CRP, IL-6, and INF-γ) were analyzed at baseline. We then analyzed these variables between patients who progressed to anemia and those without anemia. We evaluated the frequency of outcomes in these patients with elevated sFas levels. We performed a multivariate analysis of factors associated with anemia.

Results: CKD when compared to healthy individuals had lower eGFR (35.7 ± 2.5 vs 89.7 ± 3.2 ml/min; p<0.001) and Hb (12.8 ± 0.27 vs 14.4 ± 0.25 g/dL; p=0.003), major inflammatory markers, sFas (2894 ± 172 vs 1136 ± 97 mg/ml; p<0.001), and EPO/Hb (8.6 ± 1.6 vs 4.9 ± 0.58 IU/mg/dl; p=0.003). CKD with anemia, when compared to non-anemic individuals, had lower eGFR (27.7 ± 1.72 vs 54.9 ± 2.52; p<0.001) and higher sFas/ eGFR (150.9 ± 16.6 vs 45.2 ± 9.95; p<0.001), EPO/Hb (10.3 ± 5.6 ± 512 ± 0.69; p=0.04) and sFas (3339 ± 181 vs 1820 ± 240; p=0.001). We found an independent association in the multivariate analysis of serum sFas levels with long-term renal anemia sFas (OR 3.422, 95% CI 1.06–11.75; p=0.008).

Conclusions: As an elective risk factor, serum sFas levels were independently associated with long-term renal anemia.

Funding: Other NIH Support - FAPESP - Fundação de Amparo à Pesquisa do Estado de São Paulo, Brazil.

TH-P0952

Depression and Anxiety Are Associated with Iron Deficiency Anemia for Patients with Stages 2–4 CKD

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Background: Neuropsychiatric disorders, mainly cognitive decline, depression, and anxiety, are more common in CKD patients. The association between iron deficiency anemia (IDA) and cognitive decline is well-known for this population. For patients without CKD, IDA is associated with depression and anxiety. However, the link between depression, anxiety, and IDA is not clear in subjects with non-dialysis-dependent CKD. In this work, we aimed to evaluate the association above.

Methods: We selected a cohort of patients with stable stage 2–4 CKD and assessed them with Beck’s depression inventory (BDI) and Beck’s anxiety inventory (BAI). We excluded patients with acute kidney injury or decapsulation, hemodialysis patients with solid malignancies, and those suffering from psychological trauma. A diagnosis of schizophrenia, major depression, and bipolar disorder or using antidepressant/antipsychotic drugs were reasons for exclusion. We also did not include those needing FBD or those with other causes of anemia.

Results: Two hundred patients were included in the final analysis. 76 of 200 (38%) patients were anemic. Patients with anemia were older and had worse GFR. BDI scores were worse for patients with anemia. Furthermore, with a cut-off of eleven for BDI, 31.7% of patients in non-anemic and 51.4% of patients in anemic groups received further evaluation for clinical depression. The difference was significant (p=0.007). Univariate analysis did not reveal a relationship between BDI and hemoglobin, transferrin saturation, and ferritin levels. A multivariate analysis was not undertaken due to the low number of patients. A subgroup analysis of anemic patients also showed that patients who had received iron, despite being still anemic, had lower BDI scores compared to those with untreated anemia (p=0.003) BAI scores were similar between groups. In addition, frequencies of minimal, mild, moderate, and severe anxiety were similar. However, in subgroup analysis, patients who had received iron despite being still anemic had lower BAI scores than those with untreated anemia.

Conclusions: Our work hints at a viable link between depression, anxiety, and IDA in subjects with Stage 2–4 CKD. However, this study is observational and thus only can generate a hypothesis. Prospectively designed studies on iron replacement may further elaborate our understanding of these associations.
Hemoglobin Level Variability and Infectious Risk in Hemodialysis Patients in the Era of Long-Acting Injatable Erythropoiesis-Stimulating Agents

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Background: Target hemoglobin level is suggested in the management of chronic kidney disease. However, hemoglobin levels often fall below or exceed the target range. Past retrospective cohort studies of patients undergoing hemodialysis with conventional short-acting erythropoiesis stimulating agents found that hemoglobin level fluctuations predicted mortality and cardiovascular adverse events; thereafter long-acting agents have been widely available.

Methods: We adopted Cox regression models to evaluate associations between hemoglobin level variability and all-cause death, hospitalization, and cardiovascular, thrombotic, or infectious adverse event outcomes in 3,068 hemodialysis patients' data from the Japanese Dialysis Outcomes and Practice Patterns Study from 2012 to 2014.

Results: All-cause mortality was lowest in the first quartile and tended to be higher in the groups with greater hemoglobin variability (hazard ratio: 95% confidence interval for the fourth quartile of an absolute value of hemoglobin variability: 1.44 [0.99–2.08], p for trend = 0.056). Intriguingly, infectious event incidence was higher than the first quartile for the second through fourth quartiles (p for trend <0.01). The association was more pronounced in patients with lower serum ferritin levels or with iron supplementation. However, cardiovascular and thrombotic event incidence was not associated with hemoglobin variability.

Conclusions: Maintenance hemodialysis patients on erythropoiesis stimulating agent treatment with higher hemoglobin variability are at higher risk for all-cause mortality and particularly infectious events.

Funding: Commercial Support - Kyowa Kirin

TH-PO956

Hemoglobin Variability Is Associated with Nutritional Status in Hemodialysis Patients Undergoing Darbepoetin-Alfa Treatment

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Song in Baeg. 1,2 Myongji Hospital, Goyang, Gyeonggi-do, Republic of Korea; 1Hanyang University College of Medicine, Seongdong-gu, Seoul, Republic of Korea.

Background: Anemia is common in hemodialysis (HD) patients, and their response to erythropoietin (EPO) treatment is inconsistent. Fluctuations in hemoglobin levels, known as Hb variability, occur during EPO therapy. This study investigated the association between EPO responsiveness, Hb variability, and nutritional status in HD patients undergoing NESPI® (darbepoetin-alfa; Kyowa Kirin Korea Co., Ltd.) treatment.

Methods: This prospective study enrolled 98 adult HD patients (age > 20 years, HD vintage – 6 months). The target Hb level followed Korean reimbursement guidelines (10.13 g/dL). NESPI® dosage adjustments were based on monthly Hb measurements. EPO resistance index (ERI) was calculated as the average weekly NESPI® dose divided by Hb level. Hb variability was assessed using Hb Coefficient of Variation (Hb-CV) with a 24 month Hb data points. Nutritional parameters, including body mass index (BMI), fat tissue index (FTI), lean tissue index (LTI), body cell mass index (BCM), and phase angle (PhA), were evaluated using BCM® (Fresenius Medical Care a Deutschland GmbH, Germany). Clinical and biochemical parameters were also considered.

Results: The study comprised patients with a mean age of 64.0±11.9 years, of which 55.0% were male. HD vintage averaged 54.9±46.8 months, and the follow-up duration was 79.3±47.9 months. Mean Hb level was 10.7±1.3 g/dL. Patients were divided into tertiles based on ERI and Hb-CV. The average ERI was 0.02±0.01, 0.04±0.01, and 0.07±0.03 in ERI-T1, ERI-T2, and ERI-T3, respectively. The ERI-T3 group exhibited lower Hb levels (p<0.001) and higher EPO doses (p=0.001). ERI-T3 correlated with lower PhA (p=0.044), BMI (p=0.001), and FTI (p=0.046). The Hb-CV-T3 group displayed lower BMI (p=0.002) and FTI (p=0.002). FTI was negatively correlated with ERI (r= -0.193, p=0.046) and Hb-CV (r= -0.268, p=0.005) and positively correlated with age (r=0.197, p=0.017) and female sex (r=0.386, p=0.001). Multiple linear regression analysis indicated a negative association between FTI and ERI (β= -0.218, p=0.014) as well as Hb-CV (β= -0.181, p=0.039). Age (β= 0.197, p=0.017) and female sex (β= 0.386, p=0.001) were positively associated with FTI.

Conclusions: Higher EPO resistance and Hb variability were associated with compromised nutritional status, particularly reduced fat tissue, in HD patients on darbepoetin-alfa.

TH-PO957

Red Blood Cell Distribution Width Coefficient of Variation as an Indicator of the Requirement for and Efficacy of Daprodustat in Hemodialysis Patients Switching from Erythropoietin-Stimulating Agents

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Background: Red blood cell distribution width (RDW) is an index of red blood cell volume variability and is used as a marker of iron deficiency anemia. In both hemodialysis and chronic kidney disease patients, a high RDW is associated with a higher mortality risk. Indicators of the requirement for and efficacy of daprodustat have not been reported previously. Therefore, we investigated whether the RDW-coefficient of variation (CV) is an indicator of the requirement for and efficacy of daprodustat when switching to erythropoietin-stimulating agents (ESAs) to daprodustat in patients undergoing maintenance hemodialysis.

Methods: This historical cohort study included 37 patients undergoing maintenance hemodialysis and who switched from ESAs to daprodustat at our affiliated institutions.
The patients were divided into two groups by an RDW-CV cut-off of 14.2%. Propensity score matching was performed by sex, diabetes mellitus, iron deficiency, albumin concentration, and C-reactive protein concentration. We examined whether there was a difference in the requirement for daprodustat and in the hypoxia-inducible factor prolyl hydroxylase inhibitor resistance index (HRI; defined as daprodustat dose/ dry weight / hemoglobin) after 6 months between the two groups. (ESA) response index (iEResI) to be positively associated with male sex, low hemoglobin (Hb) and iron supplementation, and darboepoetin alfa (DA) administration frequency, suggesting that the iEResI could be associated with ‘adequacy of anemia treatment’.

Methods: We analyzed the data for the 1,480 patients registered in the BRIGHTEN study. The primary outcome was progression of renal dysfunction. The iEResI was calculated by dividing Hb changes resulting from 12-week DA administration by the weight-adjusted total dose of DA administered in that period. Cross-classification (4 groups) of sex, age, and Hb after 65 years was used for analysis per attribute.

Results: The baseline Hb levels were similar in all groups, ranging between 9.7–9.9 g/dl, regardless of sex or age. The DA dose/kg was the lowest in men <65 years (0.80 µg/kg/12 weeks) and the highest in women >65 years (1.08 µg/kg/12 weeks), whereas iEResI was the highest in men <65 years (0.61) and the lowest in women >65 years (0.05). Kaplan-Meier survival curves indicated that men <65 years and women >65 years had the worst and best renal prognoses, respectively, among the cross-classified sub-cohorts. Multivariate Cox analyses in the present study revealed that high levels of Hb (hazard ratio [HR] 0.75, P<0.001) and high levels of iEResI (HR 0.77, P=0.002) were associated with good renal prognosis. Notably, when divided into four subgroups for cross-classification, anemia was associated with renal prognosis in three subgroups: men <65 years, men >65 years, and women >65 years, whereas iEResI was associated with renal prognosis only in men <65 years. In men <65 years, iEResI (HR 0.63, P=0.030), Hb (HR 0.65, P=0.001), and urinary protein excretion (HR 1.12, P=0.001) were associated with renal prognosis.

Conclusions: Anemia and ESA response index (iEResI) were associated with renal prognosis, suggesting that anemia treatment may improve renal prognosis. Cross-classification clarified that men <65 years may benefit more from anemia treatment than other patients.

TH-PO959

Patient-Reported Outcomes in a Real-World Study of Anemia of CKD in the Middle East and Africa

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Background: Anemia is a common complication of chronic kidney disease (CKD) that can negatively impact quality of life. Treatment satisfaction of patients with anemia of CKD living in the Middle East or Africa was explored.

Methods: SATIFY was a real-world study in Egypt, Saudi Arabia, South Africa and Turkey (1 Jan–1 Sep 2022). Physicians and patients completed cross-sectional surveys of treatment perceptions; patients’ clinical characteristics were recorded via retrospective review of medical records. Eligible physicians were nephrologists with ≥2 years of experience. Eligible patients were aged ≥18 years with CKD stage 3b–5 at anemia diagnosis and ≥2 years of follow-up data. Data were analyzed descriptively.

Results: In total, 217 physicians and 766 patients (457 [60%] non-dialysis dependent; 286 [37%] dialysis dependent; 23 missing [3%] at data extraction) completed surveys. Mean patient age (standard deviation) was 48 (14) years; 457 (60%) were male.

Conclusion: Treatment satisfaction was high (89% of physicians and 84% of treated patients [n=478] were satisfied very/satisfied). Overall, 24% of treated patients had severe-to-very severe anemia symptoms, 15% reported worsening symptoms since initiating most recent treatment and 38% had quite-to-very bothersome side-effects (Figure). Over 80% of both patients and physicians reported that physicians made the final treatment decisions.

Conclusions: Despite high treatment satisfaction, patients with anemia of CKD in the Middle East and Africa reported high symptom burden, treatment side-effects and worsening of symptoms, suggesting a high unmet need.

Funding: Commercial Support - Astellas Pharma Singapore Pte Ltd.
Methods: We used data on incident PD patients from a cohort in Brazil (BR) and the United States (US) during Dec 2004-Jan 2011. Patient, lab, and medication data was compared by PCS categories representing an individual’s physical well-being/functioning. PCS scores were categorized as <35 (low PCS), >35 to ≤40 (moderate-low PCS), >40 to ≤50 (moderate-high PCS), >50 (high PCS).

Results: Demographics for patients who started PD (BR=2,022; US=1,657) were consistent between countries for mean age (BR=57.3 ± US=55.6 years) and albumin (both 3.7 g/dL), yet there were more males (BR=45% vs US=54%) and patients of a white race (BR=62% vs US=72%) in the US. Mean PCS scores were slightly higher in BR (41.2) vs the US (38.4). Patients in BR had higher TSAT values (43%) vs the US (30.5%). Erythropoietin-stimulating agents (ESA) use was higher in the US (90%) than in BR (35%), as was IV iron use (BR=35% vs US=42%). Across both cohorts, patients with lower PCS tended to be older, with lower albumin and higher ferritin. While use of ESA tended to be a little higher among patients with lower PCS, Hb and TSAT were similarly distributed across groups in both cohorts (Figure 1).

Conclusions: Physical QOL among patients starting PD in BR and the US appeared to be related to age, nutrition, and ferritin levels. Patients with low PCS scores had relatively preserved iron stores compared to those with better PCS. Results may suggest inflammation could be a driver of lower quality of life in patients with adequate TSAT and Hgb levels.

Funding: Commercial Support - Pontificia Universidade Catolica do Parana, Fresenius Medical Care, BaxterHealthcare

TH-PO961

Treatments Patterns and Clinical Events in Non-Dialysis-Dependent CKD Patients with Elevated C-Reactive Protein and Anemia: A Nationwide Hospital-Based Cohort Study in Japan

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Background: Treating anemic CKD patients with inflammation (identified from increased CRP) is challenging due to associated ESA resistance. Contemporary evidence for anemia management and clinical event risk in NDD-CKD patients with elevated CRP is limited.

Methods: A retrospective cohort study was conducted using a Japanese nationwide EMR-based hospital database in adult patients with stage 3A NDD-CKD and Hb <11g/dL (January 2013- November 2021; N=26,626). Serum CRP was collected during the baseline period. Anemia treatment patterns (initiation and discontinuation) and clinical events including all-cause mortality, CV events, dialysis introduction, hospitalization for AKI, and RBC transfusion were assessed.

Results: 9086 (34.1%) had normal CRP (≤0.3mg/dL, mean 0.1mg/dL), 13,642 (51.2%) had elevated CRP (≥0.3mg/dL, mean 5.4mg/dL), and 3898 (14.6%) had no CRP measurements. Compared to normal CRP, patients with elevated CRP had lower Hb (9.8 vs 10.9g/dL), higher ferritin (212.4 vs 140.9mg/mL), and lower TSAT (23.7 vs 27.5%). The cumulative incidence of anemia treatment initiation within 12 months was lower in patients with elevated CRP (34.1 vs 39.0%), including ESA 23.0%, iron 16.5% iron iv 6.0%, and HIF-PHI 0.1%. Anemia treatment discontinuation within 12 months was higher in patients with elevated CRP (88.9 vs 86.0%) including ESA 95.4%, iron oral 81.1%, iron iv 99.3%, and HIF-PHI 60.0%. Incidence rates (per 100 person-years) for all clinical events were higher in patients with elevated CRP. (Fig)

Conclusions: The proportion of patients with elevated CRP was high in anemic NDD-CKD. Combination of anemia and elevated CRP was associated with adverse effects. Despite a significantly higher rate of RBC transfusion, many patients remain untreated and for those treated discontinuation was high in both groups.

Funding: Commercial Support - Bayer Yakuhin

TH-PO962

Contemporary Treatment Patterns of Clinically Meaningful Anemia Among Non-Dialysis-Dependent CKD Patients in the United States

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Background: Anemia is a common complication in non-dialysis dependent chronic kidney disease (NDD-CKD) patients, and the appropriate management of anemia is important. This study aimed to describe the treatment patterns of clinically meaningful anemia in line with the KDIGO guidelines [90-day average hemoglobin (Hb) level ≥10g/dL after the first date of Hb < 12 g/dL following CKD diagnosis] and the characteristics of NDD-CKD patients with clinically meaningful anemia using Optum Electronic Health Records (EHR) database in the United States (US).

Methods: The data source was Optum EHR which had 73 million patients with at least 1 year of data available from January 1, 2015 to December 31, 2021. NDD CKD patients with anemia (a ≥3 eGFR results ≤60 mL/min/1.73 m² on separate dates) were included in the analysis. Among those patients, the treatment patterns of anemia were described, including the use of erythropoietin-stimulating agents (ESA), intravenous (IV) iron, and red blood cell (RBC) transfusion.

Results: The study included 14,922 NDD-CKD patients with clinically meaningful anemia. 46.3% were men, mean age was 73.8 ± 10.3 years. Comorbidities were common, with hypertension in 74.1%, peripheral vascular disease in 24.2%, and coronary artery disease in 27.2%. The average baseline eGFR was 44.3 ± 12.8 mL/min/1.73 m². The average baseline Hb level was 9.2 ± 0.6 g/dL. 96.9% had average baseline Hb between 8.0g/dL to 9.9g/dL, 3.7% in the range of 6.5 g/dL to 7.9g/dL, and 0.1% below < 6.5 g/dL. In this study, IV iron was prescribed to 18.4%, RBC transfusion to 24.6%, and ESAs to 4.8% as first anemia treatment. Throughout the study period, 24.9%, 33.1% and 9.5% of NDD-CKD patients received one or more prescriptions of IV iron, RBC transfusion, and ESAs. However, 52.2% did not receive any prescription of IV iron, RBC transfusion, or ESAs after anemia diagnosis.

Conclusions: A substantial proportion of contemporary NDD-CKD patients with clinically meaningful anemia in the US were not receiving treatment. Blood transfusions were prescribed in more than 20% of patients that the first anemia treatment which potentially may be avoidable.

Funding: Commercial Support - Aymen

TH-PO963

Anemia Management in Non-Dialysis CKD Patients

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Background: Anemia is common in CKD and is closely associated with advanced stages of CKD. KDIGO recommends treating iron deficiency when TSAT is below 30% and administering ESA when Hb levels drop below 10 mg/dL. Current guidelines suggest maintaining Hb levels between 10-11.5 mg/dL. Despite this, anemia in CKD is often undertreated. This initiative aims to improve anemia management by addressing ESA hypo-responsiveess, administrative gaps, and missed treatments through quality improvements.

Methods: Our quality improvement project aimed to improve anemia management with two goals: 1) Increase Hb levels above 10 g/dL in at least 90% of patients on ESA for six months or more; 2) Decrease transfusion and hospitalization rates by 10%. To achieve these goals, we made minor changes in our clinic and utilized a new EMR system introduced in October 2022. The EMR system allowed for easy scheduling of follow-ups and labs, reducing administrative errors, and ensuring timely interventions. We upgraded the nursing ESA protocol by adding labs to screen for B12 and folate deficiencies. Nurses received re-education on ESA use and anemia management. Nurse Practitioner clinic was
utilized to provide frequent follow-up for patients on home ESA, with a specific Retacrit protocol created for them. We maintained an “ESA panel” list to monitor and review patients on both home and in-clinic ESA for follow-up and outcomes.

Results: The intervention phase started in February 2022, and we anticipate results in the coming months. Data extraction from the EMR system spanned its entire duration to measure changes over the last three quarters. Among the 4,000 clinic patients, 1,722 were diagnosed with anemia based on the ICD codes. Preliminary analysis shows a decrease in blood transfusions from 43 in the first quarter to 30 in the current quarter. Nephrology-ordered iron infusions decreased from 60 to 30, while the use of Retacrit increased from 8 to 17. These initial findings suggest the impact of our interventions on anemia management, but further analysis and evaluation are required to determine the full extent of improvements achieved.

Conclusions: Our study highlights the inadequate management of anemia in CKD patients, leading to avoidable healthcare utilization and compromising the chances of successful transplantation. Improved anemia management is urgently needed to address these concerns and optimize patient outcomes.

TH-PO964

Red Blood Cell Transfusion Use in Dialysis-Dependent Patients with Anemia of CKD in the United States: A Systematic Literature Review

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Background: Anemia of chronic kidney disease (aCKD) occurs frequently in dialysis-dependent (DD) patients (pts). Management includes iron supplementation, erythropoiesis-stimulating agents, and when clinically indicated, red blood cell transfusions (RBCT). There are limited collated data on RBCT use in the US; thus, a systematic literature review evaluating frequency, predictive factors, complications, healthcare resource use and costs was undertaken.

Methods: A comprehensive literature search for studies published between 1980 and June 2022 was conducted in Embase, MEDLINE and grey literature sources, to identify real-world (RW) studies and randomized controlled trials (RCTs) reporting RBCT use in US DD CKD pts. Titles and abstracts were reviewed against pre-defined criteria. Results were summarized descriptively.

Results: Of 182 relevant studies identified, 37 RW studies and 22 RCTs reported data in DD CKD US pts. In RW studies, overall frequency of RBCT use ranged from 0.0–66% (n=26); for hemodialysis (HD) pts 0.0–66% (n=19); peritoneal dialysis (PD) pts 5.5–7% (n=9) and HD and PD patients 1.4–35.5% (n=4). Rates of RBCT per 100 person-years (PY) in DD CKD pts ranged from 1.1–504 (n=12); for HD pts 1.1–148.4 (n=10); PD pts 28.8–504 (n=2); and HD and PD pts 19.2–49.7 (n=1). RBCT use varied by population, pt factors and study design. For the 22 RCTs (single country [n=7], multi-country [n=15]), overall frequency of RBCT use ranged from 0.7–62%; for HD pts 1.2–62% (n=11); and HD and PD pts 0.7–21.1% (n=10), comparable to RW studies. Rates of RBCT per 100 PY ranged from 3.5–103 among HD and PD pts (n=3); no HD only/PD only studies were found. Predictors of RBCT based on quantitative multivariable analysis were identified in 6 RW studies; 5 reported RBCT complication data; 2 HCRU data and 2 direct costs associated with RBCT use and complications.

Conclusions: RBCT forms part of aCKD management in DD CKD US pts, with higher rates in RW studies than in RCTs, although frequencies were comparable. Factors accounting for the variations in frequency, and predictive factors for RBCT use were identified. There are limited data on complications, HCRU and costs of RBCT.

Funding: Commercial Support - Vifor Fresenius Medical Care Pharma Ltd

TH-PO965

Hemoglobin (Hgb) Targets in Hemodialysis (HD) Patients: What Is The Optimal Target Range?

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Background: Based on RCTs a hgb target range between 10 to 11 g/dL is mandated in the US. Retrospective analyses have shown lower hospitalization and death rates with higher values. We investigated the association between all-cause mortality hazard ratio (HR) and time spent outside the target range.

Methods: We studied incident HD patients (pts) initiated on a long-acting ESA (Mircea; Vifer) within the first 90 days. In pts with at least 12 hgb during the 6-months baseline (BL), we quantified the patient-individual area under the target excursion curve (AUC) ‘above’ and ‘below’ the target range (10 to 11 g/dL). We used these metrics as predictors in proportional hazard models predicting HR in the following 18 months. We fitted the HR as a spline function of mean BL hgb. We built an additional model, adjusting for BL hgb, age, sex, race/ethnicity, and presence of diabetes, albumin and phosphorus, as well as serum creatinine accounting for the variations in frequency, and predictive factors for RBCT use were identified. There are limited data on complications, HCRU and costs of RBCT.

Results: Among contemporary home dialysis patients, self-administration of ESAs is common with HHD and uncommon with PD. Increased frequency of ESA administration and longer duration of home dialysis was associated with higher odds of self-administration, whereas Asian race was associated with lower odds.

Conclusions: Among contemporary home dialysis patients, self-administration of ESAs is common with HHD and uncommon with PD. Increased frequency of ESA administration and longer duration of home dialysis were associated with higher odds of self-administration, whereas Asian race was associated with lower odds.

TH-PO966

The Setting of Administration of Erythropoiesis-Stimulating Agents Among Home Dialysis Patients in a Mid-Sized Dialysis Provider

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Background: For patients undergoing home hemodialysis (HHD) or peritoneal dialysis (PD), an erythropoiesis-stimulating agent (ESA) may be administered by healthcare professionals during clinic visits or self-administered at home. The latter option may be convenient for patients, including those with long travel time to the clinic, but may increase the risk of nonadherence. We assessed the incidence and predictors of self-administration of ESAs among home dialysis patients.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. In 2021 and 2022, we identified all administered doses of epoetin alfa and darbepoetin alfa among home dialysis patients. For each administered dose, we identified the prescribed frequency of administration, the home dialysis modality (HHD, PD), and months since home dialysis initiation, as well as the age, sex, and race/ethnicity of the patient. We fit a logistic regression of self-administration of the ESA, using generalized estimating equations to account for intra-patient correlation.

Results: The cohort comprised 1984 patients and 54,301 ESA dose administrations. Overall, 42.2% of ESA doses were self-administered. In HHD patients, 78.1% of doses were self-administered, in PD patients, the corresponding statistic was 25.0%. Use of darbepoetin alfa, relative to epoetin alfa, was not associated with self-administration (adjusted odds ratio, 0.88; 95% CI, 0.56-1.37). Relative to once-monthly dosing, adjusted odds ratio of self-administration were 2.04 (93% CI, 1.70-2.45) with every-other-week dosing, 3.27 (2.64-4.05) with once-weekly dosing, and 4.84 (3.49-6.73) with multiple doses per week. Neither age nor sex was associated with self-administration, but relative to non-Hispanic White patients, Asian patients were less likely to self-administer ESAs (adjusted odds ratio, 0.52; 95% CI, 0.32-0.86). Each one-month increment in home dialysis duration was associated with 3% higher adjusted odds of self-administration.

Conclusions: Among contemporary home dialysis patients, self-administration of ESAs is common with HHD and uncommon with PD. Increased frequency of ESA administration and longer duration of home dialysis were associated with higher odds of self-administration, whereas Asian race was associated with lower odds.
Randomized Assessment of Auryxia® Therapy for In-Center and Home Dialysis Patients
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Background: Auryxia (ferric citrate) is an FDA approved iron-based phosphate binder for adults with dialysis-dependent chronic kidney disease. This study investigated the impact of Auryxia as primary phosphorus lowering therapy on utilization of erythropoiesis-stimulating agent (ESA) and intravenous (IV) iron.

Methods: In this randomized, open-label, active-controlled, multicenter study (NCT04922645), subjects receiving ESA and either in-center hemodialysis or home dialysis were randomized 1:1 to Auryxia (starting dose of 6 tablets per day) or remain on standard of care (SOC) phosphate lowering therapy for up to 6 months. Dose adjustments were at investigator discretion to achieve target serum phosphorus. The primary endpoint was difference in change from baseline (BL, Month -3 to Day 1) to efficacy evaluation period (EEP, Months 4-6) in mean monthly ESA and IV iron doses between groups. Secondary endpoints included difference in proportion with HB ≥10.0 g/dL and serum phosphate ≤5.5 mg/dL.

Results: 289 subjects were randomized to Auryxia (n=103) or SOC (n=186). The two groups had generally similar baseline characteristics, although arteriosclerotic CV disease and congestive heart failure were more common in the SOC group. During the EEP, the mean treatment difference in ESA administration was -31 mcg/month (p=0.02). A non-statistically significant change in mean monthly IV iron administration of -37 mcg/month (p=0.17) was observed. Mean HB, TSAT, and ferritin all increased from BL to the EEP in the Auryxia vs. SOC group. The proportion of subjects with HB ≥10.0 g/dL and serum phosphate ≤5.5 mg/dL did not differ between groups. Three subjects stopped Auryxia due to GI adverse events (AEs) or adverse events (AEs) occurred in 39% of subjects receiving Auryxia vs. 59% in those receiving SOC. No related AEs were reported. Fewer patients randomized to Auryxia experienced CV (8.7% vs. 13.2%) or infectious (8.7% vs. 17.9%) AEs.

Conclusions: Treatment with Auryxia as compared to remaining on SOC phosphate binders resulted in increased HB, increased iron stores, statistically significantly less average monthly ESA use and a non-statistically significant reduction in monthly IV iron use.

Funding: Commercial Support - Akebia

Survey of Erythropoiesis-Stimulating Agent (ESA) Use in Non-Dialysis-Dependent CKD (NDD-CKD) in Civilian vs. Military Practice
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Background: There is a paucity of data on barriers to ESA use in the pre-dialysis chronic kidney disease (CKD) population. In the context of universal health care coverage within the Military Health System (MHS), we evaluated ESA use in patients with stage 3-5 NDD-CKD among nephrologists practicing in military facilities vs. civilian nephrologists practicing in the civilian sector.

Methods: We conducted an anonymous online survey of nephrologists assigned to military facilities and graduates of the Walter Reed Nephrology fellowship program from 1998-2022 who have transitioned to civilian practice (n=104).

Results: The response rate was 63/104 (61%) with a 95% complete rate. Most of the respondents (97%) were in active clinical nephrology practice; 53% were in military facilities and 44% in civilian practice. Fifty-five percent of military and 29% of civilian nephrologists estimated that 5%-10% of their NDD-CKD patients were receiving ESA therapy (p=0.04). Sixty-eight percent of military nephrologists vs. 58% of civilian nephrologists would start an ESA if the hemoglobin (Hgb) was 9 g/dL (p=0.46). Sixty-eight percent of military nephrologists vs. 62% civilian nephrologists targeted a Hgb between 10-11 g/dL on ESA (p=0.09). Patients had their ESA administered in the clinic, at home, or in both settings in 42%, 10%, and 45%, respectively, in military practice vs. 38%, 8% and 42%, respectively, in civilian practice (p=0.49). Compared to military nephrologists, civilian nephrologists were more likely to identify low reimbursement rate (29% vs. 0%, p=0.0013), drug cost and affordability (54% vs. 0%, p=0.001), and restriction on ESA formulations by health insurance (38% vs. 3%, p=0.001) as barriers to ESA therapy. Military nephrologists were more likely to report that there were no particular barriers to ESA therapy compared to their civilian counterparts (52% vs. 12%, p=0.002).

Conclusions: Although the practice patterns of ESA therapy in NDD-CKD are comparable between military and civilian nephrologists who had similar training/background, the former group experiences less barriers to implementing therapy in the MHS. Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.

Funding: Other U.S. Government Support

Conversion from Darbepoetin Alfa to Epoetin Alfa in a Multi-Center Cohort of In-Center Hemodialysis Patients
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Background: Over the past two decades of anemia treatment, many dialysis patients have been reported from a nation-wide erythropoiesis-stimulating agent (ESA) to a long-acting ESA. However, there is little data about conversion of a population in the opposite manner, from a long-acting ESA to a short-acting ESA. We investigated the initial results of conversion of a population of in-center hemodialysis patients from darbepoetin alfa to epoetin alfa in early 2023.

Methods: During January and February 2023, 69 outpatient hemodialysis centers at Satellite Healthcare converted from first-line anemia treatment with darbepoetin alfa (Aranesp) to treatment with epoetin alfa (EpoPro). Patients were converted according to a protocol-based dosing algorithm derived from the Aranesp package insert and published studies. To assess changes in anemia-related parameters before and after conversion, we analyzed hemoglobin, ESA dose, transferrin saturation, and ferritin in patients who completed ≥4 hemodialysis treatments during a 2-week period of each month from July 2022 to April 2023; the period comprised the prescheduled week of blood draws and the week thereafter.

Results: On average, monthly cohorts included 6633 patients, among whom 6193 (93.4%) completed ≥4 treatments during the 2-week observation period. In 2022, 5.0% of ESA-treated patients received epoetin alfa, 94.8% received darbepoetin alfa, and 0.2% received both agents. In February 2023, 99.3% of ESA-treated patients received epoetin alfa, 0.4% received darbepoetin alfa, and 0.3% received both agents; by April, 99.6% received epoetin alfa. The distribution of hemoglobin was stable during and after the conversion process (table). The ratio of mean weekly epoetin alfa dose (IU) in February 2023 to darbepoetin alfa dose (mcg) in 2022 was 109. From February to April, mean weekly epoetin alfa dose decreased 3%. From December 2022 to March 2023, distributions of transferrin saturation and ferritin shifted modestly downward.

Conclusions: A protocol-based ESA dosing algorithm can be used to convert in-center hemodialysis patients from darbepoetin alfa to epoetin alfa in a short timeframe, without disruption of the hemoglobin distribution.

Efficiency and Efficacy of Anemia Therapy with Epoetin Beta: Results from a Randomized Controlled Trial of Therapy Software vs. Standard of Care
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Background: Anemia is common in patients on hemodialysis (HD) and typically treated with erythropoiesis-stimulating agents (ESA). Recurrent ESA dose adjustments are challenging due to delayed effects on patient hemoglobin (Hb) levels and interpatient variability in ESA responsiveness. We developed a novel software providing personalized ESA-dose recommendations based on a mathematical model of anemia. Here, we report results from a randomized controlled trial, comparing the software versus standard-of-care (SOC) anemia treatment in using ESAs efficiently to bring patients’ Hb levels into a given target range.

Methods: We enrolled 96 subjects on HD; 82 of them completed the study. Patients were randomized to be managed by our anemia therapy software (intervention group, “INT”, 40 patients) or continued SOC treatment (42 patients). For 26 weeks, the software generated biweekly patient-specific ESA recommendations to target a Hb of 10–11 g/dL. Recommendations were passed on to clinicians.

Results: In the SOC group, mean Hb levels across the study period showed a negative dependence on the mean amount of ESA per month (Fig. 1A) and total number of ESA administrations during the study period (Fig. 1B). In the INT group, this effect was significantly reduced (Fig. 1). The mean amount of ESA per kg patient weight was significantly reduced in the INT group (INT: 1.1 [0.6–1.5] mcg/30/kg/day, median [IQR]; SOC: 1.5 [0.9–2.1] mcg/30/kg/day, Wilcoxon rank-sum test, p=0.031) while the number of ESA administrations within the study period was comparable in both groups (INT: 9 [6–10]; SOC: 8 [6–10]; Wilcoxon rank-sum test, p=0.76).

Conclusions: Trial results suggest that our therapy software utilizes ESA more efficiently and controls Hb levels better at low and high ESA doses than SOC treatment, while requiring less ESA per kg patient weight and a comparable number of ESA administrations.

Funding: Commercial Support - Fresenius Medical Care
Anemia in CKD: Risk Factors, Practice Patterns, Therapies

TH-P0971

Medication Evaluation of Early Post-Transplant Anemia Management
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Background: Post-transplant anemia (PTA) is a common phenomenon in kidney transplant recipients (KTR). There are currently no consensus guidelines for PTA, however patients are commonly treated with erythropoiesis-stimulating agents and receive iron deficiency correction. Dosing and duration for these regimens remain unclear. The purpose of this study is to evaluate the efficacy of erythropoiesis use and intravenous iron supplementation on hemoglobin in KTR with PTA.

Methods: This is a single center, retrospective cohort study from 10/1/2021 – 4/1/2022. Primary outcome was hemoglobin at 6 months in KTR who received ESA, iron sucrose or neither. Secondary outcomes included kidney function, iron studies, transfusions, dapsone use >7 days post-transplant. All continuous data was analyzed using a student T-test. All categorical data was analyzed using a chi square test.

Results: Ninety-seven KTR were included in our final analysis. A total of 59 (60.8%) of KTR received either ESA alone or in combination with IV iron. Hemoglobin and renal function trends over time are represented on Figure 1 and 2. Of note, 16 (42.1%) of the patients who did not receive ESA or IV iron were living donor transplant recipients. There was no difference in hemoglobin outcomes at 6 months in patients who received IV iron repletion with ESA versus ESA alone (Figure 3). Patients who received IV iron < POD 30 had significantly higher Hgb outcomes than those who got IV iron > POD 30 (Figure 4). Dapsone use >7 days was associated with significantly reduced Hgb during the duration of use (Figure 5).

Conclusions: Patients with PTA did not show additional hemoglobin increases when given any ESA as compared to those who received no ESA. Differences in treatment groups including higher numbers of deceased donors and poor graft function may have contributed to the poor response to ESA. A prospective, randomized study is warranted for the best use of these interventions in a judicious manner.

TH-P0973

Hospitalizations and Red Blood Cell (RBC) Transfusions in Patients with Dialysis-Dependent-CKD (DD-CKD) on Auryxia® Compared with Other Phosphate Binders
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Background: Auryxia (ferric citrate) is an FDA approved iron-based phosphate binder for adults with dialysis-dependent chronic kidney disease (DD-CKD). Primary efficacy results of this study of Auryxia as phosphorus lowering therapy compared to standard of care (SOC) in patients with CKD undergoing dialysis showed a statistically significant reduction in erythropoiesis-stimulating agents (ESAs) and a reduction in intravenous (IV) iron. Here, we further explore hospitalizations and red blood cell (RBC) transfusions.

Methods: This open-label, active-controlled, multicenter study (NCT04922645), in subjects receiving ESA and either in-center or home dialysis, were randomized 1:1 to receive Auryxia or remain on SOC phosphorus-lowering therapy for up to 6 months. Dose adjustments were at investigator discretion to achieve target serum phosphorus. The primary endpoint was the difference in change from baseline (BL; Month -3 to Day 1) to efficacy evaluation period (EEP, Months 4-6) in mean monthly ESA and IV iron doses between groups. Safety and exploratory analyses estimated the rate of hospitalizations, hospital days, RBC transfusion, and units of packed red blood cells (PRBC) per person-month from day 1 through the end of study.

Results: 209 subjects were randomized to Auryxia (n=103) or SOC (n=106). The two groups had generally similar baseline characteristics, although atherosclerotic CV disease and congestive heart failure were more common in the SOC group. Hospitalization event rates per 100 person-months were 7.4 and 10.6 in the Auryxia (40 events) and SOC (25 events) treatment groups, respectively. Subjects in the Auryxia groups, respectively. 60 hospitalization days per 100 person-months compared to 82.6 days in the SOC group. RBC transfusion rates per 100 person-months were 1.5 and 4.2 in the Auryxia (8 events) and SOC (25 events) treatment groups, respectively. The rates of PRBC transfusions, per 100 person-months were 2.4 and 7.1 with Auryxia (13 units) and SOC (42 units), respectively.

Conclusions: Treatment with Auryxia as compared to remaining on SOC phosphate binders resulted in lower hospitalization rates, fewer hospitalization days, fewer RBC transfusions, fewer PRBC units used.

Funding: Commercial Support - Akemia

TH-P0974

Validate Optimal Iron Management When Using Hypoxia-Inducible Factor-Prolyl Hydroxylation Inhibitor (HIF-PHI) in Renal Anemia: Excessive Iron Administration Is Unnecessary
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Background: Hypoxia-inducible factor prolyl hydroxylation domain inhibitors (HIF-PHIs), new therapeutic agent for renal anemia, shows its effects through a mechanism not only by transcription factor-mediated erythropoiesis production but also by iron metabolism. Therefore, although the importance of iron supplementation has been emphasized, it is presumed that iron utilization is also promoted endogenously and that a mischievous iron overdose is not necessary. In the present study, we examined optimal iron management under HIF-PHI administration.

Methods: The subjects were 30 maintenance hemodialysis patients who switched from darbepoetin alfa (DA) to Roxadustat (Rox). To examine iron kinetics during the switchover, reticuloocyte hemoglobin content (CHR), which reflects recent Hb synthesis, was measured in addition to conventional iron-related parameters. The iron-regulated biomarker hepcidin was also measured. Iron deficiency was defined as CHR<32.0 pg. ROC curves were used to determine cut off values for the point at which CHR sufficiency was met.

Results: After the switching to Rox, there was a significant increase in Hb and RBC and a decrease in ferritin and hepcidin (all p<0.01), suggesting increased iron demand. In the results of the ROC curve with the endpoint CHr32pg on Day6, cutoff values for s-ht and TSAT were respectively 49.7 ng/mL and 21.6% on Day 0 and 35.5 ng/mL and 16.2% on Day 28. With the endpoint CHr a 32.0 pg on Day 28, cutoff values for s-ht and TSAT were 31.1% and 23.8%, respectively. In a patient with s-ht 104.18 ng/mL and TSAT 10.6%, there was a rapid increase in Hb from 8.0 to 10.0 g/dL after 2 weeks of switching.

Conclusions: The present study suggests that a serum ferritin of at least 81.6 ng/ mL at the time of switching, and most recently 35.5 ng/mL, may avoid iron deficiency when switching from DA to Rox. Iron deficiency is pointed out to increase the risk of thrombosis due to hypercoagulability and increased platelet count. In our previous report (Acta Haematol 2022), the cutoff value of ferritin for platelet increase was 77.2 ng/mL (area under the curve 0.76, 95% CI 0.55 – 0.96) when ROX was administered. Moreover, it has also been shown that functional iron deficiency with ferritin sufficiency may result in a rapid rise in Hb. Thus, the amount of iron required at the time of switchover may be less than expected.

TH-P0975

A Regional Perspective of Hypoxia-Inducible Factor-Prolyl Hydroxylase (HIF-PHI) Inhibitors in Dialysis
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Background: Hypoxia-inducible factor prolyl hydroxylation enzyme inhibitors (HIF-PHIs) were developed as an alternative to erythropoietin-stimulating agents (ESA) to treat anemia in chronic kidney disease (CKD) patients. As of fielding, daprodustat was the only approved HIF-PHI in the United States (US) and roxadustat and vadadustat were approved in the European Union (EU); all agents are indicated to treat dialysis patients, while only roxadustat is approved to treat CKD non-dialysis patients in the EU. This qualitative nephrologist attitudes provides insight into regional perceptions of HIF-PHIs as a treatment option for dialysis patients.

Methods: Responses were collected via online surveys with 207 US-based nephrologists (February 2023) and 208 EU-based nephrologists (March through April 2023). Additional insights were captured via an independent, retrospective chart audit of 1,282 CKD non-dialysis patient records collected from 263 EU-based nephrologists (December 2021 through February 2022). EU countries surveyed included the UK, Germany, Italy, France, and Spain.

Results: To date, roxadustat has experienced slow uptake among EU nephrologists, with physicians reporting that 6% of their HD patients and 8% of their PD patients are currently on therapy. In the CKD non-dialysis setting, audited patient records reveal that roxadustat treatment rates are even lower at 3.5%, with increased use as patients progress in their CKD. As of fielding in the US, daprodustat had not been officially launched; however, 52% of physicians report that they are likely to be more reserved and selective in their prescribing once it is available, relying heavily on peers and KOLs for guidance. US physicians also expect that availability and dialysis center protocols will be key drivers of adoption. Looking towards future use, 55% of EU nephrologists report that the advantages of roxadustat outweigh the potential risks in dialysis patients, compared...
to 44% of US physicians believing the same for daprodustat. Most nephrologists across regions (70% EU, 55% US) indicate they are anxious to gain clinical experience with the drugs.

**Conclusions:** Despite recognition of the benefits of HIF-PHIs in dialysis patients, slow adoption of roxadustat in the EU and hesitancy among US-based nephrologists to prescribe daprodustat may stifle treatment evolution in the anemia space, with ESA likely to remain the standard of care in the dialysis setting.

**TH-PO976**

**Efficacy and Safety of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs) in Patients with CKD: Metaanalysis of Phase 3 Randomized Controlled Trials**

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**Background:** HIF-PHIs are new therapeutic agents for anemia of CKD. We evaluated by metaanalysis and meta-regression efficacy and safety of HIF-PHIs in patients with CKD-related anemia.

**Methods:** We selected phase-3 RCTs comparing HIF-PHIs and ESA in dialysis and non-dialysis CKD patients. Efficacy outcomes were the changes from baseline of hemoglobin (Hb), iron parameters and intravenous iron dose; safety outcomes included cancer, major adverse cardiovascular events (MACE), MAC+ (MACE plus hospitalization for HF, unstable angina or thromboembolism), thrombotic events (deep vein thrombosis, pulmonary embolism), thrombotic event rates (RERs) for dichotomous outcomes. The meta-analysis was executed using R version 4.0.3, employing the metafor and meta packages.

**Summary of difference between HIF-PHI and ESA for efficacy and safety is depicted in Figure 1.** Random effect meta-analysis of unstandardized mean difference between HIF-PHIs and ESA showed a significant change from baseline in Hb levels. Meta-regression analysis identified significantly higher Hb change for HIF-PHIs in younger patients and in studies using short-acting ESA as comparator (+0.21 g/dL, 95%CI, 0.12-0.29 vs -0.01, 95%CI, -0.09-0.07 in studies using long-acting ESA, P<0.001). Heterogeneity was not significantly enhanced by publication bias. In comparison with ESA, HIF-PHIs induced a significant decline in hepcidin and ferritin and a significant increase in serum iron and TIBC; IV iron dose was lower with HIF-PHI. Rate ratio of cancer, MACE, MAC+, thrombotic events and death did not differ between HIF-PHIs and ESA.

**Conclusions:** In comparison with ESA therapy, HIF-PHIs are effective in correcting anemia and improving with a significant impact on iron metabolism without notable difference among various agents. No safety signals emerged with use of HIF-PHI.

**TH-PO977**

**Evaluating the Outcomes of Roxadustat Treatment for Anemia in Dialysis-Dependent CKD: A Systematic Review and Meta-Analysis**

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**Background:** Chronic kidney disease (CKD) patients often grapple with anemia, a complication that severely impinges on their quality of life and overall prognosis. Roxadustat, an innovative oral hypoxia-inducible factor prolyl hydroxylase inhibitor, has emerged as a potential solution to this pervasive issue. However, its effectiveness and safety need to be comprehensively analyzed. This study aims to investigate the efficacy and safety of Roxadustat for anemia in CKD patients.

**Methods:** We systematically searched PubMed, Web of Science, and Cochrane Library databases until October 2022. We sought randomized controlled trials (RCTs) that compared Roxadustat with Epoetin Alfa or a placebo in the dialysis-dependent CKD patients. The primary outcomes were changes from baseline in hemoglobin, hepcidin, ferritin, and transferrin saturation (TSAT) levels. Secondary outcomes were the incidence of adverse and major adverse events. The data were aggregated using a random-effects model and expressed as standardized mean differences (SMDs) for continuous outcomes or relative risks (RRs) for dichotomous outcomes. The meta-analysis was executed using R version 4.0.3, employing the metafor and meta packages.

**Results:** We included five studies comprising 3,478 participants (1,847 administered Roxadustat, 1,631 given ESA). Roxadustat showed significantly to enhance hemoglobin (SMD: 0.32, 95% CI: 0.12-0.52, P < 0.01, I²=39%) and lower hepcidin levels (SMD: -0.29, 95% CI: -0.45 -0.14, P < 0.01, I²=23%) from baseline, as compared to the control group. However, changes in ferritin (SMD: 0.03, 95% CI: 0.01-0.05, P = 0.24, n = 0.76, I²=0%) and TSAT levels (SMD: 0.14, 95% CI: -0.07-0.34, n = 0.19, I²=0%) were not statistically significant. Adverse events (RR: 1.02, 95% CI: 0.96-1.07, P = 0.5, I²=33%) and major/critical adverse events (RR: 1.05, 95% CI: 0.96-1.16, P = 0.3, I²=20%) were marginally more frequent in the Roxadustat group, but these differences lacked statistical significance.

**Conclusions:** Roxadustat may potentially elevate hemoglobin and decrease hepcidin levels in dialysis-dependent CKD patients. However, its effects on ferritin and TSAT levels are unclear. Future, more extensive studies are needed to validate these findings and determine Roxadustat’s optimal use.

**TH-PO978**

**Roxadustat vs. Erythropoiesis in the Nephroprotection Treatment of Patients with CKD and Anemia**

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**Background:** Roxadustat has been approved for patients with chronic kidney disease(CKD) and renal anemia in China since 2019. It is now widely used around the world. Although studies have found that roxadustat may improve tissue fibrosis, inflammation, and oxidative stress, there have been few studies on its nephroprotection. We aim to elucidate the nephroprotection of roxadustat versus erythropoiesis-stimulating agents (ESA) in CKD patients with anemia.

**Methods:** We conducted a retrospective cohort study of CKD patients with anemia diagnosed in rijn hospital between January 2010 and December 2022. CKD patients aged 14 years at diagnosis, coexisting with anemia, an estimated glomerular filtration rate (eGFR) ≤ 15 ml/min/1.73m², 24-hour follow-up data, and received roxadustat three times a week or ESA, were included. The patients were 1:1 assigned to two groups by propensity score matching based on indicators including sex, age, eGFR, 24-hour urine protein and follow-up time. The primary outcome was composite renal endpoint defined as a 50% decline in eGFR and end-stage kidney disease (ESKD).

**Results:** A total of 288 patients were included after PSM. The significantly lower incident of composite renal outcomes in the roxadustat group compared with the ESA group was observed (39.58% vs. 26.39%, P=0.017). By multivariate Cox regression analysis, roxadustat was associated with a lower risk for the composite kidney outcomes compared to ESA (HR = 0.61, 95% CI: 0.40-0.94, P=0.023) after adjusting for age, gender, baseline eGFR, 24-hour urine protein, MAP, and hemoglobin. Moreover, subgroup analysis showed similar results in different subgroups defined by hyperlipidemia, high urine acid. Notably, in the roxadustat group, eGFR decreased at a slower rate than in the ESA group (median eGFR slope: -2.14 vs. -7.46 ml/min/1.73m²/yr, P=0.099). We found that roxadustat group had a higher hemoglobin level than the ESA group (110.64 ± 104.33 vs. 23.14 g/L, P=0.04). Compared to the ESA group, the roxadustat group had more 50% decline in proteinuria after 12 months (43.06% vs. 29.86%, P=0.02).

**Conclusions:** Roxadustat is superior than ESA in treating CKD patients combined with anemia, especially for nephroprotection. Our findings need to be validated further.

**TH-PO979**

**Efficacy and Safety of Desidustat for the Treatment of Anemia in Patients with CKD: A Retrospective, Open-Label, Single-Centre Study**

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**Background:** CKD is associated with an increased risk of anemia, significantly impacting patients’ quality of life. Current therapy includes injectable erythropoiesis-stimulating agents which have limitations and safety concerns. Desidustat has shown promise in stimulating endogenous erythropoiesis and addressing anemia in CKD. This study assesses the real-world clinical efficacy & safety of the desidustat treatment in CKD patients with anemia.

**Methods:** This is a retrospective, observational, open-label, single-centre, single-arm study in anaemic patients who were administered with desidustat and assessed thrice a week for a period of 24 weeks. 83.3% of patients received 300mg/ week dose of desidustat as starting dose. Dose adjustment was done every 4 weeks as per the Hb level of the patients. The primary outcome was to assess the change in the Hb from baseline to the end of 24 weeks and the secondary outcome was the evaluation of AEs if occur.

**Results:** Out of 84 patients, 51.2% were previously on ESA therapy, 48.8% were treatment naive, 38.1% were on dialysis and 56% non-dialysis patients. The results show statistically significant improvement in mean Hb level at the end of 24 weeks (1.308g/dL, d=0.24). Within groups, treatment naive patients on ESA, non-dialysis on dialysis and patients improvement in mean Hb from baseline to end of 24 weeks was statistically significant, with most significant improvement seen in treatment naïve patients (P<0.01) and non-dialysis patients (P<0.01), the improvement in composite renal risk being 9.5±0.91 to 11.3±0.87, 9.7±1.6 to 11.2±0.87 respectively. The serum potassium showed mild variation from a mean of 4.7±0.80 to 4.8±0.76. AEs were observed in 13.1% patients, including AV Fistula failures (4.8%), LVF (2.4%), Arterial thrombosis (1.2%), DVT (1.2%), Acute Pancreatitis (1.2%), Haemorrhagic stroke (1.2%) and Aplasia (1.2%).

**Conclusions:** The short-term desidustat treatment demonstrated statistically significant improvement in Hb levels in patients. Therefore, making it a viable alternative.
to current treatment options. Since the present study was retrospective in nature the causality assessment was not assessed. Hence, further research is needed to gather long-term data and compare the cardiovascular safety of desidustat with the injectable ESAs.

TH-PO980

A National, Multi-Center, Prospective Study Evaluating the Long-Term Safety and Effectiveness of Roxadustat for Anemia Treatment in Patients with CKD (ROXSTAR Registry)

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Background: Anemia is associated with increased morbidity/mortality in chronic kidney disease (CKD) patients. Roxadustat (RDX) stimulates erythropoiesis & has demonstrated effectiveness for anemia treatment. We conducted a real-world clinical study to evaluate the safety/efficacy of RDX for CKD-associated anemia (CKD-anemia) treatment & its effect on quality of life (QOL).

Methods: This phase 4, prospective, clinical study enrolled patients aged ≥18 years with CKD-anemia (with or without dialysis) in 61 centers in China. Patients received a starting dose of 70–120-mg RDX orally thrice a week for 52 weeks. Primary & secondary outcomes were long-term safety & effectiveness. Safety assessments included the number of patients with treatment-emergent adverse events (TEAEs). Effectiveness was assessed by hemoglobin (Hb) change from baseline & percentage of patients with mean Hb ≥100 g/L.

Results: Of 2024 patients enrolled, 1830 were RDX-naive, 193 were previously RDX-treated, & 1 was missing. In total 2021 (99.9%) received ≥1 RDX dose (hemodialysis: n=851 [42.1%]; peritoneal dialysis: n=676 [33.4%]; non-dialysis-dependent: n=494 [22.4%]) & 1592 (78.8%) completed the study. The mean±SD (age) was 50.2±20.5 years. The weekly RDX dose was 254.3±136.15 mg & mean Hb was maintained at 80–120 g/L in 80% of patients. Patients ≥65 years accounted for 25.5% of the total population. There were 428 TEAEs, of which 341 were treatment-emergent. The most common TEAEs were injection site reactions (10.7%), hypertension (4.8%), & cough (4.8%).

Conclusions: RDX had tolerable safety & increased Hb ≥100 g/L in >85% of patients over 24–52 weeks; these results support RDX treatment for CKD-anemia patients in a real-world setting.

TH-PO981

Low vs. Standard Starting Dose Oral Roxadustat for Treating Anemia in Chinese Patients with CKD on Dialysis: A Prospective, Randomized Clinical Trial

Bi-Cheng Li,1 Yun Tu,1 Yan Xu,2 Li Yao,3 Bei ru Zhang,4 Tiekun Yan,3 Aiping Yin,1 Xinzhou Zhang,4 Min Yang,1 Jun Liu,3 Cuili Wang,3 Xiaomei Peng,1 Wang Jin,5 Wei Niu,1 Wenqing Jiang,1 Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing, China; 2The Affiliated Hospital of Qingdao University, Qingdao, China; 3The First Hospital of China Medical University, Shenyang, China; 4Shengjing Hospital of China Medical University, Shenyang, China; 5Tianjin Medical University General Hospital, Tianjin, China.

Background: The AFFIRM study found that the incidence of ADRs was similar to the known roxadustat in Japan. A previous study in China found that patients receiving oral roxadustat thrice weekly had a similar safety profile compared to the known roxadustat in Japan. A recent study in Japan found that the incidence of ADRs was similar to the known roxadustat in Japan. A recent study in Japan found that the incidence of ADRs was similar to the known roxadustat in Japan.

Methods: This randomized trial enrolled hemodialysis patients aged ≥18 years with anemia of chronic kidney disease (AKI) to receive oral roxadustat thrice weekly for 12 weeks, then oral roxadustat twice weekly for 12 weeks. Patients were randomized to receive either a lower (70–100 mg) or standard (100–120 mg) starting dose of roxadustat. The primary endpoint was the proportion of patients with mean Hb ≥100 g/L and the secondary endpoint was the proportion of patients with mean Hb ≥110 g/L in the first 20 weeks of treatment.

Results: A total of 465 patients were enrolled and randomized to receive either the lower (70–100 mg) or standard (100–120 mg) starting dose of roxadustat. The proportion of patients with mean Hb ≥100 g/L was 83.7% in the lower dose group and 85.9% in the standard dose group. The proportion of patients with mean Hb ≥110 g/L was 77.3% in the lower dose group and 78.2% in the standard dose group. The percentage of patients with mean Hb ≥120 g/L was 57.2% in the lower dose group and 61.1% in the standard dose group. There were no significant differences in the incidence of treatment-emergent adverse events (TEAEs) or serious TEAEs between the two groups.

Conclusions: Oral roxadustat had tolerable safety & comparable efficacy in Chinese patients with CKD on dialysis. Further studies are needed to evaluate the long-term safety and efficacy of oral roxadustat in this population.

TH-PO982

Real-World Clinical Use of Roxadustat in Patients with Anemia of CKD: Interim Results from a Post-Marketing Surveillance Study in Japan

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) approved in Japan to treat anemia of non-dialysis-dependent (NDD) or dialysis-dependent (DD) chronic kidney disease (CKD). A post-marketing surveillance study is underway in Japan to examine the safety and effectiveness of roxadustat in real-world clinical use. Here, we report the results of a planned interim analysis from this study.

Methods: This open-label, non-comparative, non-interventional observational study had an observation period of 104 weeks. Eligible patients had anemia of CKD and were naïve to roxadustat. Enrollment began in June 2020 (DD CKD patients receiving hemodialysis [HD] or peritoneal dialysis [PD]) and January 2021 (NDD CKD), with a planned interim analysis as of December 16, 2022. Incidence of adverse drug reactions (ADRs) were reported. Vitality (V) & Physical Functioning (PF) subscales & self-reported Rapid Assessment of Physical Activity (RAPA) scores were also assessed.

Results: In total, 1468 patients (safety analysis population: NDD: 778; HD: 608; PD: 90; 2 patients received both HD and PD) were analyzed. A total of 839 patients (57.2%) switched from erythropoiesis-stimulating agents (ESA) to roxadustat, 16 patients (1.1%) in hemodynamically used ESA and 566 patients (39.9%) were ESA naïve. 23 patients switched from a HIF-PHI (1.6%), and 4 (0.3%) were missing data for prior RDX use. ADRs and serious ADRs occurred in 17.03% and 6.54% (overall), respectively (53.2% (NDD CKD), 20.39% and 9.70% (HD), and 23.56% and 10.00% (PD), respectively). Treatment-emergent AEs (TEAEs) and serious TEAEs were reported descriptively after 12 weeks of roxadustat treatment.

Conclusions: The results from this interim analysis of a post-marketing surveillance study in Japan found that the incidence of ADRs was similar to the known roxadustat in real-world clinical practice for up to 12 weeks.

Funding: Commercial Support - This study was funded by Astellas Pharma, Inc.

Table. Incidence of ADRs and Serious ADRs

<table>
<thead>
<tr>
<th>ADRs</th>
<th>% of Patients</th>
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<tr>
<td>Any ADRs</td>
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</tr>
<tr>
<td>Serious ADRs</td>
<td>6.54%</td>
</tr>
</tbody>
</table>

TH-PO983

Safety and Efficacy of Vadadustat Thrice Weekly in Patients with Anemia Due to Dialysis-Dependent CKD

Hakan R. Toka,1 Wendi Luo,2 Zhizhi (Sunny) Yang,1 Zhiquan Zhang,2 Steven K. Burke,1 Nova Clinical Research, Bradenton, FL; 2Akebia Therapeutics Inc, Cambridge, MA.

Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). This study investigated the efficacy and safety of vadadustat in anemia of chronic kidney disease (DD-CKD) in Japan.

Methods: This randomized (1:1:1), open-label, active-controlled, sponsor-blinded trial compared VADA, at starting doses of 600 mg and 900 mg TIW, and CERA treatment in patients with DD-CKD for up to 52 weeks. Primary and secondary endpoints were mean Hb level (g/dL) at baseline to the primary endpoint (PPE, weeks 20–26) and secondary evaluation period (SEP; weeks 46–52), respectively (noninferiority margin, –0.75 g/dL). Other key endpoints included the proportion of patients requiring red blood cell (RBC) transfusions during the PEP and those with Hb levels ≥11 g/dL and the proportion of treatment-emergent adverse events (TEAEs) and serious TEAEs were reported as primary endpoints.

Results: VADA TIW (n=304) was noninferior to CERA (n=152) for mean change in Hb from baseline during the PEP (least-squares mean difference: –0.33 g/dL; 95% CI: –0.56, –0.10). Other key endpoints included the proportion of patients requiring RBC transfusions during the PEP and those with Hb levels ≥11 g/dL and the proportion of treatment-emergent adverse events (TEAEs) and serious TEAEs were reported as primary endpoints.

Conclusions: VADA TIW (n=304) was noninferior to CERA (n=152) for mean change in Hb from baseline during the PEP (least-squares mean difference: –0.33 g/dL; 95% CI: –0.56, –0.10). Other key endpoints included the proportion of patients requiring RBC transfusions during the PEP and those with Hb levels ≥11 g/dL and the proportion of treatment-emergent adverse events (TEAEs) and serious TEAEs were reported as primary endpoints.
CERA had similar incidences of TEAEs and serious TEAEs. The proportion of patients with TEAEs resulting in death was 9% in the VADA group and 11% in the CERA group. The most common TEAEs were COVID-19 and diarrhea in both groups. Incidence of cardiac arrest was more common in the CERA group (7.3%) compared to the VADA group (1.7%). No differences in abnormal liver enzymes were observed between treatment groups.

Conclusions: VADA TIW was noninferior to CERA in Hb efficacy. VADA had a lower proportion of patients with Hb excursions compared to CERA. The incidence of TEAEs and serious TEAEs was similar between VADA and CERA.

Funding: Commercial Support - Akemia Therapeutics, Inc.

TH-PO984
Effects of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors on Copper Metabolism and Association with Organ Damage in CKD
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Background: Excess copper accumulates in visceral organs throughout the body producing reactive oxygen species which ultimately causes organ damage. In patients with chronic kidney disease (CKD), excess copper accumulation is known to be a risk factor for worsening renal function. HIF-PhD inhibitors are recently used to treat renal anemia worldwide. Several studies have demonstrated that HIF-PhD inhibitors affect iron kinetics. Meanwhile, there are few reports on copper metabolism. In the present study, we investigated whether HIF-PhD inhibition has an impact on copper metabolism in CKD rodents model and patients with CKD or patients with peritoneal dialysis (PD).

Methods: 7 patients with advanced CKD and 9 patients with PD were enrolled in the present study. Serum was evaluated before and after 3 months after the initiation of HIF-PhD inhibitors. In vitro, CuSO4 was administered to cultured proximal tubules to explore whether excess copper accumulation causes cellular damage. In vivo experiments, GSK360A, a HIF-PhD inhibitor; GSK360A plus HIF-1α inhibitor, or GSK360A plus HIF-2α inhibitor were injected into C57BL/6 mice after induction of CKD by repeated low dose cisplatin injections to examine which HIF compartment is involved in copper metabolism.

Results: Serum copper was elevated after the treatment with HIF-PhD inhibitors in patients with PD and mice. In vitro, copper, iron, and zinc were evaluated before and after 3 months after the initiation of HIF-PhD inhibitors. In vitro experiment, co-incubation with CuSO4 increased α-SMA and cleaved caspase3, suggesting that excess copper causes fibrotic pathway and ultimately cell death. In vivo experiments, copper was elevated in CKD rodents when compared to controls, which was further enhanced by treatment with GSK360A. Pharmacological inhibition of HIF-1α did not affect GSK360A-induced increase in copper accumulation, suggesting that HIF-2α might be involved in copper metabolism in response to HIF-PhD treatment.

Conclusions: Copper accumulation can be induced by HIF-PhD inhibitors which might be associated with renal fibrosis and cell death. HIF-2α might mediate copper metabolism in response to HIF-PhD inhibitors.

TH-PO986
Anemia Treatment Among Prevalent Hemodialysis and Peritoneal Dialysis Patients in the United States
Jiamong Liu1, Julie Rouette2, Suying Li, Sally Wetten,3 Haifeng Guo,1 Gema Requena,2 George Mu,2 Liyuan Ma,3 Jolyon Fairburn-Beech,3 David T. Gilbertson,1 Anna Richards,3 James B. Wetmore.1,2,3 Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN; GS, Montreal, QC, Canada; 2: GS, Toronto; 3: GS, Cleveland, United States; 4: GS, Buffalo, NY

Background: This study aims to assess anemia treatment in chronic kidney disease (CKD) patients (pts) undergoing dialysis to understand the evolving landscape of CKD anemia management.

Methods: Using USRDS data, we conducted an observational, descriptive cohort study of adults (≥18 years) receiving dialysis on Jan 1, 2018 (index) and with 6 months of Medicare fee-for-service coverage pre-index. Pts with prior kidney transplant, cancer, and hospitalization for heart failure, myocardial infarction, or stroke in the previous month were excluded. Follow-up was from index until death, loss of Medicare coverage, kidney transplantation, or Dec 31, 2018. Use of erythropoiesis-stimulating agents (ESA), IV iron, and blood transfusions were assessed during follow-up. ESA, IV iron, and transfusions were identified by a combination of HCPCS codes, ICD-10-PCS procedure codes, and/or revenue center codes. ESA use was calculated as days covered/week (total days covered by ESA divided by follow-up time in weeks); 3 epoetin alfa administrations covered 7 days; 1 darbepoetin for 14 days), IV iron calculated as number of administrations per week, and transfusions as number per 100 person-years. Overall rates were calculated as weighted mean of pt-level rates using follow-up as weight.

Results: Overall, 209,408 pts were on HD and 20,647 on PD; median follow-up was 24.0 months (HD, IQR: 14.6–24.0; PD, 13.0–24.0). PD pts were younger (median age 62.2 vs 64.7 yrs). More PD pts were White (53.5 vs 39.1%), higher income (34.0 vs 48.7% with Medicare/Medicaid dual enrollment), and with glomerulonephritis as the cause of end-stage kidney disease (15.2 vs 8.5%). PD pts had fewer comorbidities and shorter dialysis duration (median 2.7 vs 3.9 yrs). During follow-up (Table), PD pts had lower ESA and IV iron use (1.24 vs 2.64 days of ESA coverage/week; 0.15 vs 0.48 iron administrations/week) and a higher transfusion rate (38.3 vs 32.4/100 person-years).

Conclusions: In this descriptive study, PD pts had lower ESA and iron use and a higher transfusion rate than HD pts during follow-up. Anemia management may need improvement among PD patients.

Funding: Commercial Support - Funded by GSK (Study 217316)

Table 1: Baseline Characteristics and Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HD</th>
<th>PD</th>
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<tbody>
<tr>
<td>ESA use (days/week)</td>
<td>1.24</td>
<td>2.64</td>
</tr>
<tr>
<td>IV iron use</td>
<td>0.15</td>
<td>0.48</td>
</tr>
<tr>
<td>Transfusion (days)</td>
<td>38.3</td>
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</table>

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
TH-PO987

Long-Term Safety of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors in CKD: A Systematic Review and Meta-Analysis of Randomized Trials

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Background: Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors are an oral treatment for anemia of chronic kidney disease (CKD). We assessed long-term safety of HIF prolyl hydroxylase inhibitors in CKD.

Methods: In this systematic review and meta-analysis, MEDLINE, Embase, and Cochrane databases were searched to March 2023. Randomized trials comparing HIF prolyl hydroxylase inhibitors with an erythropoiesis-stimulating agent (ESA) or placebo with ≥48 weeks of follow-up were eligible. Major adverse cardiovascular events (MACE), individual components of composite cardiovascular endpoints, thrombotic events, and non-cardiovascular adverse events were evaluated. We conducted analyses separately in people with CKD treated with dialysis and those not treated with dialysis (PROSPERO registration CRD42021278011).

Results: Twenty-five trials involving 26,478 participants proved eligible. Of these, 13 trials were conducted in 13,230 participants with dialysis-dependent CKD, and 12 trials involved 13,248 participants with CKD not requiring dialysis. There was no evidence that HIF prolyl hydroxylase inhibitors and ESA had different effects on MACE in people with dialysis-dependent CKD (relative risk [RR] 0.99, 95% CI 0.92 to 1.08) and non-dialysis CKD (RR 1.08, 95% CI 0.95 to 1.22). Similarly, there was no evidence that HIF prolyl hydroxylase inhibitors and placebo had different effects on MACE (RR 1.10, 95% CI 0.96 to 1.27) in people with non-dialysis CKD. The lack of difference between HIF prolyl hydroxylase inhibitors and ESA or placebo was observed in individual components of MACE, and for cardiovascular death. The safety of HIF prolyl hydroxylase inhibitors for other outcomes was similar to ESA in dialysis-dependent CKD. In non-dialysis CKD, dialysis access thrombosis, infections, hyperkalemia and seizures occurred more frequently with the HIF prolyl hydroxylase inhibitor group than the placebo group. In non-dialysis CKD, esophageal or gastric erosion was more frequent with HIF prolyl hydroxylase inhibitors than ESA.

Conclusions: The long-term effects of HIF prolyl hydroxylase inhibitors were similar to ESA in dialysis-dependent CKD. However, HIF prolyl hydroxylase inhibitors increased the incidence of some adverse outcomes in non-dialysis CKD.

TH-PO988

The Effect of Sodium-Glucose Cotransporter 2 Inhibitors on Hemoglobin Levels in Patients with CKD

Carmen E. Cervantes,1 Tareq Hanouneh,2 Veena K. Acharya,1,3 Jonathan G. Lim,1,4 Hyung M. Lim,1,5 Mohamad A. Hanouneh,1,3 Johns Hopkins University, Baltimore, MD; 2Mayo Clinic in Florida, Jacksonville, FL; 3Nephrology Center of Maryland, Baltimore, MD

Background: Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is) confer kidney and cardiovascular protection in patients with chronic kidney disease (CKD). Some studies have analyzed the effects of SGLT2is on hemoglobin levels. Potential mechanisms for reduced hemoglobin include hypoxia-induced activation of HIF, hepcidin inhibition resulting in iron metabolism modulation, and hemoconcentration. We aimed to assess the effect of SGLT2is on hemoglobin levels in CKD patients.

Methods: We conducted a retrospective study in patients seen in a community nephrology practice with eGFR 25-90 ml/min per 1.73 m² who received either dapagliflozin 10 mg daily or empagliflozin 10 mg daily between 1/2022 and 9/2023. The primary outcome was the mean difference in hemoglobin levels 8 months prior and 8 months post initiation of SGLT2i therapy.

Results: Among 402 patients screened from 1/2022 to 9/2023, 72 were prescribed either dapagliflozin 10 mg daily or empagliflozin 10 mg daily, with a mean eGFR of 51.2 mg/min/1.73 m². Of those 72 patients, 46 (63.88%) were male and 26 (36.11%) female. No one received any iron supplements or erythropoietin therapy. The mean hemoglobin level 8 months before initiating SGLT2i therapy was 12.8 g/dL, with a mean drop of 0.13 g/dL (95% CI –0.32 to +0.06) in 8 months. Eight months following the addition of SGLT2is, patients experienced an increase in hemoglobin levels of 1.06 g/dL (95% CI, 0.88 to 1.25). Overall, we observed a mean hemoglobin difference of 1.19 g/dL (95% CI, 0.88 to 1.5, p < 0.001) before and after initiating SGLT2i therapy. (Figure 1)

Conclusions: The use of either dapagliflozin or empagliflozin for eight months resulted in a significant elevation in hemoglobin levels in patients with CKD. Larger prospective trials can help better understand the size of the effect and confirm the mechanisms that explain this finding. Elevation of hemoglobin with SGLT2is may be closely linked to the reduction of cardiovascular mortality and heart failure hospitalization risk.
Trace Proteinuria Is a High-Risk Marker for Developing ESRD and for Shortening the Lifespan: Findings from an 18-Year Follow-Up Cohort with Half a Million Asian Participants

Min Kuang,1,2 Chi Pang Wen,3 Taipei Medical University, Taipei, Taiwan; National Health Research Institutes, Zhunan, Taiwan.

Background: Trace proteinuria, obtained by urine dipstick, has not received its due attention in clinical visits. It was particularly overlooked in the younger people, even though it had three times more trace proteinuria than the elderly. This study aims to investigate its role in kidney diseases such as End Stage Renal Disease and its association with mortality outcomes and life-shortening effects in a large Asian cohort.

Methods: A cohort of 646,987 adults, who have undergone health screening programs successively since 1994, were followed for a median of 18 years. Through encrypted identification numbers, 49,216 deaths and 4,101 ESRD cases were identified. Dipstick, in contrast to the old color-comparison method, is a semi-automated computer-assisted urinalysis system. Results reported as trace, 1+, 2+, and more. The association between proteinuria, ESRD, and mortality risks was evaluated using Cox proportional hazards models.

Results: Trace proteinuria existed around 5% among healthy adults, contributed to nearly half of all CKD (9.5%), with younger adults (age <60 years) having a threefold higher prevalence than the elderly (age ≥60 years). Trace proteinuria significantly increased the risk of ESRD independent of eGFR, with up to 4-5 folds in normal eGFR subjects. The HR was 3.54, 95% CI: 2.67, 4.69 when eGFR ≥ 90; HR: 3.86, 95% CI: 3.08, 4.84 when eGFR 60-89; HR: 12.26, 95% CI: 9.24, 16.28 when eGFR 45-59; HR: 44.60, 95% CI: 31.39, 60.55 when eGFR 30-44 ml/min/1.73m² when compared with normal proteinuria. Participants with trace proteinuria also had a significantly higher risk of all-cause mortality (HR: 1.48, 95% CI: 1.42, 1.54), and associated with a reduction in life expectancy of up to 4-5 years. Dipstick tests demonstrated relatively high sensitivity (80%) and specificity (96%) in detecting microalbuminuria. More than 80% with microalbuminuria in an apparently healthy population could be identified.

Conclusions: Trace proteinuria, overlooked in the clinics, was associated with a 4-5 fold increase in developing ESRD later in life and a shortened lifespan of five years, with nearly 50% increase in all-cause mortality. Trace proteinuria can be screened easily in the clinic using the positive dipstick, an inexpensive test with instant results. More than 80% with microalbuminuria in an apparently healthy population could be identified.

TH-P0992

Cost-Effectiveness of Home-Based Screening for Albuminuria in the General Population in the Netherlands

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Background: Screening the general population for albuminuria may identify individuals at high risk of chronic kidney disease (CKD) and cardiovascular disease (CVD) and allow early preventive interventions. Previous studies on the cost-effectiveness of albuminuria population screening were incoherent, modelled screening by family physicians, and included only CKD events. We evaluated the cost-effectiveness of home-based general population screening for increased albuminuria to prevent CKD and also CVD events.

Methods: We developed an individual-level health-state transition model to assess cost-effectiveness from the Dutch healthcare perspective with a lifetime horizon. Inputs were based on the THOMAS study, a prospective study in which we screened the general population aged 45-80 years, published in Lancet 2023. THOMAS consisted of a home-based albuminuria screening and subsequent elaborate screening of individuals with elevated albuminuria for CKD and CVD risk factors, to be treated by their family physicians. Risks of CKD and CVD events were calculated by simulating albuminuria and eGFR progression and the SCORE2 algorithm. Treatment relative risk reduction, quality of life weights, resource use, and cost inputs were obtained from the literature. Outcomes included the number of events, total costs, quality-adjusted life years (QALYS), and incremental cost-effectiveness ratio (ICER) of screening versus usual care (no screening), based on probabilistic analysis.

Results: The relative reduction in lifetime dialysis, kidney transplantation, non-fatal myocardial infarction, non-fatal stroke, and fatal CVD events of screening was respectively 11%, 12%, 6%, 5%, and 2%. The incremental costs and QALYS of screening were €1,584 and 0.18 QALYS. This resulted in an ICER of €8,689/QALY, which would be considered cost-effective at the Dutch willingness to pay threshold of €20,000/QALY. The probability of screening being cost-effective for this threshold was 96%. Screening was more cost-effective in subjects aged 65-80 years, compared to those aged 45-65, and if implementation of care after screening was improved.

Conclusions: Home-based screening for increased albuminuria to prevent cardiovascular and chronic kidney disease events is likely cost-effective.

TH-P0993

Screening for Urine Protein as a Risk Factor for ESRD Using a Large Claims Database

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Background: Proteinuria screening serves as a crucial diagnostic tool in identifying chronic kidney disease (CKD) and mitigating the risk of progression to end-stage renal disease (ESRD). Timely detection and intervention can enhance patient outcomes and provide cost savings, as proteinuria serves as a predictor for ESRD and all-cause mortality rates.

Methods: A large health insurance claims database was used to analyze the relationship between estimated glomerular filtration rate (eGFR), urine albumin-creatinine ratio (uACR), and the progression to ESRD in a population of Medicare members with CKD stages 3a to ESRD during the index month of January 2021. The analysis included data from the 12 months prior to the index month to determine the presence or absence of proteinuria and the data from the 12 months following the index month to determine ESRD transition. Data from 32,194 individuals was included. Sources included Medicare claims, labs, and demographics.

Results: Of the 32,194 members in this analysis, 47% were female and the average age was 57.3 years. Thirty-six percent of individuals who had eGFR stage G5 and A3 (severely increased) degree of proteinuria in the twelve months starting January 2021 progressed to ESRD. Twenty-three percent of individuals with eGFR stage G5 patients without proteinuria screening progressed to ESRD. Eighteen percent of the population had proteinuria screening and 22.9% of these patients were CKD 3B, 12.1% were stage 4, and 13.8% were stage 5. Of these patients, 26% were A3, 42% were A2 (Moderately increased) and 32% were A1 (Normal to mildly increased).

Conclusions: Proteinuria screening can provide an early warning of CKD that may progress to ESRD and potentially allow for risk mitigation. In this analysis, more than one-third of CKD G5A3 patients progressed to dialysis within a year. Prompt detection of patients with proteinuria and management, coupled with adherence to ACE and SGLT2 inhibitors, may curtail progression. Utilizing a health plan database is a useful tool to identify individuals who have proteinuria and are at risk of CKD progression and earlier diagnosis can lead to improved outcomes and delay in CKD progression.
TH-PO994

Development of a New Equation for Estimated 24-Hour Proteinuria: Modified Urine Protein-Creatinine Ratio Adjusted by Urinary Creatinine Excretion

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Background: Instead of the 24h proteinuria, the urinary protein-to-creatinine ratio (Up/Ucr) in spot urine, based on the assumption of 24h urinary creatinine excretion (CER) of 1 g/day, is widely used in clinical practice. However, the actual CER is often deviated from 1g/day because it is affected by individual muscle mass and kidney function, and Up/Ucr is often not accurately estimated for 24h proteinuria.

Methods: Data from a prospective observational study in patients with chronic kidney disease or cardiovascular disease in our hospital were used. Patients with both 24h urine collection and spot urine the day after 24h urine collection were included. First, we examined the relationship between Up/Ucr in 24h urine collection and Up/Ucr in spot urine, and then created estimated CER using age, sex, and serum creatinine. Finally, a modified Up/Ucr equation was developed adjusting for estimated CER and the relationship between Up/Ucr in 24h urine and Up/Ucr in spot urine.

Results: Among 1031 patients, 813 patients for whom spot urine and 24h urine data were available were included in the analyses of this study. Up/Ucr in spot urine increased by 7% compared to Up/Ucr in 24h urine, and both were closely associated with each other (R2=0.99), suggesting an increase in proteinuria due to exercise in spot urine at hospital visit as compared with 24h urine. Mean CER for males and females was 1.04 and 0.69 g/day, respectively, meaning 4%-overestimation in males and 31% underestimation in females when using Up/Ucr compared with measured 24h proteinuria. CER was also negatively associated with older age especially >60 years and increased in serum creatinine. The mean difference from measured 24h proteinuria for Up/Ucr in spot urine was -45.4% and that for modified Up/Ucr was -21.2% (P<0.001). The numbers within 15% and 30% of measured 24h proteinuria was 17% and 34% for Up/Ucr in spot urine, respectively and 24% and 46% for modified Up/Ucr, respectively (P<0.001).

Conclusions: Using spot urine immediately after 24h urine collection and estimated CER, a modified Up/Ucr equation was newly developed, which could be more useful in clinical practice than classical Up/Ucr.

TH-PO995

Disparities in Etiologic Classification of CKD

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Background: Understanding the etiology of CKD is critical for targeted therapy. No prior study has evaluated disparities in assigning an etiology for CKD in practice. Due to widespread health disparities in CKD, we hypothesized that etiologic assignment would be lower for patients of Black race, Hispanic ethnicity, and female sex.

Methods: We identified adults in the Veterans Health Administration who had incident CKD stage G3 or higher (G3+) from 2005-2015. Incident CKD G3+ was defined as the first occurrence of two eGFRs <60 ml/min/1.73m2 ≥90 days apart. Patients with ICD-9/ICD-10 codes for general CKD (i.e., 585.X; N18.X) before the index date were excluded. Using 290 specific ICD-9/ICD-10 codes (e.g., N03.3) classified in 6 etiologic domains (diabetic, hypertensive/vascular, obstructive/urologic, glomerular, cystic/congenital, tubulointerstitial), we identified specific etiologic diagnoses of CKD within 3 yrs before or after incident CKD G3+. Logistic regression was used to evaluate disparities in assignment of a specific etiologic code by race/ethnicity and sex, stratified by age. We adjusted for geographic region, year of incident CKD, and comorbidities. We adjusted for geographic region, year of incident CKD, and comorbidities. Disparities in assignment of a specific etiologic code by race/ethnicity and sex, stratified by age. We adjusted for geographic region, year of incident CKD, and comorbidities.

Results: Out of 452,851 patients (438,414 male/14,437 female), 42.5% received an etiologic assignment. Contrary to our hypothesis, rates of etiologic assignment among patients of non-Hispanic Black race or Hispanic ethnicity were higher compared to non-Hispanic White race/ethnicity. We found consistently lower rates of etiologic assignment among females compared to males in all age groups (Table).

Conclusions: Efforts are needed to improve the assignment of etiology of CKD, particularly among female Veterans. More work is needed to evaluate rates of specific etiologies and their accuracy in CKD.

Funding: NIDDK Support

TH-PO996

Incorporation of Cystatin C in Estimating Kidney Function: Real-World Experience in Sweden

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Background: Cystatin C is a filtration marker that, when used in combination with serum creatinine, provides a more precise estimate of GFR than using serum creatinine alone. However, many US physicians are unfamiliar with cystatin C and guidelines are vague on use of cystatin C as an adjunct test. Cystatin C has been routinely tested in Sweden for over a decade.

Methods: Using routine clinical data collected from 2010-2018 in the Stockholm Creatinine Measurements (SCREAM) project, we investigated rates of routine outpatient cystatin C testing over time as well as clinical care and patient characteristics associated with cystatin C testing. We used logistic and Cox proportional hazards regressions, stratified by ACR testing status, to further examine associations with cystatin C testing.

Results: Among the 1.37M adult individuals with serum creatinine tested, 11.2% also had serum cystatin C tested. The annual rate of cystatin C testing ranged between 4-7% each year. Those who had both markers tested were more likely to be older, male, have a lower eGFRcr, have more comorbidities, and more likely to have an ACR test. Among those with ACR testing, we found higher odds for a lower eGFRcr and, much higher risks of KFRT for the same level of eGFRcr in the population with cystatin C testing compared to those without. Among those without ACR testing, we found higher odds for older age and anemia, similar KFRT risk, but higher mortality risk among those with cystatin C testing compared to those without.

Conclusions: Cystatin C testing in Sweden followed two distinct patterns: for those at heightened risk of kidney failure (who were also receiving albuminuria testing) and for older adults who were more likely to have anemia and at higher risk of mortality. This study provides a real-world account of cystatin C testing and supports the utility of cystatin C for clinical practice.

Funding: NIDDK Support, Private Foundation Support
TH-PO997
Cystatin C as a Marker for GFR Estimation in Clinical Populations: A Systematic Review
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Background: GFR estimated using creatinine (eGFRcr) is often inaccurate in populations with acute and chronic illness. The accuracy of GFR equations that use cystatin C (eGFRcys) or creatinine-cystatin C (eGFRcr-cys) is not well studied in these populations.

Methods: Using a systematic review, we identified 21 studies of populations with comorbid illnesses that evaluated eGFRcr and eGFRcys compared to measured GFR (mGFR) using standardized assays for the markers: cancer (5); HIV (5); cirrhosis (2); liver transplant (3); heart failure (1); critical illness (3); and obesity (2). The performance of each equation was the unit of analyses (“report”). We assessed equation performance using bias as the median or mean difference between eGFR and mGFR, and accuracy as the percentage of eGFR within 30% of mGFR (P30).

Results: eGFRcr had more reports of moderate-to-large bias than for eGFRcys and eGFRcr-cys, and of overestimation, than underestimation, of mGFR. There were large inconsistencies in the relative performance of eGFRcr vs eGFRcys even for populations with the same illness. eGFRcr-cys was most accurate in populations with cancer, HIV and obesity, but did not perform consistently better in cirrhosis, liver transplant, heart failure and critical illness populations. Notable limitations are that participants were selected because of concern for inaccurate eGFRcr, and most studies had small sample sizes, limiting generalizability.

Conclusions: eGFRcr-cys improves GFR estimation in populations with a variety of acute and chronic illnesses, supporting current recommendations for more frequent use of cystatin C into more clinical practice. These data provide early evidence base for indications for cystatin C.

Funding: NIDDK Support

TH-PO998
Estimating GFR from Cystatin C Without Including a Sex Variable: CKD-EPI 2023 Equation
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Background: Use of a binary sex variable in eGFR equations may limit their use in gender subgroups. There are smaller differences between sex groups in cystatin C than creatinine independent of GFR. Other research groups have developed equations to estimate GFR using cystatin without sex [Pottel et al, NEJM 2023; Grubb et al, Clin Chem 2014]. We developed a CKD-EPI cystatin C equation that does not include a variable for sex and evaluated its performance in an external validation population.

Methods: Using the same population (5,352 participants from 13 studies) used for development of the current equation that includes age and sex (CKD-EPI 2012 eGFRcys AS), we developed a new eGFR cystatin C equation without sex (CKD-EPI 2023 eGFRcys A). We used least squares linear regression of measured GFR (mGFR) vs serum cystatin C and age on the logarithmic scale, with separate slopes for cystatin C at low vs. high values using the same spline knot as the 2012 equation (0.8 mg/L), and assessed model performance using root-mean-square error (RMSE). We assessed performance in the CKD-EPI 2021 external validation population (4,050 participants from 12 studies) using bias (systematic error, mL/min/1.73m²) as the median difference between mGFR and eGFR, and accuracy as the percentage of eGFR within 30% of mGFR (P30).

Results: In the development and validation population, 2,245 (42%) and 1,557 (38%) were female, respectively. Removing the sex variable led to a minimal increase in RMSE overall and in both sex subgroups (Table). In the external validation population, removing the sex variable led to a small increase in bias in both subgroups, with greater decrease in accuracy for females vs males although at levels considered acceptable (P30 >80%).

Conclusions: The availability of acceptably accurate eGFRcys equations that do not include a sex variable provides an option to use in people whose gender identification differs from their sex assigned at birth. Further studies can explore the impact of using these equations in the general population.

Funding: NIDDK Support
Effect of Race-Free Estimated Glomerular Filtration (eGFR) Equation on CKD Prevalence in the US Military Health System (MHS)

**Background:** The 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation removed race as a factor in the calculation of eGFR. We assessed the potential impact on CKD prevalence using the MHS Data Repository, a large network health care database covering a diverse population comparable to the US general population.

**Methods:** We extracted MHS data from 2016-2019 for adults age ≥18. We compared CKD prevalence using eGFR calculated from the 2009 race-adjusted vs. the 2021 race-free CKD-EPI equations. Race was classified as Black or non-Black and was imputed in 23.7% of the population. CKD stages 3-5 were defined as eGFR < 60 mL/min/1.73 m² for ≥90 days. We evaluated additional population changes at eGFR thresholds (<45, <30, <20 mL/min/1.73m²) important for clinical decision-making.

**Results:** The study included 1,970,433 adults with median (IQR) age 40 (29–55) yrs, 49.2% female, and 18.0% Black adults. With the 2021 equation, Black adults with CKD increased from 5,828 to 8,928, a change in crude prevalence from 1.6 to 2.5% (Table). The Black adult population with eGFR <60, <45, <30, and <20 mL/min/1.73 m² increased from 5828 to 8928, a change in crude prevalence from 1.6 to 2.5% (Table). The opposite effect on non-Black adults. The Black adult population with eGFR <60, <45, <30, and <20 mL/min/1.73 m² increased from 5828 to 8928, a change in crude prevalence from 1.6 to 2.5% (Table). The opposite effect on non-Black adults.

**Conclusions:** The new eGFR equation in the MHS will reclassify many Black adults to new or more advanced CKD stages, with the opposite effect on non-Black adults. The impact on time to diagnosis, clinical management, and outcomes is unknown but there may be shifts in referral patterns to nephrology, diabetologists, and transplant services. Ongoing surveillance of CKD is warranted. The views expressed in this abstract are those of the authors and do not reflect the official position of the Henry M. Jackson Foundation for the Advancement of Medicine Inc, Bethesda, MD.

**Funding:** Other U.S. Government Support

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**TH-PO1000**

CKD Epidemiology, Risk Factors, Prevention - I

Effect of Race-Free Estimated Glomerular Filtration Rate (eGFR) Has Good Efficacy to Predict Clinical Outcomes in a Large Prospectivie Cohort of Adult Koreans

**Background:** A new eGFR equation using serum creatinine (CKD-EPI 2021) without race were developed by Chronic Kidney Disease Epidemiology Collaboration in 2021. We projected the changes of eGFR, CKD prevalence, and incidence of end stage renal disease (ESRD) and mortality in a large prospective cohort of adult Koreans who had voluntary health check-ups, using current (CKD-EPI 2009) and new equation (CKD-EPI 2021).

**Methods:** We included 112,772 adult participants, aged 18 years or older, who had voluntary routine health check-ups at three medical centers in Korea from 2003 to 2009. We compared the difference of eGFR and predictability of mortality and ESRD between eGFR values calculated by CKD-EPI 2009 and 2021. The incidence of mortality data was extracted from Statistics Korea and the ESRD data from the ESRD registry of the Korean Society of Nephrology.

**Results:** At baseline study, there were 60,723 males (53.8%). The value of IDMS-traceable serum creatinine was 0.86 ± 0.21 mg/dL. Levels of eGFR at baseline study were 93.5 ± 15.6 ml/min/1.73 m² by CKD-EPI 2009, and 97.1 ± 15.0 ml/min/1.73 m² by CKD-EPI 2021. CKD stage was improved in 11,828 (10.5%) participants using eGFR calculated by CKD-EPI 2021 instead of CKD-EPI 2009, however, only 0.63 % of participants with eGFR <60 ml/min/1.73 m² by CKD-EPI 2009 was reclassified into eGFR ≥60 ml/min/1.73 m² by CKD-EPI 2021. During 11.6 ± 2.0 years, 33,543 (3.00%) subjects were dead and 1,151 (0.13%) subjects had end stage renal disease (ESRD) care before death. Any eGFR or stage of eGFR was an independent risk factors to ESRD or mortality estimated by Cox’s hazard proportional model adjusted by related factors. AUC to estimate renal survival by eGFRs was not different between eGFRs by CKD-EPI 2021 and 202009 [0.739 (0.687-0.790) vs 0.740 (0.688-0.792), p=0.170], p<0.001]. AUC to estimate survival by eGFRs calculated through CKD-EPI equation was slightly higher than that by CKD-EPI 2021 [0.673(0.664-0.682) vs 0.667(0.658-0.676), p<0.001]. However, the difference of AUC was negligible [standard error of AUC difference by two eGFRs; 0.96 (95% CI: 0.006-0.007)].

**Conclusions:** The eGFR calculated by CKD-EPI 2021 was higher compared to eGFR calculated by CKD-EPI 2009. The power to estimate renal survival was not different between eGFRs by CKD-EPI 2021 and CKD-EPI 2009.

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**TH-PO1003**

CKD Epidemiology, Risk Factors, Prevention - I

Identifying CKD Stage 3 with Excess Disease Burden

**Background:** Chronic kidney disease (CKD) is a widely prevalent disease with heterogeneous disease progression. Current practice guidelines recommend nephrology referral when patients are diagnosed with CKD stage 4. Prior studies suggest earlier referral to nephrologists can improve health outcomes for patients with chronic kidney disease (CKD), however claims-based methods to identify high-risk CKD stage 3 patients remain lacking. We assessed cost, utilization, and disease progression in patients with various stages of CKD, including an identified subset of patients with CKD stage 3 and common medical morbidities.

**Methods:** This is a retrospective study of Medicare fee-for-service beneficiaries with CKD stages 3-5. We identified seven comorbidities with high prevalence in patients with progressive CKD and segmented beneficiaries with CKD stage 3 based on the presence of and very high risk). Finally, we investigated patient characteristics among those who were reclassified in eGFR categories (switchen; yes/no).

**Results:** Study sample included 16,037 patients, median age 74 years, 54% male. Compared to 2009 equation, eGFR calculated using 2021 equation was on average 1.80-2.60 ml/min higher in women and 2.86-3.33 ml/min higher in men. The 2021 equation downgraded the CKD severity in the highest % of patients downgraded in G5 category (Fig.1). In KDIGO risk categorization, ~4% of patients in the very high risk group were reclassified to a lower risk group. The switchers appeared to be older male, majority (~43%) were in eGFR category G4 followed by 27% in G3b. KFRE 2-year risk score calculated using eGFR from 2009 equation showed comparison was negligible when eGFR calculated using eGFR from 2009 equation, median (IQR) in difference was -0.854 (-2.516, -0.258). Difference was larger in males.

**Conclusions:** The eGFR calculated using CKD-EPI 2021 was higher compared to the 2009 equation. A large number (~17%) of patients currently under the care of nephrologists in BC would have categorically less severe CKD. The implications of this on resource utilization, care plans and outcomes are unknown.
these comorbidities. Outcomes including costs, utilization, and disease progression were then compared across beneficiaries with different stages of CKD.

Results: We identified that beneficiaries with CKD stage 3 and at least one of the selected comorbidities (CKD stage 3-plus), represented 35.4% of all beneficiaries with CKD stage 3. The CKD stage 3-plus cohort had cost and utilization patterns that were more similar to beneficiaries with CKD stages 4 and 5 compared to beneficiaries with CKD stage 3 without the selected comorbidities.

Conclusions: Our findings demonstrate the use of a claims-based algorithm to identify patients with CKD stage 3 that are high cost and at risk of disease progression, highlighting a potential subset of patients who might benefit from earlier nephrology intervention.

TH-PO1004

Undiagnosed Early CKD in Patients with Hypertension and Cardiovascular Disease in the United States

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Background: Chronic kidney disease (CKD) is a growing public health issue and widely under-recognized in the United States. Hypertension (HTN) and cardiovascular diseases (CVD) are well-known risk factors for CKD; and KDIGO recommends screening for early diagnosis of CKD and active management can slow disease progression and improve outcomes, but the prevalence of undiagnosed early-stage CKD in patients with comorbidities other than type 2 diabetes (T2D) has not been reported. This analysis assessed the prevalence of undiagnosed stage 3 CKD in patients with HTN and CVD in the absence of T2D.

Methods: Data were extracted from the US TriNetX database. Patients were aged ≥18 years with 2 consecutive estimated glomerular filtration rate (eGFR) results ≥30 and <90 mL/min/1.73 m² recorded 91-730 days apart between 2015 and 2020. Undiagnosed CKD was defined as the absence of a CKD diagnosis code any time before and up to 6 months after the second eGFR (index date). The analysis cohorts included patients with the following at or before index: 1) HTN ICD 9/10 diagnosis code but not for T2D; 2) HTN or atherosclerotic cardiovascular disease (ASCVD) ICD 9/10 diagnosis code but not for T2D; 3) HTN or heart failure (HF) ICD 9/10 diagnosis code but not for T2D; and 4) ICD 9/10 diagnosis code for T2D.

Results: In the absence of T2D, the proportion of undiagnosed stage 3 CKD in patients with HTN or ASCVD was 68.4% (95% CI: 68.2%, 68.7%). Similar proportions were observed in patients with either HTN or ASCVD. The proportion of patients with HTN or ASCVD was 68.4% (95% CI: 68.4%, 68.8%), and with HTN or HF was 68.6% (95% CI: 68.3%, 68.8%). These proportions were greater than those with undiagnosed stage 3 CKD and T2D (51.7%, 95% CI: 51.3%, 52.0%) (Figure). The results highlight an opportunity to increase early identification of CKD in people with high-risk comorbidities other than T2D in order to implement targeted evidence-based therapies to slow progression of CKD and improve patient outcomes.

Funding: Commercial Support - AstraZeneca

TH-PO1005

Renal Protective Treatment Use for Non-Diabetic CKD in Japan, Sweden, and the United States

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Background: Chronic kidney disease (CKD) is an underdiagnosed disease affecting 10% of people worldwide. Appropriate management of CKD delays progression and reduces its burden. Renin-angiotensin system inhibitors (RASis) have been the mainstay of CKD treatment until recently. Here we describe the use of RASis and the sodium–glucose co-transporter-2 inhibitor dapagliflozin in a contemporary population of patients with CKD.

Methods: This study used secondary data extracted from electronic health records or claims data sources. Adult patients with CKD (either two estimated glomerular filtration rate [eGFR] measurements ≥ 90 days apart of which both were ≥ 60 mL/min/1.73 m² or an eGFR ≥ 60 mL/min/1.73 m² followed by a CKD diagnosis) who were new RASi or dapagliflozin users during 2021–2023 were included. Patients with type 1 or gestational diabetes, stage 3 CKD or on dialysis were excluded. RASi and dapagliflozin doses and persistence were assessed in the year following initiation.

Results: Overall, 159,220 patients were included (Japan, 57,222; Sweden, 10,861; USA, 91,137). Median ages were 75, 72 and 72 years, and 63%, 66% and 52% were males in Japan, Sweden and the USA, respectively. Of patients without type 2 diabetes, a high proportion receiving dapagliflozin remained on the evidence-based 10 mg target dose (Figure). A large proportion of patients treated with RASis received low doses. At 12-month follow-up, dapagliflozin persistence was approximately 65%, 80% and 55% in Japan, Sweden and the USA, respectively, and was 34%, 75% and 64% for RASi, respectively.

Conclusions: CKD treatment with dapagliflozin was associated with a high likelihood of receiving and remaining on target dose compared with RASI treatment. Efforts to maintain patients on renal protective treatment are needed.

Funding: Commercial Support - AstraZeneca

TH-PO1006

Prevalence of Antihypertensive Use in CKD

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Background: Treatment-resistant hypertension (TRH) is a comorbidity of concern in patients with chronic kidney disease (CKD) and elevates the risk of cardiovascular events. The aim of this analysis was to identify the prevalence of antihypertensive medication (AHM) use in patients with persistent TRH concurrent with CKD, overall and stratified by CKD stage.

Methods: The study cohort was comprised of adults with CKD in the US TriNetX database between 2008 and 2020. The study cohort was defined as the second of two consecutive eGFR measurements <75 mL/min/1.73 m² between 91-730 days apart or ICD-9/10 code of CKD or dialysis. Patients with ≥1 systolic blood pressure (SBP) ≥130 mm Hg within 6 months before or any time after index date were included, and of these, TRH was defined as taking ≥3 AHM classes. The number of AHM prescribed 0 to ≥4 were described overall and by CKD stage. A sensitivity analysis using SBP ≥140 mm Hg was also performed.

Results: In the cohort with CKD and SBP ≥130 mm Hg (N = 109,385), mean (SD) age was 64 (13) years, 57% were female, and 77% were White and 20% were Black. Median (IQR) SBP measurements was 3 (1.5). Proportion of patients with TRH was 18.6% overall, and by CKD stage was 13.3% (S1 and 2), 21.5% (S3), 35.7% (S4), and 37.5% (S5). These proportions were modestly increased in the sensitivity analysis. The results indicate that TRH is a comorbidity of concern in patients with chronic kidney disease (CKD) and elevates the risk of cardiovascular events. The prevalence of antihypertensive medication (AHM) use in patients with persistent TRH concurrent with CKD, overall and stratified by CKD stage.

Funding: Commercial Support - AstraZeneca
The Prevalence of CKD in Australian Primary Care: Analysis of a National General Practice Dataset

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Background: CKD prevalence in Australia varies substantially across reports. Using a large, nationally-representative general practice data source in Australia, we determined the contemporary prevalence and staging of CKD in Australian primary care.

Methods: We performed a retrospective, community-based observational study using healthcare data from Medicinsight, a national general practice data source in Australia. We included all adults with ≥1 visit to a general practice participating in Medicinsight and ≥1 serum creatinine measurement (with or without a UACR measure) between 2011-2020; n=2,720,529 patients. CKD prevalence was estimated using 3 definitions: (1): an eGFR (mL/min/1.73m²) <60 or an eGFR >100 with a UACR (mg/mmol) >2.5 for M and >3.5 for F; (2) 2 consecutive eGFR measures <60, a90 days apart or an eGFR >100 with a UACR >2.5 for M and >3.5 for F; and (3) 2 consecutive eGFR measures <60, a90 days apart and/or 2 consecutive UACR measures >2.5 for M and >3.5 for F. Patient characteristics were assessed across the 3 definitions.

Results: CKD prevalence progressively increased over the 10-year study period, irrespective of the method used to define CKD. The annual prevalence of CKD varied across the 3 CKD definitions, with definition 1 resulting in the highest estimates. In 2020, CKD prevalence in the study cohort was 8.4% (n=123,988), 4.7% (n=69,110) and 3.1% (n=45,560) using definitions 1, 2 and 3, respectively. The number of patients with UACR measurements was too small such that, among those identified as having CKD in 2020, only 3.8%, 3.2% and 1.5% respectively, had both eGFR and UACR measures available in the corresponding year. Patients in whom both eGFR and UACR measurements were available mostly had moderate or high risk of CKD progression (83.6%, 80.6% and 76.2%, respectively). Comorbid burden in patients with CKD was also frequently observed.

Conclusions: In this large, nationally-representative study, we observed an increasing trend in CKD prevalence in primary care settings in Australia. Most patients with CKD were at moderate to high risk of CKD progression with a significant comorbid burden. These findings highlight the need for early detection and effective management to slow progression of CKD.

Funding: Commercial Support - This study was supported by an unrestricted research grant from Boehringer Ingelheim.

Predictors of Differences in Cystatin C- and Creatinine-Based eGFR

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Background: Large differences between eGFR based on cystatin C (eGFRcys) and creatinine (eGFRcr) are common. A comprehensive evaluation of factors that account for these differences is needed to guide the interpretation of discrepant eGFR values.

Methods: We studied the prevalence of 468,869 UK Biobank participants into 2 nonoverlapping cohorts, 80% for model training and 20% for model testing. In the training set, we used Bayesian model averaging to identify a parsimonious set of predictors among 34 candidate variables, including sociodemographic, lifestyle, physical and clinical factors. Predictors of large eGFRdiff were defined as eGFRcys minus eGFRcr <15 (negative eGFRdiff) or a15 mL/min/1.73 m² (positive eGFRdiff). We incorporated the identified set of predictors into a multinomial logistic regression model to estimate the odds of negative or positive eGFRdiff. We assessed model performance in the test set.

Results: The mean age was 56y; 46% were male. The overall mean ± SD of eGFRcys was 88±16 and eGFRcr was 95±13 mL/min/1.73 m²; 25% of participants had negative eGFRdiff, and 5% had positive eGFRdiff. Strong predictors of negative eGFRdiff included older age, male sex, South Asian ethnicity, current smoker (vs. never smoker); history of thyroid dysfunction, chronic inflammatory disease, steroid use, higher waist circumference and body fat, and UACR >300 mg/dl (Table 1). Odds ratio estimates for these high-risk factors were largely in the same direction for positive eGFRdiff. The model’s AUC was 0.75 in the test set, with good calibration (1.00).

Conclusions: This study highlights the multitude of demographic, lifestyle, and health characteristics associated with wide eGFRdiff. This may help clinicians to interpret discrepant eGFRcys and eGFRcr values.

Funding: NIDDK Support, Veterans Affairs Support
Prevalence and Outcomes of Kidney Disease Among Ethiopian Immigrants Compared with Other Immigrant and Native Populations in Israel
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Background: The worldwide prevalence of kidney disease in the Ethiopian population is unknown. This study assessed the prevalence of CKD and risk factors for progression among Ethiopian immigrants compared with other immigrant populations, as well as Israeli-born Jewish and Arab population.

Methods: The study included all people above 25 years old who were insured by Clalit Health Services from 01/01/2007 until 31/12/2017, and had more than two plasma creatinine measurements at least 28 days apart, which demonstrated similar CKD stage. Follow-up was until 31/12/2020. Primary outcome was at least 50% decrease in estimated glomerular filtration rate (eGFR) calculated with CKD-epi equation. Cox regression model was used to analyze risk-factors for CKD progression.

Results: The study included 1,734,501 people, of whom 41,260 (2.4%) were Ethiopian immigrants, mean age 44.8±16.6 years, baseline eGFR 111.0±16.5 ml/min/1.73m²; 273,476 (15.8%) former Soviet Union immigrants, mean age 56.3±18.1 years, baseline eGFR 88.2±22.5 ml/min/1.73m²; 366,789 (21.1%) native Israeli Arabs, mean age 42.5±14.5 years, baseline eGFR 107.9±8.18 ml/min/1.73m², and 1,052,976 (60.7%) native Israeli Jews, mean age 43.1±14.3 years, baseline eGFR 102.6±18.7 ml/min/1.73m². (p<0.001 for age and eGFR). Decrease in eGFR ≥50% was documented in 38,913 (2.2%) people: 573 (1.4%) were Ethiopian immigrants. Cox regression model was performed in three age groups: Ethiopian ethnicity was associated with higher risk for CKD progression in the young group (<50 years), HR 1.70 (95% CI: 1.54-1.90, p<0.001), but had no effect in the 50 to 70 years age group, HR 1.14 (95% CI: 1.05-1.24, p=0.099) and had a protective effect in the older, ≥70 years group, HR 0.62 (95% CI: 0.57-0.68, p<0.001).

Conclusions: Young Ethiopian immigrants had higher risk for CKD progression which was absent among older Ethiopian immigrants, suggesting a genetic/familial etiology or adaptive factors. Further research is desirable.
TH-PO1013
Prevalence and Risk Factors for CKD and CKDu in León, Nicaragua

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Background: CKD of unknown etiology (CKDu) disproportionately affects young people in Central America who lack traditional CKD risk factors (diabetes and hypertension) and is instead linked to heat stress, occupational and environmental exposures, nephrotoxic medications, and/or genetic conditions. This study aimed to estimate the prevalence of CKD and to identify risk factors for traditional CKD and CKDu in Nicaragua.

Methods: Surveys and assessment for CKD markers in urine and serum were performed in 15-59 year olds in households of the León municipality of Nicaragua. The survey included questions on demographics, health behaviors, occupation, and medical history. Participants with CKD were subdivided into traditional CKD and suspected CKDu based on history of diabetes, hypertension, or other specified conditions. A multinomial logistic regression model was used to identify factors associated with traditional CKD and CKDu, compared to the non-CKD reference group.

Results: In 1795 study participants, CKD prevalence was 8.6%. Prevalence in males was 2.9-fold higher than females (6.8% vs. 3.6%). Of those with CKD, 30% had suspected CKDu. Both traditional CKD and CKDu were associated with male sex and increasing age. Traditional CKD was associated with a family history of CKD and lower socioeconomic status, while CKDu was associated with non-treated water sources and a lower body mass index.

Conclusions: Both traditional CKD and CKDu are significant burdens in this region. Our study supports previous hypotheses of CKDu etiology and emphasizes the importance of CKD screening.

Odds ratios and 95% confidence intervals from a multinomial logistic regression model for CKD from traditional risk factors and suspected CKDu compared to the non-CKD reference group.

TH-PO1014
CKD of Unknown Origin (CKDu) Is Associated with Subhelical Rhabdomyolysis

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Background: CKDu is a type of chronic kidney disease, unrelated to diabetes and hypertension, mostly described in young sugar cane workers in El Salvador, Nicaragua and Mexico (Mesamerican Nephropathy). Many etiologies have been assessed, including pesticides, heavy metals, silica, fructose-rich soft drinks, tobacco use, nutritional factors, and strenuous work in hot climate. Occupational heat stress is now an accepted key etiologic factor, but pathophysiological pathways need further clarification. The role of rhabdomyolysis has been considered but myoglobin levels are unknown and serum creatine kinase (CK) levels during the harvest season are only mildly elevated.

Methods: We determined serum myoglobin (ng/ml, electrochemiluminescence immunoassay), CK (units/L) and creatinine (Ser, mg/dl) before (Pre) and after (Post) a 5 to 12 hour working shift in 109 sugar cane cutters (1 female), 19-78 years old from Tierra Blanca, Veracruz, a previously identified hot spot region for CKDu.

Results: Levels (mean±SEM) of myoglobin (Pre=33.2±14.2; Post=60.0±5.02; p<0.0001), CK (Pre=164.4±24; Post=218.9±12.10; p=0.0001) and Scr (Pre=0.98±0.05; Post=1.17±0.058; p<0.0001) increased significantly (paired T test) during the working shift. There was a direct linear correlation between the increment in Scr and both the increments in CK (r=104; r2=0.161; p<0.0001) and myoglobin levels (n=104; r2=0.284; p<0.0001) (Figure).

Conclusions: The serum levels of myoglobin and CK are below the levels usually reported in rhabdomyolysis-related acute kidney injury. Nevertheless, subclinical rhabdomyolysis occurs daily during the harvest season in sugar cane workers and the role of repeated mild episodes of rhabdomyolysis in CKDu deserves to be investigated.

Funding: Private Foundation Support

TH-PO1015
Long-Term Exposure to High Perceived Temperature and Risk for Mortality Among CKD Patients

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Background: Risks for climate change is emerging and interest in health risks from high temperature exposure is growing. The perceived temperature (PT) is an equivalent temperature based on a complete heat budget model of the human body. We aimed to analyze the effect of PT on the overall mortality among chronic kidney disease (CKD) patients.

Methods: A total of 32,870 patients with CKD in Seoul participated in a retrospective cohort (2001-2018) at three medical centers. PT during summer season was calculated using meteorological factors including air temperature nearby automated weather station, dew point temperature, wind velocity, and total cloud amount. We assessed the association of PT using Kriging spatial interpolation on mortality in CKD patients in the time-varying Cox proportional hazard model that was adjusted for sex, age, body mass index, hypertension, diabetes mellitus, estimated glomerular filtration rate, smoking, alcohol consumption, and education level.

Results: During the 6.14 ± 3.96 years of follow-up, 3,863 deaths (13%) were observed. In multivariable analysis, average level of PT (hazard ratio (HR) 1.292, 95% confidence interval (CI) 1.255-1.311) and maximum level of PT (HR 1.356, 95% CI 1.309-1.404) showed increased risk for overall mortality among CKD patients. The c-index for mortality was high in the order of PT, temperature, discomfort index, and heat index (average level, 0.790, 0.785, 0.785, and 0.784; maximal level, 0.790, 0.784, 0.782, and 0.781). When stratified by age, diabetes mellitus, and estimated glomerular filtration rate, CKD patient with old age (age above 65 years old), without diabetes mellitus, and estimated glomerular filtration rate above 60 ml/min/1.73 m2 showed higher c-index levels. In addition, the risk for death in winter and spring seasons was also proved as significant with HR of 1.152 (95% CI 1.088-1.220) and 1.067 (95% CI 1.014-1.123) compared with the summer and autumn season mortality with according to HR of 1.401 (95% confidence interval 1.313-1.496).

Conclusions: Long-term exposure to high perceived temperature during summer season increase the risk of mortality among CKD patients.

TH-PO1016
Long-Term Exposure to Low Perceived Temperature in Winter Increases the Risk of Death in CKD Patients

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Background: Because of the rapid climate change, global interest about its impact on human health has been heightened. Perceived temperature (PT) is defined as a temperature that reflects the actual effect of temperature on the human body by considering the wind speed, amount of clouds, and humidity information. Due to the insufficiency of data on the health effects of long-term exposure to low temperature in chronic kidney disease (CKD) patients, we aimed to analyze the effect of PT in winter on the overall mortality among CKD patients.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: 32,870 CKD patients in Seoul participated in a retrospective cohort at three medical centers. PT was calculated by the Staiger’s equation, using the temperature of a nearby automated weather station, dew point temperature, wind velocity, and cloud amount. PT is interpolated using Kriging method and mortality was assessed by using the time-varying Cox proportional hazard model. The Cox regression model was used to assess the PT corresponding to the temperature for cold wave watch or warning.

Results: During the 6.14 ± 3.96 years of follow-up, 6,147 (18.7%) deaths were observed Since 2000, maximal and average PT had not significantly been changed. In multivariable analysis, the hazard ratio (HR) of maximum PT was 1.091 (95% confidence interval (CI) 1.073-1.109, p-value <0.0001), and HR of average, minimal PT were 1.042 (CI 1.018-1.065, p-value 0.0004), 1.036 (CI 1.022-1.049, p-value <0.0001) respectively. The maximum PT had the highest C-index for mortality (0.783), followed by the risk of average and minimal PT (0.780). In addition, each PT for cold wave watch and warning were -21.6°C, -25.6°C. The cold wave warning at a PT of -25.6°C indicated the risk of death as HR 1.874 (CI 1.806-1.944, p-value<0.0001) and c-index 0.807.

Conclusions: Exposure to lower PT during winter season could increase the risk of mortality among CKD patients.

TH-PO1017
Particulate Matter and Risk of CKD: A Global Exposure-Response Analysis
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Background: Associations between particulate matter (PM) air pollution and chronic kidney disease (CKD) have been increasingly reported, yet the exposure-response association is insufficiently estimated. This study aimed to combine all available associations of PM of two different sizes (PM2.5 and PM10) and CKD to generate exposure-response functions over concentrations experienced by populations in the globe.

Methods: Based on data from two prospective, population-based cohorts in the United Kingdom and China (UK biobank and China Health and Retirement Longitudinal Study), we estimated a shape-constrained health impact function to generate exposure-response functions between both PM2.5 and PM10 and CKD within each country. We then collected additional data on PM2.5 and PM10 associations from published literature and used the global exposure mortality model to construct exposure-response functions for CKD over a full range of global PM2.5 and PM10 concentrations.

Results: In the United Kingdom, the exposure-response functions for both PM2.5 and PM10 and CKD showed a linear association at lower concentrations and then a sublinear association at higher concentrations. In China, the risk of CKD also increased linearly with the increasing PM2.5 and PM10 at lower concentrations, but the associations for both air pollutants did not reach the statistical significance. After combining with all other published associations, the exposure-response function revealed a near linear exposure-response association is insufficiently estimated. This study aimed to combine all available associations of PM2.5 and PM10 and CKD to generate exposure-response functions over concentrations experienced by populations in the globe.

Conclusions: Both PM2.5 and PM10 exposure increased the risk of CKD, particularly at higher concentrations. Our findings highlight the urgency for air pollution management in areas with severe PM pollution to protect kidney health.

Figure 1 Exposure-response relationships between particulate matter and chronic kidney disease. (a) PM2.5, (b)PM10. Red line represents the log (relative risk) and grey shaded area represents its 95% confidence intervals.

TH-PO1018
Exposure to Organic Pollutants in Adults with CKD: A Pilot Study
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Background: In pediatric patients with chronic kidney disease (CKD), exposure to organic pollutants is associated with intra-renal oxidant stress and tubular injury; however, the impact on longitudinal estimated glomerular filtration rate (eGFR) or proteinuria is minimal. Less is known about the adverse effects of exposure to these chemicals in adults with CKD.

Methods: In this pilot study, we utilized HPLC-MS/MS to measure urinary concentrations of bisphenols, phthalates, organophosphate pesticides, polycyclic aromatic hydrocarbons, melanin, and cyanuric acid at years 1, 3, and 5 after enrollment in 40 adults with CKD from the Chronic Renal Insufficiency Cohort (CRIC) study. We assessed associations with clinical kidney and cardiovascular outcomes, cardiovascular function markers, markers of mineral and bone metabolism, and baseline and longitudinal trajectories of eGFR and proteinuria.

Results: Mean baseline eGFR and urinary protein:creatinine ratio were 33 ml/min/1.73 m2 and 0.58 mg/mg. Of 52 compounds assayed, 30 were detectable in ≥50% of participants. Urinary concentrations were comparable in CKD stage 3 to healthy subjects from contemporaneous National Health and Nutrition Examination Survey (NHANES) cohorts. Phthalates were the only class with a trend towards higher exposure in CKD patients. In a univariate analysis of time updated exposure to the individual compounds, there was a wide range of association with changes in kidney function. There was an inverse relationship between the level of exposure and eGFR slope for select compounds in the chemical classes including bisphenol F, mono-(3-carboxypropyl) phthalate, mono-benzyl phthalate, mono-[2-(carboxymethyl) hexyl] phthalate, and melanine. There were no significant associations between organic pollutants exposure and cardiovascular outcomes.

Conclusions: Simultaneous measurement of multiple organic pollutants in adults with CKD is feasible. Exposure levels are comparable to that in the healthy population. A subset of contaminants may be associated with more rapid deterioration in kidney function especially in the phthalate class. Our findings provide a useful reference for future studies of the impact of organic pollutant exposure in the CKD population.

Funding: NIDDK Support

TH-PO1019
The Increased Burden of CKD in Young Adults with Questionable Levels of Education and Health Literacy
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Introduction: This case highlights the harmful effects of unsatisfactory healthcare education that may contribute to poor patient insight in certain communities across the United States.

Case Description: This patient is a 29-year-old G2P2113 black female with a past medical history of uncontrolled hypertension (HTN), chronic kidney disease (CKD), and morbid obesity. Her health insurance is managed by Medicaid. At age 17, she had her 1st spontaneous vaginal delivery (SVD) in the emergency department (ED) with no prenatal care (PNC). Urinalysis (UA) during her 3rd trimester was significant for 3+ proteinuria. She was discharged with normal blood pressure (BP). The patient was noncompliant with post-partum follow-up. Her 2nd term SVD was at age 18 with limited PNC (2 ED visits were severe HTN and proteinuria was noted). BP at discharge was normal but she had proteinuria. In the next 5 years, she lost her 3rd pregnancy. At age 25, she presented for an annual gynecology (GYN) exam where she was diagnosed with HTN and given Nifedipine-C. ED visits documented that she had no primary care provider (PCP) and showed CKD stage 3A. A year later, she returned to the ED with uncontrolled HTN to confirm her 4th pregnancy. She had CKD stage 3B with 2+ proteinuria and a GFR of 45 ml/min. She was admitted to labor and delivery and had a preterm SVD. When seen post-partum, the patient was in denial about her diagnosis of CKD. She did not comply with a renal diet and refused anti-hypertensives. To date, she does not have a PCP or nephrologist although she was referred and told about the gravity of the diagnosis.

Discussion: Many factors contributed to the progression of this patient’s illness: individual, inter-personal, societal and institutional factors. This patient lacked insight into the consequences of proteinuria and HTN that progressed to CKD. She had 3 children without family support. Her early pregnancies interfered with her high school education. We believe that her low socio-economic status (SES) negatively impacted her access to a healthy diet. Her race, gender and SES predispose her to poorer health outcomes (HO). The effect of her education and health literacy highlights the impact of healthcare on young adults: It must be further studied to provide focused upstream interventions. An education program incorporating health literacy in high school may help prevent adverse HO.

TH-PO1020
First Detection of Microplastics Fragments in Human Urine and Kidney Tissues
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Background: Microplastics (MPs) are small plastic particles (< 5 mm) continuously released into the environment, contaminating natural habitats. Humans are constantly exposed to this kind of pollution: studies proved the presence of MPs in their lungs, liver, placenta, blood, and breast milk. To date, risks related to the uptake of plastic fragments are not well classified, but their correlation with emerging diseases of unknown etiology cannot be a priori excluded. Due to an epidemic of Chronic Kidney Disease (CKD) that steadily increases over the decades and emerging new diseases worldwide as CKD of uncertain etiology (CKDu), the presence of MPs in human urinary and kidney was investigated, to clarify their contribute to kidney damage.

Methods: MicroRaman spectroscopy is a technique of election for MPs detection in different matrices, thanks to its high sensitivity towards different polymers and its
High spatial resolution. Urine samples from healthy individuals and kidney tissues from nephrectomies were collected, digested in a KOH 10% solution, and filtered. Particles retained on the surface of the filters were analysed with a Renishaw System 2000 Raman imaging microscope (633 nm laser source). The collected spectra were investigated, to determine the nature of the detected particles.

Results: This study revealed the presence of different polymer fragments in both urines and kidneys (polyethylene, polystyrene, and styrene-nioprene gum, Figure 1), as well as pigments residuals (e.g., hematite, Cu-phthalocyanine (blue), and cerulean blue).

Conclusions: This study revealed for the first time the presence of microfragments of materials of anthropogenic origin (polymer, pigments, and inorganic particles) in human kidney and urine. The current investigation laid the foundations for further studies on the mechanisms of renal clearance and deposition of these particles, and on their possible role in promoting kidney damage.

Polymer fragments detected in the samples.

TH-PO1021
Association of Co-Exposure to Cadmium and Lead with CKD and Cardiovascular Disease (CVD) Comorbidity in US Adults: NHANES 2003-2018
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Background: Environmental exposure to cadmium (Cd) and lead (Pb) have been associated with cardiovascular disease (CVD) and chronic kidney disease (CKD). However, it is unknown whether they act independently or synergistically to increase the risk of CVD and CKD.

Methods: We included data from the National Health and Examination Survey (NHANES) 2003-2018 participants 20 years and older with urine Cd, blood Pb, serum creatinine, and urine albumin/creatinine measurements (n=12,851). Pregnant women and participants with CKD stage 5 were excluded. We used general linear regression to calculate adjusted ratios for CVD, CKD, or both CVD and CKD relative to none of these co-morbidities. We tested for interactions, both on multiplicative and additive scales, between the two metals with and without other covariates (gender, race/ethnicity, attained education, smoking, alcohol use, body mass index (BMI), and quadratic age).

Results: Both multiplicative and additive interaction effects were not statistically significant at the p-value of 0.05 level. It is possible that our sample size was too small to detect the effect. The final model included urine Cd, blood Pb, gender, race/ethnicity, education, smoking, alcohol use, BMI, and quadratic age. The Cd effect was statistically significantly associated with CKD+CVD (OR=1.19, 95% CI 1.03-1.38, p=0.02) after adjusting for the effect of Pb and other covariates, whereas Pb was significantly associated with CKD (OR=1.22, 95% CI 1.07-1.39, p=0.003) and CVD (OR=1.39, 95% CI 1.16-1.65, p=0.0004) after adjusting for the effect of Cd and other covariates.

Conclusions: These results suggest that the effects of Cd and Pb are independent each other and were pronounced in participants who had both Cd and CVD, supporting their role as risk factors even at exposures below the levels typically associated with occupational hazards. However, reverse causation because of underlying kidney damage cannot be ruled out.

Funding: Other U.S. Government Support

TH-PO1023
Nonlinear Associations Between Serum Manganese with CKD: Results from Two Nationwide Studies in the United States and China
Yang Li, Zhongshan Hospital Fudan University, Shanghai, China.

Background: This study aimed to better evaluate the association between serum manganese (Mn) and chronic kidney disease (CKD) by using data from the US National Health and Nutrition Examination Survey (NHANES) and the Chinese Longitudinal Healthy Longevity Study (CLHLS).

Methods: A total of 15411 and 451 participants were selected from NHANES and CLHLS, respectively. The primary diagnosis of CKD was defined as eGFR <60 mL/min/1.73m² and urinary albumin-creatinine-ratio (ACR) ≥30 mg/g. Multivariable regression and threshold analyses were used to assess the associations between Mn level and CKD.

Results: The prevalence of CKD was estimated to be 8.1% in NHANES and 47.7% in CLHLS. After adjusting for covariates, participants with the highest quartile (Q4) of Mn had an increased likelihood of CKD than those with Q1 (OR=0.67, 95% CI 0.55-0.82 in NHANES, and OR=0.31, 95% CI 0.16-0.58 in CLHLS). The non-linear associations revealed that the OR values of Cd were decreased with Mn before reaching the threshold (OR=0.64 per 1 µg/L increase of Mn in NHANES and 0.98 in CLHLS). The trends of protective effects then became flat with no longer significance. This association remained robust by using the continuity of eGFR and ACR as the outcome. Exploration analysis showed that superoxide dismutase (SOD) mediated 6.7% of the effect of Mn on eGFR.

Conclusions: The higher Mn concentration was significantly associated with a lower prevalence of CKD through different non-linear patterns.

Funding: Government Support - Non-U.S.
TH-PO1024

Comparison of National and Global Utilization Trends of Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2i) and Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA) in CKD

Iqra Cotransporter 2 Inhibitors (SGLT2i) and Glucagon-Like Peptide 1

Background: Despite the mounting evidence demonstrating the renal and cardiovascular benefits of SGLT2i and GLP-1RA in diabetic and non-diabetic CKD, there appears to be a degree of therapeutic inertia in using these agents in routine clinical practice. The assessment of the utilization rates and practice patterns of these drugs in patients with CKD remains scarce.

Methods: We used TriNetX Analytics, including Stony Brook Healthcare, US- networks, AMA (Asia), and EMEA (Middle east, Europe, Africa) collaborative networks. The estimated glomerular filtration rate (eGFR) mL/min/1.73 m² (CKD-EPI equation) lab values and the KDIGO eGFR classification were used to define the CKD stages. Individuals with age ≥ 18 years with ambulatory visits (CPT 1013626) from 2000 to 2022 were included. Patients with end-stage renal disease (CPT 1019051), acute kidney injury (ICD-10-CM N17), and kidney transplant recipients (CPT 50380) were excluded.

Results: SGLT2i and GLP-1RA use were highest among non-Hispanic white males (55% vs 55%) with Type 2 DM (86% vs 79%) and Hypertension (87% and 82%). The use rates of ACEi/ARB were noticeably low among all cohorts; 34% (280,0219) in the US, 28% (77,611), and 11% (38,599) in the AMA and EMEA groups. In the AMA group, the SGLT2i use rate was 4% (11,786), and the lowest prescription rate was noticed in the EMEA group at 0.40% (1681). The prevalence of GLP-1RA use was relatively higher in Stony Brook and US cohorts, 2.60% (4370) and 7% (230,925), as compared to AMA and EMEA groups at 0.50% (1763) and 0.12% (431), respectively.

Conclusions: Despite the high national and global burden of CKD, the prescription rates of ACEi/ARBs are alarmingly low. In contrast, a relatively high prevalence of potential nephrotoxins (i.e., NSAIDs and PPIs) use has been noticed. Overall national and global SGLT2i and GLP-1 RA utilization rates have increased over the last few years. However, the use rates of these agents are still significantly suboptimal among CKD patients.

TH-PO1025

Predictors and Outcomes of Discontinuation of Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2is) in CKD

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Background: SGLT2is decrease the progression of CKD and improve cardiovascular outcomes. However, their utilization remains low. Little is known about treatment discontinuation and its association with patient characteristics and outcomes.

Methods: We identified adults with CKD stages 3-4 receiving care at Veterans Affairs (VA) facilities from 2005-2022 from the VA Corporate Data Warehouse. Individuals who had an incident prescription for an SGLT2i were included, with the date of prescription considered the index date. The primary outcome was treatment discontinuation, defined as an interruption in SGLT2i prescription for at least 90 days. Cox proportional hazards regression identified factors associated with time to treatment discontinuation. Cox proportional hazards regression treating SGLT2i discontinuation as a time-varying covariate assessed the association of treatment discontinuation with time to all-cause death.

Results: Of 96,345 individuals who received an SGLT2i, 97% were male, 71% were White, 24% were Black, 71% were age ≥70, and 84% had CKD stage 3a. Discontinuation (at least once) occurred in 35,953 (37%) SGLT2i users over a median (IQR) of 1.01 (0.58, 1.74) years of follow up. Black race, female sex, younger age, and more advanced stage of CKD were associated with SGLT2i discontinuation (Figure). There were 8698 deaths. SGLT2i discontinuation, included as a time-varying covariate, was associated with all-cause death (HR 1.57 [95% CI 1.49, 1.66], P<0.0001) independent of age, sex, race, CKD stage, medical comorbidities, and concomitant medication use.

Conclusions: Discontinuation of SGLT2is is common and is associated with an increased risk of mortality. Further studies to understand the reasons for SGLT2i discontinuation (both temporary and permanent), and additional efforts to improve adherence are warranted.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

TH-PO1026

ACEi/Angiotensin Receptor Blocker (ARB) Prescribing Practices and Patient Experiences in CKD: A Qualitative Study of Clinicians and Patients

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Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) improve clinical outcomes but are underutilized in chronic kidney disease (CKD). Little is known about reasons for discontinuation and lack of reinitiating these medications, which contributes to underutilization.

Methods: We conducted in-depth interviews with a multi-profession sample of clinicians and patients with documented ACEi/ARB side effects in the past 6 months. Participants were recruited from 2 Veterans Affairs (VA) healthcare systems. We used inductive and deductive qualitative data analysis approaches to identify themes related to experiences with ACEi/ARB. Thematic analysis focused on prescribing decisions and practices, clinical guidelines, and perception of side effects. Data were analyzed as they amassed. Recruitment was stopped at the point of thematic saturation.

Results: Participants included 15 clinicians (primary care, geriatrics, cardiology, and endocrinology, 8 physicians, 3 NPs/PAs, 4 clinical pharmacists) and 10 patients (mean age 69 years, 40% men). Clinicians prescribe ACEi/ARB for blood pressure control and kidney protection, and many emphasized the role these agents play in diabetes management. Clinicians described providing comprehensive patient education about CKD and ACEi/ARB. However, patient interviews revealed knowledge gaps about CKD and the need for ACEi/ARB, with many patients unaware of their CKD diagnosis or why they had been prescribed ACEi/ARB. Clinicians’ drug management strategies and understanding of prescribing guidelines varied widely. They identified structural and patient-level barriers to prescribing, and many endorsed the development of a decision support tool to facilitate ACEi/ARB prescribing and management (Figure).

Conclusions: Our qualitative exploration of clinicians’ and patients’ experiences with ACEi/ARB will inform the development of a decision support tool to improve prescription rates of these agents for patients with CKD.

Funding: Veterans Affairs Support

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

Underline represents presenting author.
Methods: From data records/claims from the US (Optum’s de-identified Market Data) and Japan (Medical Data Vision) were analyzed. Pts with CKD Stage 3/4 and baseline RAASi use with an HK episode (ICD-10 code E87.5) during July 2019–Sept 2021 (US)/May 2020–Sept 2021 (Japan) were included. Based on RAASi prescriptions 3 months (mo) before vs after the HK episode, pts were categorized as down-titrated, discontinued, or maintained treatment. Risk of progression to ESKD (diagnosed CKD Stage 5/ESKD or dialysis initiation) within 6 mo in pts who down-titrated/discontinued vs maintained RAASi was assessed.

Results: In total, 11,873 (US) and 1427 (Japan) pts were included. Mean age was 71 (US) and 76 (Japan) years; 52% and 66%, respectively, were male. In the US, 7506 pts filled a RAASi prescription within 3 mo prior to index event and had ≥3 mo follow-up; of these, 33% discontinued and 6% down-titrated. Of the corresponding 1179 pts in Japan, 27% discontinued and 5% down-titrated. Risk of progression to ESKD was 70–74% higher in all pts who discontinued, and 60% higher in US pts who down-titrated vs maintained RAASi (Table).

Conclusions: HK-prompted RAASi therapy reduction is associated with increased risk of progression to ESKD, indicating a need for improved guideline adherence in managing HK to maintain RAAS therapy.

Funding: Commercial Support - AstraZeneca

Risk of progression to ESKD in patients with CKD Stage 3/4 who discontinued or down-titrated vs maintained RAASi therapy followed HK episode

<table>
<thead>
<tr>
<th>Country</th>
<th>RAAS status</th>
<th>N</th>
<th>Events</th>
<th>Adjusted HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Maintained</td>
<td>3096</td>
<td>67</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Down-titrated</td>
<td>104</td>
<td>15</td>
<td>1.13 (0.86–1.47)</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Discontinued</td>
<td>1945</td>
<td>55</td>
<td>1.22 (1.07–1.40)</td>
<td>0.003</td>
</tr>
<tr>
<td>Japan</td>
<td>Maintained</td>
<td>439</td>
<td>5</td>
<td>1.00 (reference)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Down-titrated</td>
<td>71</td>
<td>10</td>
<td>1.52 (0.93–2.47)</td>
<td>0.113</td>
</tr>
<tr>
<td></td>
<td>Discontinued</td>
<td>323</td>
<td>26</td>
<td>1.58 (1.01–2.45)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

* Concomitant use of RAASi was included in the Cox regression analysis due to the low patient numbers.

**CI, confidence interval; ESKD, end-stage kidney disease; HK, hyperkalemia; HR, hazard ratio; RAAS, renin-angiotensin-aldosterone system inhibitors; US, United States.

Background: Despite the existence of effective antihypertensive drugs, blood pressure (BP) remains off-target in a large number of CKD patients. We aimed to assess patient- and provider-related factors associated with changes in antihypertensive drug prescription in CKD.

Methods: We included 2,755 patients with CKD stages 3–4 and hypertension, under nephrology care, from the French CKD-REIN cohort study. We collected all drug prescriptions over 5 years and classified antihypertensive drugs in 14 mutually exclusive classes. We estimated cause-specific hazard ratios (HR) of add-on and withdrawal of antihypertensive drugs associated with patient- and provider-related factors by using multivariable models, to account for clustering at the nephrologist level.

Results: At baseline, 81% of the patients (median age, 69; 66% men; mean eGFR 33 mL/min/1.73 m2) had BP ≥130/80 mmHg. Over a median 5-year follow-up (IQR 4.6–5.2), the rates of any antihypertensive drug class change, add-on, withdrawal, and switch were 50, 23, 25, and 4 per 100 person-years, respectively. In multivariable models, drug add-on hazard was higher for older patients (HR, 1.11; 95% confidence interval [CI], 1.04–1.18), for those with higher BMI (HR, 1.04 95% CI, 1.01–1.07), and poor medication adherence (HR, 1.39; 95% CI, 1.10–1.70). Drug withdrawal hazard was higher for patients with cardiovascular history (HR, 1.19 95% CI, 1.04–1.35), and those with shorter formal education (HR, 1.23; 95% CI, 1.02–1.45 for 9–11 years versus ≥12). The higher the number of nephrologist visits, the higher the add-on and withdrawal hazards (HR for 4 versus none, 1.50; 95% CI 1.14–1.86 and 1.57; 1.24–1.90, respectively). Associations with withdrawals and add-ons of specific antihypertensive drug classes and the number of other physicians’ visits differed according to their specialty.

Conclusions: Our findings highlight the dynamics of antihypertensive drug prescriptions in the search for BP control, with heterogeneity in practices among the physicians involved in the care of CKD patients.

Funding: Commercial Support - Fresenius Medical Care; GlaxoSmithKline; Lilly France; Otsuka Pharmaceutical; AstraZeneca; and Boehringer Ingelheim France, Vifor France;; Sanofi-Genzyme; Baxter and Merck Sharp & Dohme-Chibret; Amgen; multiple physicians involved in the care of CKD patients.

Association Between Hyperkalemia, CKD Progression, and All-Cause Mortality: The REVOLUTIONIZE II Study

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Background: The association of hyperkalemia (HK) with progression of chronic kidney disease (CKD) has not been well studied. This real-world study described and compared CKD progression and mortality among patients with HK and matched patients without HK.

Methods: Adults with stage 3b or 4 CKD with HK (defined as serum K≥5.5 mmol/L and a HK diagnosis) and matched patients without HK were identified from the Optum de-identified Market Data Clarity database (1/2016-8/2022). Index date was the first eligible HK diagnosis. Time to CKD progression (defined as stage 4 or 5 CKD, provision of dialysis, or kidney transplantation) and time to death were compared between cohorts using cause-specific Cox proportional hazard models reported as hazard ratios (HR) and 95% confidence intervals (CI). Subgroup analyses were conducted by CKD stage and renin-angiotensin-aldosterone system inhibitor (RAASi) use.

Results: 6,619 matched pairs were included in the overall sample. Mean age was 74.7 years, 51% were male, 76% were white, and 71% had stage 3b CKD at index date. Among all groups, patients with HK had statistically significantly higher rates of CKD progression (overall: HR 1.60 [95% CI 1.50, 1.71], p<0.001) (Figure 1). Patients with HK also had higher rates of all-cause mortality than patients without HK in the overall cohort (1.09 [1.02, 1.16], RAASi subgroup 1.14 [1.05, 1.23] and CKD stage 3b subgroup 1.11 [1.03, 1.20]) (all p<0.01).

Conclusions: Patients with HK have experienced significantly higher rates of CKD progression and all-cause mortality compared to patients without HK, with consistent findings irrespective of use/non-use of RAASi.

Funding: Commercial Support - AstraZeneca

Association Between Reduced RAASi Therapy and Progression to ESKD in Hyperkalemic CKD Patients

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Background: Renin-angiotensin-aldosterone system inhibitor (RAASi) therapy is renoprotective in patients (pts) with chronic kidney disease (CKD) but increases hyperkalemia (HK) risk. Despite recommendations to maintain RAASi using novel anti-HK treatment, RAASi therapy is often limited/withdrawn in pts with HK. This observational study aims to assess the risk of progression to end-stage kidney disease (ESKD) associated with HK-related RAASi reduction in CKD.

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

Underline represents presenting author.
TH-PO1030
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Background: Among patients with CKD, hyperkalemia has been independently associated with poorer outcomes. However, the prevalence, risk factors, and severity of hyperkalemia in the US by demographic groups, KDIGO risk categories, eGFR categories and levels of albuminuria have not been reported.

Methods: We used data of 101,316 participants from the National Health and Nutrition Examination Survey (NHANES) between 1999 to 2018. We calculated 20-year weights to account for the complex survey design and the oversampling of certain age and minority groups. We defined and examined hyperkalemia by different levels of elevated serum potassium > 5.0, >5.5, and >6 mmol/L. Univariate and multivariate regression analysis was performed to identify independent predictors for hyperkalemia. Each model was adjusted for age, gender, race/ethnicity, diastolic blood pressure, hypertension, diabetes, HbA1c, hemoglobin, triglyceride, and CVD history. In the model of eGFR as exposure, UACR was additionally adjusted and in the model of UACR as exposure, eGFR was additionally adjusted.

Results: In a nationally representative sample of US adults with CKD, the prevalence of mild hyperkalemia (K>5.0 mmol/L) was 2.46%, moderate hyperkalemia (K>5.5 mmol/L) was 0.43%, and severe hyperkalemia (K>6 mmol/L) was rare at 0.06% (Table). While mild hyperkalemia was common in patients with KDIGO very high-risk category (9.72%) and in eGFR <15 to 29 ml/min/1.73m2 (15.67%), severe hyperkalemia was rare at 0.54% and 1.45%, respectively. Both KDIGO risk and eGFR categories independently predicted mild and moderate hyperkalemia.

Conclusions: Mild hyperkalemia is relatively common in patients with advanced CKD, although not as high as previously reported in unweighted samples of CKD patients. Severe hyperkalemia is rare. The most important predictors of hyperkalemia are high and very high KDIGO risk categories as well as eGFR of <15-29 ml/min/1.73m2.

TH-PO1031
Instantaneous and Persistent Elevation of Serum Potassium and Progression of CKD
Jinwei Wang, Fang Wang, Ming-Hui Zhao. Peking University First Hospital, Beijing, China.

Background: The adverse effect of hyperkalemia on chronic kidney disease (CKD) progression has not been well studied.

Methods: The study population was recruited from outpatients of Peking University First Hospital for patients with CKD G1-4 between 2010 and 2020. Those with ≥2 measurements of serum potassium during the first year after recruitment (baseline period) were included in the analysis. Instantaneous hyperkalemia was defined as occurrence of serum potassium ≥5.0 mmol/L for once or lasting for < 3 months, while persistent hyperkalemia as repeated occurrence lasting for a 3 months. The initiation of kidney replacement therapy (KRT) was followed after baseline period until death, loss of follow-up or Dec. 31 of 2020. Cox proportional hazards regression model was used to estimate the association between exposure and outcome, while linear mixed effects model to estimate the slope of estimated glomerular filtration rate (eGFR) with interactions between time and hyperkalemia status indicating difference of slope. Two-sided P<0.05 was statistically significant.

Results: A total of 527 patients were included in the analysis, with mean age of 56±16 years and 54.7% of male. CKD stage 1, 2, 3 and 4 accounted for 3.6%, 12.0%, 55.4% and 29.0% of the patients. There were 331, 85 and 111 patients with no, instantaneous and persistent hyperkalemia, respectively. During a mean follow-up of 4.4±3.27 years, 61 events of KRT occurred. Hyperkalemia was associated with higher risk of KRT (Figure 1). After multivariable adjustment, both instantaneous hyperkalemia and persistent hyperkalemia were associated with increased risk of KRT (hazard ratio: 2.43 [95%CI: 1.14-5.18] and 2.86 [95%CI: 1.48-5.54], respectively) and higher rate of eGFR decline (-2.23 and -3.92 versus -1.97 ml/min/1.73m2/year).

Conclusions: Hyperkalemia, especially persistent status, was associated with higher risk of CKD progression among patients with CKD.

TH-PO1032
Performance of the European Kidney Function Consortium (EKFC) Creatinine-Based Equation in American Cohorts
Pierre Delanaye,1 Andrew D. Rule,2 Elke Schaeffner,3 Etienne Cavalier,1 Ulf Nyman,1 Jonas Björk,1 Hans Pottel,1 EKFC (European Kidney Function Consortium).1 Université de Liege. Liege, Belgium; 2Mayo Clinic Minnesota, Rochester, MN; 3Charité Universitätsmedizin Berlin, Berlin, Germany; 4Université de Liege, Liege, Belgium; 5Lunds Universitet, Lund, Sweden.

Background: The new creatinine-based European Kidney Function Consortium (EKFC) equation has been developed and validated in datasets of European subjects. This equation is based on rescaled creatinine, with the rescaling factor (Q-value) which is the median normal value of serum creatinine in a given population. The EKFC equation performed well across the whole age spectrum. However, the validation was limited in Black and non-Black Americans.

Methods: Cross-sectional analysis with separate pooled datasets for validation from 9 US research and clinical studies with measured GFR, age, sex, and self-reported race available. Two strategies were considered with population specific Q-values in Black and non-Black Americans.

Results: In the whole adult population (n=12,854), the EKFC CRE equation showed no statistical bias (0.14 [95%CI [-0.07;0.35] ml/min/1.73m2), and the statistical bias of the EKFC CRE (0.74 [0.51;0.94] ml/min/1.73m2) was closer to zero than the CKD-EPI CRE equation (1.22 [0.99;1.47]) ml/min/1.73m2). The percentage of estimated GFR within

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30% of measured GFR was similar for CKD-EPI2021 (79.2% [78.5%–79.9%]) and EKFC (80.1% [79.4%–80.7%]) but improved with the EKFC equation (81.1% [80.5%–81.8%]).

Conclusions: The EKFC-equation can be used in the USA to estimate GFR incorporating either self-reported race or unknown race at the patient’s discretion per hospital registration records. The performance of the EKFC equation is as at least good as the CKD-EPI2019 equation.

TH-PO1033
New Argentine Equation to Estimate the Glomerular Filtration Rate
Peluén Fernández,1,2 Maria Laura Nores,1 Pablo R. Luján,1 Sofia Naser,1 Javier De Arteaga,1,2 Jorge de la Fuente,1,2 Walter Douthat,1,2 Carlos R. Chirichelu,1 Hospital Privado Centro Medico de Cordoba, Cordoba, Argentina;1 Instituto Universitario de Ciencias Biomedicas de Cordoba, Cordoba, Argentina;1 Universidad Nacional de Cordoba, Cordoba, Argentina.

Background: Latin Americans are poorly represented in the current glomerular filtration rate equations (eGFR), so their predictions are difficult to extrapolate in our population. Objective: to develop a new equation to estimate GFR based on data from Argentina and compare its performance with those currently available.

Methods: Cross-sectional study. We included all adults whose GFR was measured with urinary clearance of iothalamate (mGFR) between 2007 and 2017 (development sample–DS–, n=583). The chosen equation was based on a quasi-likelihood model with identity variance function and logarithmic link to predict mGFR from the square root of creatinine, age, sex, monoren, albumin and the logarithm of urea. Later, an independent sample was added between 2018 and 2019 (temporary validation sample–TVS–, n=78).

Results: There were no differences in the baseline characteristics in both samples and they presented a wide range in the mGFR (1.9–186.6 ml/min/1.73 m²). Within the previous equations, CKD-EPI (2009 and 2021) obtained the best performance (comparator). In the DS, Argentine Equation (AE) presented a lower RMSE, higher P15, bias median closer to zero, and a higher %CC compared to CKD-EPI in its two versions. In addition, it presented a median bias closer to 0 and a higher P15 compared to CKD-EPI 2021.

Conclusions: AE presented a better global performance to estimate GFR in residents of Argentina compared to the currently available equations.
The Impact of Muscle Mass on eGFR Accuracy with Creatinine and Cystatin C

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Background: The use of creatinine (Cr) for estimating glomerular filtration rate (eGFR) is limited by non-GFR factors such as muscle mass, diet and drugs. Calculating lean tissue mass (LTM), a surrogate for muscle mass, or cystatin-c (Cys-c) – an alternative filtration marker unaffected by muscle mass or diet – may improve GFR estimation. We explored the relationship between LTM and eGFR accuracy using Cr and/or Cys-c, compared to measured GFR (mGFR) at multiple timepoints.

Methods: Participants with CKD were recruited. Demographics (age, sex, ethnicity) and weight, 0-6 and 12-month weight (kg), body mass index (BMI), waist circumference (WC), and 0, 6- and 12-month weight (kg), LTM (kg), mGFR, Cr and Cys-c were recorded. eGFR was calculated using the Modification of Diet for Renal Disease (MDRD), European Kidney Function Consortium (EKF), CKD Epidemiology Collaboration (CKD-EPI) 2009, 2012 and 2021 equations for Cr, Cys-c and combined Cr-Cys-c.

Results: Of 41 participants, 28 (68.3%) were male and mean age was 53.2 ± 14.1 yrs. Baseline median (IQR) weight, LTM and mGFR were 85.5kg (71.2, 104.4), 44.3kg (36.5, 53.6) and 35 mL/min/1.73m² (23.0, 46.0) respectively. Baseline LTM (kg) was associated with higher values of nMFR-eGFR beta-coefficients for all Cr-based equations (p<0.001). LTM as percentage of BMI was weakly associated with CKD-EPI 2021 Cr equation (0.66; 95% CI 0.01-1.31; p<0.05). Cys-c eGFR equations compared with mGFR showed no significant associations with LTM. At 12 months, there was also a significant relationship between mGFR-eGFR Cr-based beta-coefficients (figure 1).

Conclusions: LTM was associated with Cr-based eGFR’s relationship with mGFR. There was no significant association involving Cys-c based equations, providing further evidence of independence of muscle mass, making its use more appealing in specific cohorts (e.g. liver cirrhosis, malignancy). Analysis of a larger cohort may allow a factor to impact further eGFR improvement and equation accuracy.

Indicesing to Body Surface Area Diminishes GFR Estimation and Increases CKD Staging in Overweight and Obese Population

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Background: Estimated glomerular filtration rate (eGFR) is usually indexed to a standard body surface area (BSA) of 1.73m². This allows comparing values of individuals of different sizes but can potentially affect eGFR in individuals with extreme BSA. We aimed to evaluate the differences in eGFR with and without indexing for BSA in a cohort of ambulatory patients with different body mass index (BMI) and how indexing affects CKD classification.

Methods: 390 patients of a nephrological clinic were evaluated with ambulatory 24-hour creatinine clearance (CrCl) and their demographic and anthropometric data was registered in an anonymous database. Patients were divided in 3 groups according to BMI (18.24-9, 25-29.9, ≥30 kg/m²). GFR was estimated with MDRD-4, CKD-EPI 2009 and 2021 equations, with and without indexing to 1.73m². CKD classification was also performed with and without indexing eGFR.

Results: 224 of 390 patients were men (57.4%). 103 (26.4%) had normal BMI (group 1), 193 (49.5%) were overweight (group 2) and 94 (24.1%) were obese (group 3). The difference between non-indexed and indexed CrCl was +2.2 mL/min, -2.9 mL/min – y 9.3 mL/min in groups 1, 2 and 3, respectively. Using MDRD-4, CKD-EPI 2009 and 2021 equations, the differences were +2.0, -2.1 and -2.2, in group 1; +2.2, +2.3 and +2.5 in group 2; and +7.3, 7.6 and +8.0 mL/min in group 3. Non-indexed eGFR was significantly higher in obese patients (p<0.001). Classification of CKD was significantly affected by removing indexing using CKD-EPI 2004 indexation, with almost 20% of the patients changing stage of CKD (17.5% group 1, 18.7% group 2 and 12.8% group 3). Diagnosis of GFR <60 mL/min was more frequent when GFR estimation was indexed in overweight and obese patients (15% and 13.3% more, respectively). Conversely, removing indexing reclassifies 11.7% of patients with normal BMI into GFR<60 mL/min.

Conclusions: Indexing to standard BSA lowers eGFR in overweight and obese patients, leading to a higher prevalence of < 60 mL/min CKD diagnosis.

Potential Value of Near Real-Time Transdermal GFR Measurement: Estimated GFR Results by CKD-EPI Serum Creatinine Misclassifies CKD Stage in One of Three Adults

Stuart Goldstein, 1,2 Richard B. Dorshow. 1 Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2MediBeacon, St.Louis, MO.

Background: Currently, chronic kidney disease is most often staged using the serum creatinine-based CKD-EPI equation to estimate GFR (eGFR). Serum creatinine is confounded by several well-known factors including chronic inflammation, muscle mass, medications, tubular Scr secretion and hydration status. Available measured GFR methods are challenged by need for multiple blood draws, radiological equipment and time or prolonged urine collections which are unreliable. We have previously shown our novel GFR assessment (nGFR) with novel fluorescent tracer agent, relmarkapir (also known as MB-102 in the literature), demonstrates outstanding correlation with iohexol measured GFR in Phase I and II studies (n=120 patients, r²=0.99). We have also previously shown transdermal MB-102 GFR assessment (iGFR) shows outstanding correlation with iohexol measured GFR within 90-120 minutes at the bedside. We assessed the agreement between nGFR and eGFR in the 120 Phase I and II subjects.

Methods: This prospective study evaluated nGFR with the MediBeacon Inc system in 120 adult patients with CKD Stages 1-4. MB-102 distributes in body tissues over 90-
120 minutes and starts to be cleared solely by glomerular filtration. We compared the CKD Stage by KD-DI and nGFR using plasma measurements MB-102 over 8-12 hours.

**Results:** Data from all 120 subjects (64 female, median age 55.5 years, median BMI 29 kg/m²) were available for analysis. Reported patient race was White (69), Black (48), American Indian/Alaskan Native (2), Asian (1) and all 6 of the Fitzpatrick Skin Scales were represented. Figure 1 shows that nGFR and CKD-DI eGFR differed by at least one CKD Stage in 32% and at least CKD Stages 4% of the time. Over- and underestimation of CKD was evenly divided.

**Conclusions:** CKD-EPI eGFR misclassifies true GFR based CKD stage in more than 1/3 of patients. We have completed a Phase II study comparing nGFR to eGFR to demonstrate accurate near-real-time GFR assessment at the bedside.

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**TH-PO1039**

**Machine Learning and Multimetric MRI for Noninvasive Diagnosis of the Etiology of CKD**

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**Background:** Multimetric magnetic resonance imaging (MRI) has the potential to provide various types of biological information about the kidney. In this study, we aimed to diagnose the underlying etiology of chronic kidney disease (CKD) non-invasively by combining MRI images and machine learning.

**Methods:** T1-weighted images (water-weighted images using the Dixon method), T1 value maps, T2* value maps of blood oxygen level-dependent MRI, perfusion maps of arterial spin-labeling, fractional anisotropy value maps from diffusion tensor imaging, and apparent diffusion coefficient value maps from diffusion-weighted imaging were used. We calculated the cortical values and cortical-medullary gradients using a 12-layer concentric object method. We created a multiclass classifier using a support vector machine and features such as MRI measurement values, age, estimated glomerular filtration rate (eGFR) at the time of imaging, and hemoglobin value. K-fold cross-validation was used to evaluate classifier accuracy.

**Results:** A total of 197 patients (60.9 ± 14.9 years old, 65.0% male, 15.2% with diabetic kidney disease (DKD), 34.0% with chronic glomerulonephritis (CGN), 50.8% with nephrosclerosis (NS), and a mean eGFR of 42.3 ± 22.2 ml/min/1.73 m²) were included. After model optimization, we obtained a relatively good overall accuracy of 0.65, and area under the curve values of 0.72 for DKD, 0.76 for CGN, and 0.73 for NS on the receiver operating characteristic curve. There were some estimation errors, particularly in cases diagnosed with DKD by physicians, and accuracy of the etiology tended to be low. Among cases of DKD, there were also cases that showed imaging characteristics similar to those of NS or CGN, suggesting an overlap of pathologies.

**Conclusions:** Conventional and functional kidney MRI and machine learning/ augmented intelligence diagnosis have the potential to be useful noninvasive diagnostic tools, and further improvements in accuracy can be achieved by refining the features. We observed some cases diagnosed with DKD by nephrologists based on the clinical course and results of blood/urine test that showed MR imaging characteristics resembling those of NS or CGN. Kidney biopsy or renal MRI may be effective for accurate diagnosis and determination of an appropriate treatment plan.

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**TH-PO1040**

**Feasibility and Safety of Percutaneous Kidney Biopsy in Small Kidneys: Breaking the Paradigm**

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**Background:** Percutaneous kidney biopsy (PKB) is a vital diagnostic tool, there are absolute and relative contraindications. Kidney size considered a relative contraindication due to poor accessibility and risk of complications, therefore, there is no consensus regarding the best approach in this setting.

**Methods:** Retrospective cross sectional at the Interventional Nephrology Department of the Instituto Nacional de Cardiologia Ignacio Chavez. Patients older than 16 years old who had kidney length of a 8 cm and underwent a PKB of native kidneys from July 2019 to December 2022 were included. Sampling was performed in real time guided by ultrasound. For the comparative analysis, the Chi-square or Fisher’s exact test were used for qualitative variables, and the T-student or Mann-Whitney U test for quantitative variables, according to their distribution.

**Results:** 25 patients were included, 19 women and 6 men. The mean age was 42.3 ± 18.04. The mean kidney length was 7.56 ± 0.33 and the mean width was 4.2 cm. All patients received only one puncture, with an average of 12 glomeruli. The mean serum creatinine was 1.94 mg/dL. Minor complications occurred in 5 patients, perirenal hematoma 3, hematoma in 1, and hematoma plus hematuria in 1 patient. Histological examination showed FSGS in 36% of cases, lupus nephritis in 20%, other glomerular diseases in 16%, crescentic glomerulonephritis in 16%, and tubulointerstitial nephritis in 12%. Management was modified in 64% of cases. A bivariate analysis was performed for complications versus without complications based on clinical and ultrasound characteristics, where statistical significance was found for complications with pre-biopsy DBP of 89 ± 5.80 mmHg (p < 0.001).

**Conclusions:** PKB in small kidneys is a feasible and safe procedure when properly planned, providing an adequate sample in all cases, with an insignificant number of minor complications, and that is clinically relevant.

**Funding:** Government Support - Non-U.S.
Exploring the Spectrum of Retroperitoneal Fibrosis
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Background: Retroperitoneal fibrosis (RF) is a rare disease characterized by fibroinflammatory tissue surrounding the aorta, renal arteries, and iliac arteries. Due to the nonspecific nature of its clinical presentation, diagnosis is challenging and often delayed. This study aims to systematically analyze the clinical characteristics, treatment approaches, and renal outcomes in a diverse cohort of RF patients.

Methods: Electronic Health Records of patients who underwent evaluation for RF between 01/2015 to 09/2022 at Johns Hopkins Hospital were reviewed to collect data on demographics, clinical information, laboratory findings, imaging results, histopathology, and outcomes. Follow-up was from the first nephrology visit until end of study or last follow-up.

Results: 43 patients underwent evaluation for RF. The most common lesion was idiopathic RF (18 patients, 42%), followed by valvular or ischemic heart disease, and coagulopathy. However, when all clinical and laboratory criteria were applied, patients with classical idiopathic RF were identified. The mean age was 64 years (range: 14-82 years). The most common symptom was flank pain, followed by dysuria and hematuria. On imaging, the most common finding was a soft-tissue mass surrounding the aorta and renal arteries. Histopathologically, the presence of dense fibrosis with lymphocytic infiltrate was observed.

Conclusions: This study provides valuable insights into the diagnosis, management, and outcomes of patients with RF. Our results underscore the importance of a systematic approach to evaluating and treating these patients, highlighting the need for further research to improve diagnostic accuracy and therapeutic outcomes.

Bilateral Multiple Renal Arteries as a Cause for Renal Infarction
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Introduction: Atrial fibration is the most common cause of renal infarction followed by valvular or ischemic heart disease, and coagulopathy. However, when all tests are unremarkable, renovascular abnormalities must be kept in the differential. We present one such case of bilateral double renal artery as a likely cause of renal infarction.

Case Description: Forty-six-year-old male with no known past medical history presents to the emergency department for sudden onset left lower quadrant pain radiating to left flank and abdomen, severe 10/10, constant and progressively worsening. Patient denied any dysuria, hematuria, or change in urine output. Patient is hemodynamically stable. The physical exam elicited left sided flank tenderness, left testicular tenderness without swelling or evidence of varicoceal veins. Lab results showed elevated white blood cell count of 16,500 with left shift and CRP. The echocardiography normal sinus rhythm normal ejection fraction. 3D coronary CT revealed normal coronary arteries.

Discussion: This case presentation highlights the importance of considering renovascular abnormalities in the differential diagnosis of renal infarction. Early recognition and appropriate imaging studies are essential to make an accurate diagnosis and initiate timely treatment.

Case Presentation: A 46-year-old male presented with acute onset of left flank and lower abdominal pain of 24 hours duration. He had no history of atrial fibrillation or recent surgery. On examination, his vital signs were within normal limits. Abdominal examination revealed tenderness over the left upper quadrant. Initial laboratory investigations showed a white blood cell count of 16,500 with left shift and C-reactive protein of 20 mg/L. Echocardiography was normal.

Conclusions: Early recognition and appropriate imaging studies are essential to make an accurate diagnosis and initiate timely treatment. This case presentation highlights the importance of considering renovascular abnormalities in the differential diagnosis of renal infarction.
Methods: This was a cross-sectional analysis of the international, prospective, iCaReMe Global Registry (NCT03549754) which enrolled patients from February 2018 to December 2022. Patients were recruited from 21 countries across the six WHO regions, DDK and IBD were the most common etiologies. HTN, T2D, dyslipidemia, and HF were present in 80.2%, 72.1%, 44.1%, and 35.3% of patients, respectively. Mean UACR was 556.7 mg/g in patients with eGFR < 60 ml/min/1.73 m². The medications included ARB (26.5%), ACEi (11.0%); about 19.6% were on SGLT2i.

Results: Overall, 2977 adults with CKD (mean age 60.6 years, 54.6% male) were enrolled in 21 countries across the six WHO regions. The prevalence of KDOGO GFR G3-5 was 77.0% and albuminuria A2/A3 was 72.5%. The medications included ARB (26.5%) and ACEi (11.0%); about 19.6% were on SGLT2i.

Conclusions: The iCaReMe registry assesses the management and quality of care of patients with CKD, T2D, HTN, and/or HF. We present baseline cross-sectional descriptive analysis of the iCaReMe registry between February 2018 and December 2022.

Methods: Baseline cross sectional descriptive analysis of clinicoodemographic characteristics, cardiovascular conditions and treatment patterns in CKD patients enrolled from MEA region in the iCaReMe registry between February 2018 and December 2022.

Results: 1629 adults with CKD (mean±SD age: 59.7±14.5 years, 56.1% male) were enrolled from 8 MEA countries (Egypt, Ethiopia, Jordan, Kenya, Lebanon, South Africa, Tunisia, and United Arab Emirates). HTN (75.6%), T2D (54.8%) and HF (36.4%) were the most common comorbidities. UACR and eGFR were available in 31.7% and 79.1% of patients, respectively while 10.9% had both. The prevalence of KDOGO GFR G3-5 was 77.0% and albuminuria A2/A3 was 72.5%. The medications included ARB (26.5%) and ACEi (11.0%); about 19.6% were on SGLT2i. (Figure)

Conclusions: Most of the enrolled patients were at high/very high risk of CKD progression. Only one third had UACR testing. Less than one third received optimal guideline-directed medical therapy (GDMT). Our results highlight underutilization of UACR screening and suboptimal adherence to GDMT in patients with CKD in the MEA region.

Methods: A cross-sectional survey enrolled individuals with CKD in the US, UK, Germany and Mexico. HRQoL was assessed using the EQ-5D-5L instrument, scoring problems in five domains – anxiety/depression, mobility, pain, self-care, and usual activities. EQ-5D index scores were estimated by the inclusion of local tariffs. Scores were compared against a general population cohort, matched in sample size and key demographic characteristics (e.g. sex, age).

Results: Patients were enrolled from the US (n=199), UK (n=212), Germany (n=201) and Mexico (n=204). Inclusion criteria included patients with CKD stages 1-5 and those receiving dialysis. Of patients enrolled, a proportion were dialysis dependent (DD) in the US (32.2%), UK (54.8%), Germany (42.3%) and Mexico (56.9%). Across all countries, patients received haemodialysis more commonly than peritoneal dialysis and the majority were on treatment for less than five years. Patients with CKD had a 28% reduction in mean EQ-5D-5L scores than non-dialysis dependent (NDD) patients (0.66 [0.21] vs 0.77 [0.07]; p ≤ 0.001). Patients in Mexico and the UK receiving dialysis had lower median mean SD EQ-5D-5L scores than non-dialysis dependent (NDD) patients (0.66 [0.21] vs 0.60 [0.25]; p = 0.03). There was no difference in HRQoL between DD and NDD patients in the US and Germany.

Conclusions: This survey provides evidence across multiple countries on the HRQoL decrement associated with CKD. Evidence based policy interventions should be aimed towards slowing CKD progression to improve patient quality of life.

Methods: Clinical Characteristics and Treatment Pattern in Patients with CKD: Real-World Insights from iCaReMe Registry-Middle East and Africa (MEA) Cohort

Background: Chronic kidney disease (CKD) has a substantial burden on patients' health-related quality of life (HRQoL). The aim of this study was to quantitatively determine the effect of CKD on patient HRQoL from early disease to kidney failure in a multinational setting.

Methods: A cross-sectional survey enrolled individuals with CKD in the US, UK, Germany and Mexico. HRQoL was assessed using the EQ-5D-5L instrument, scoring problems in five domains – anxiety/depression, mobility, pain, self-care, and usual activities. EQ-5D index scores were estimated by the inclusion of local tariffs. Scores were compared against a general population cohort, matched in sample size and key demographic characteristics (e.g. sex, age).

Results: Patients were enrolled from the US (n=199), UK (n=212), Germany (n=201) and Mexico (n=204). Inclusion criteria included patients with CKD stages 1-5 and those receiving dialysis. Of patients enrolled, a proportion were dialysis dependent (DD) in the US (32.2%), UK (54.8%), Germany (42.3%) and Mexico (56.9%). Across all countries, patients received haemodialysis more commonly than peritoneal dialysis and the majority were on treatment for less than five years. Patients with CKD had a 28% reduction in mean EQ-5D-5L scores than non-dialysis dependent (NDD) patients (0.66 [0.21] vs 0.77 [0.07]; p ≤ 0.001). Patients in Mexico and the UK receiving dialysis had lower median mean SD EQ-5D-5L scores than non-dialysis dependent (NDD) patients (0.66 [0.21] vs 0.60 [0.25]; p = 0.03). There was no difference in HRQoL between DD and NDD patients in the US and Germany.

Conclusions: This survey provides evidence across multiple countries on the HRQoL decrement associated with CKD. Evidence based policy interventions should be aimed towards slowing CKD progression to improve patient quality of life.

Methods: Clinical Characteristics and Treatment Pattern in Patients with CKD: Real-World Insights from iCaReMe Registry-Middle East and Africa (MEA) Cohort

Background: The global burden of CKD has witnessed a nearly 30% rise in past 30 years with increasing prevalence of hypertension (HTN) and type 2 diabetes (T2D). The MEA region shares disproportionate burden of CKD with paucity of data on patients’ characteristics and management. The iCaReMe Global Registry (NCT03549754 multinational, prospective, observational study) aims to generate real world data on characteristics, management patterns, and outcomes in patients with CKD, T2D, HTN, or HF.
Aversive Response Against High Salt Taste Is Disturbed in CKD Patients

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Background: Reducing salt intake is a vital lifestyle modification in the management of hypertension. Initiatives aimed at reducing salt intake are based on the premise that we prefer salt, but we exhibit an aversive response against high salt taste. It is postulated that salt intake behavior is influenced by the balance between attraction to low salt taste and aversion to high salt taste. However, aversion to high salt has not been quantitatively investigated in both healthy individuals and CKD patients.

Methods: As a pilot study, we performed a salt taste test on 125 healthy volunteers, wherein we devised nine different concentrations of NaCl (ranging from 0.3% to 20%). The participants placed a filter paper containing each solution on their tongues, and we assessed the recognition threshold as a parameter of taste accuracy, and “minimum aversion level” where the initial dislike sensation emerged. Based on the results of the pilot study, a definition of “lack of salt taste aversion” was determined, and the same test was conducted on 70 CKD patients.

Results: In the pilot taste test conducted on 125 healthy subjects, the number of subjects exhibiting an aversive reaction increased with higher salt concentrations. The threshold for normal taste perception was arbitrarily defined as 10% NaCl, with approximately 20% NaCl, suggesting that taste perception is significantly impaired in CKD patients. Age and the use of dentures were factors associated with lower taste perception thresholds in 20% NaCl, suggesting that taste perception is significantly impaired in CKD patients. A high proportion (84%) of CKD patients exhibited decreased aversive reactions to high salt concentrations.

Conclusions: This study confirmed the anticipated aversive response to high salt taste in humans and demonstrated its attenuation in CKD patients, implying that CKD patients have reduced resistance to high salt intake. When implementing salt reduction strategies in clinical practice, it is crucial to pay attention to the decrease in aversive response to high salt taste as well as the increase in salt preference.

Funding: Commercial Support - House Foods Group Inc.
Results: Treatment effects on the acute and chronic slopes jointly predicted treatment effects on each TTE endpoint with high accuracy (all trial-level R^2 ≥ 0.91). After accounting for the treatment effect on the chronic slope, a 1 ml/min/1.73m^2 greater negative acute effect led to a positive shift in the HR (against the treatment) by 15.4%, 11.4%, and 5.7%, respectively, for TTE endpoints based on 30% GFR decline, SCR doubling, and KFRT and GFR ≤ 15 ml/min/1.73m^2, showing that the role of the acute slope substantially attenuated for TTE endpoints based on larger GFR decline.

Conclusions: Acute effects have a small but measurable impact on KFRT or GFR decline to less than 15 ml/min/1.73m^2 after accounting for the chronic slope. However, relative to their small impact on progression to kidney failure, the role of the acute effect is moderately overstated by the established CE based on SCR doubling, and more severely by TTE endpoints based on 30% or 40% GFR decline.

Funding: Private Foundation Support

Meta-Regressions Relating Treatment Effects on Time-to-Event Endpoints to Treatment Effects on the Acute and Chronic Slopes

Results: Across the 66 RTCs, the multivariable model showed that optimally weighting the acute and chronic slopes accurately predicted treatment effects on the CE, with a trial-level R^2 (95% Bayesian credible interval) of 0.95 (0.78, 1.00). For a fixed treatment effect on the chronic slope, each 1 ml/min/1.73m^2 greater acute GFR decline for the treatment vs. the control increased the HR for the CE by 11.3%, in the direction against the treatment. For a fixed acute effect, each 0.75 ml/min/1.73m/year greater treatment effect on the chronic slope reduced the HR for the CE by 22.8%, in favor of the treatment. The Figure shows the model’s decomposition of the estimated treatment effects on the CE into separate components due to the acute and chronic slopes for each RTC.

Conclusions: Treatment effects on both the acute and chronic slopes are strong, independent determinants of the treatment effect on the CE. Optimal weighting of the acute and chronic slopes accurately predicts treatment effects on the CE.

Funding: Private Foundation Support

**TH-POI1054**
Association Between Initial Dip and Long-Term Prognosis After Dapagliflozin Administration in Patients with CKD

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Background: Renoprotective effects of dapagliflozin (sodium glucose cotransporter 2 inhibitor) have been reported in several randomized controlled trials. The main mechanism considered is correction of hyperfiltration, which can be observed as an acute decline in eGFR referred to as “initial dip”. While association between initial dip and long-term renal prognosis has been reported, no consistent conclusions have been reached. We aimed to investigate this relationship in real-world clinical practice.

Methods: We performed a retrospective observational cohort study of patients at Yokohama City University Medical Center in Japan. Patients administered to dapagliflozin between May 2014 thru December 2022 were included. Excluding those with eGFR over 90 or less than 15ml/min/1.73m^2 at baseline, history of kidney transplant, dialysis, or cancer, and those with dosage changes of dapagliflozin, 146 patients had complete data at baseline, 4 weeks, and 12 months, and were applicable for this study. We defined initial dip as eGFR decline from baseline to 4 weeks. Chronic change, which reflect long-term renal prognosis, was defined as eGFR decline from 4 weeks to 12 months. The association between initial dip and chronic change was examined using linear regression models. Also, eGFR changes between a year before and after starting dapagliflozin were compared for those whose data were available.

Results: Absolute eGFR changes before and after starting dapagliflozin were -4.8±6.6 and -1.5±3.9 ml/min/1.73m^2 per year, respectively. (p<0.05) Long term renoprotective effect of dapagliflozin was observed regardless of initial dip. Furthermore, Pearson’s correlation coefficient revealed that the degree of initial dip and chronic change were inversely correlated (r=-0.37, p<0.001). Multivariate regression analysis demonstrated initial dip was an independent determinant factor for chronic change. (p<0.001)

Conclusions: The real-world clinical data showed that the greater the initial dip, significantly smaller the subsequent decline in eGFR. Renoprotective effect of dapagliflozin was observed regardless of initial dip.

**TH-POI1055**
Caffeine Effects on eGFR Dip in Patients Who Started SGLT2 Inhibitors

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have widespread effects including antihyperglycemia, renoprotection, and cardioprotection. Renoprotection is thought to be mainly mediated by a reduction in glomerular filtration rate (GFR) via tubuloglomerular feedback (TGF), which is referred to as the GFR “dip”. Adenosine plays an important role in signal transmission in the TGF mechanism and caffeine is a nonselective adenosine receptor antagonist. We hypothesized that patients with high caffeine intake have reduced eGFR dip after starting SGLT2i compared to patients with no or small caffeine intake.

Methods: This is a retrospective cohort study conducted at Saint Louis University. Caffeine consumption was collected via survey. Retrospective chart review was performed to trend creatinine before and 1-2 months after the initiation of SGLT2i. Inclusion criteria included adult patients receiving SGLT2i regardless of indication (diabetes mellitus, heart failure, or chronic kidney disease) and eGFR ≥ 50 ml/min/1.73m^2 at the time of initiation. Student’s t test was used to analyze differences of eGFR change (% change from the baseline) between patients with high caffeine intake and low caffeine intake. Pearson’s correlation coefficient was used to analyze correlation between caffeine intake and eGFR change.

Results: The survey was collected from 56 patients (N=13 on Dapagliflozin, N=22 on Empagliflozin, and N=1 on Eragliitol). The mean age of the study cohort was 62.9±11.1 years old and 58.3% were female. The median eGFR at SGLT2i initiation was 50 ml/min/1.73 m^2. Top quartile caffeine takers (≥400 mg/day, N=9) had significantly lower % eGFR dip compared to the low caffeine takers (<400mg/day, N=27); 0.46±12.51 vs 11.83±14.45, respectively (p<0.05). In a subgroup analysis of those who were not on loop diuretics, which could affect TGF, % eGFR dip was inversely correlated with the caffeine intake (N=24, r=-0.55, p<0.01).

Conclusions: Our study shows that caffeine consumed at high levels (above 400mg daily) can mitigate the eGFR dip after SGLT2i initiation. Further study is needed to assess its long-term effects on SGLT2i’s renoprotective property.

Funding: Private Foundation Support
Clinical Characteristics and Predictors of Glomerular Filtration Rate Decline in Patients with CKD of Unknown Etiology (CKDu) in Agricultural Communities of Odisha, a CKDu Hotspot

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Background: Chronic Kidney Disease of Unknown Etiology (CKDu) is characterized by the absence of traditional risk factors for CKD such as diabetes mellitus, hypertension, and glomerulonephritis. Odisha in India has been identified as a potential 'hotspot' for CKDu.

Methods: Patients aged 18–60 years who met clinical criteria for CKDu from 1st April 2021 to 31st April 2023 were enrolled in the study. A kidney biopsy was performed according to the study’s protocol. The clinical characteristics and predictors for glomerular filtration rate (eGFR) decline.

Results: A total of 120 patients were enrolled in the study. The mean age of participants was 39.78 ± 8.85 years, with 85% males. About 96.3% of cases belonged to rural areas, 90% belonged to lower socioeconomic classes, and only 3% had a family history of diseases. 75.4% were farmers, exposure to agrochemicals was reported in 20.4% of cases; and 25.7% of patients had no formal education. 40% and 25% of the participants were of CKD stage 3 and stage 4 respectively. The mean hemoglobin level and uric acid levels were 10.3 ± 0.4 and 5.9 ± 0.3 respectively. A kidney biopsy was performed on 20 patients. Histopathology was predominantly interstitial fibrosis with mononuclear infiltration, tubular atrophy, and global glomerulosclerosis. After adjustments for confounding factors, predictors of GFR decline were found to be baseline GFR, lower serum albumin, lower haemoglobin, and male sex.

Conclusions: There is a need for a multipronged approach to address the CKDu epidemic, particularly in CKDu hotspots. The need to take steps to increase awareness, prevention, appropriate screening, and surveillance is imperative.

Mediators of the Kidney Protective Effects of Dapagliflozin in Patients with CKD with or Without Type 2 Diabetes

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Background: The DAPA-CKD trial demonstrated that dapagliflozin attenuates progression of chronic kidney disease (CKD) in patients with and without type 2 diabetes. This post-hoc analysis assessed possible mediators of the observed kidney protective effect.

Methods: In DAPA-CKD, 4304 patients with an estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urine albumin-to-creatinine ratio (UACR) 200–3000 mg/g were randomized to receive dapagliflozin 10 mg or placebo. The primary outcome was a composite of sustained ≥50% eGFR decline, end-stage kidney disease, or kidney or cardiovascular death. We considered biomarkers that were significantly affected by dapagliflozin versus placebo over time, as assessed using mixed effect model for repeated measures: UACR, HbA1c, blood pressure (systolic [SBP] and diastolic [DBP]), serum sodium and potassium, and body weight. We calculated the proportion of the effect of dapagliflozin explained by the change in each biomarker by fitting a multivariable-adjusted, time-dependent, Cox model, adjusted for baseline age, sBP, and UACR. We estimated confidence intervals using 1000-iterations bootstrap. Analyses were repeated by type 2 diabetes status.

Results: Compared with placebo, dapagliflozin reduced UACR (29.3% [95%CI: 23.5–33.1]), SBP (2.9mmHg [2.3–3.6]), DBP (1.0mmHg [0.6–1.4]), HbA1c (0.08% [0.03–0.14]), serum potassium (0.035mg/dL [0.01–0.05]) and body weight (0.85kg [0.6–1.1]), and increased hematocrit (2.3% [2.1–2.5]) and serum sodium (0.14mEq/L [0.02–0.26]). The effect of dapagliflozin on the primary outcome was explained by changes in hematocrit (35.5% [95%CI: 24.3–69.0]), UACR (35.4% [23.0–58.2]), and SBP (4.9% [1.3–9.1]), but not through the other tested biomarkers. The proportion of dapagliflozin’s effect explained by change in hematocrit was 31.2% (20.0–70.3) in participants with type 2 diabetes, and 32.4% (14.3–76.5) in those without type 2 diabetes. The respective proportions explained by the change in UACR were 41.7% (26.1–75.9) and 16.6% (3.2–34.4).

Conclusions: The kidney protective effect of dapagliflozin in patients with CKD is associated with its effects on albuminuria and hematocrit.

Funding: Commercial Support - AstraZeneca

TK-PO1056

Associations Between Albuminuria and Clinical Outcomes in Patients with CKD with and Without Diabetes: New Insights from DAPA-CKD

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Background: Albuminuria is a strong determinant of kidney and cardiovascular (CV) risk in patients with chronic kidney disease (CKD) with and without type 2 diabetes (T2D). Albuminuria reduction may be an indicator of decreased risk. In the DAPA-CKD trial, dapagliflozin reduced the risk of kidney and CV events in patients with CKD with similar effects in those with and without T2D. We examined risk associations between baseline and early changes in albuminuria and kidney outcomes in patients with CKD with and without T2D.

Methods: In DAPA-CKD, 4304 patients with and without T2D with urinary albumin-to-creatinine ratio (UACR) 200–5000 mg/g and eGFR 25–75 mL/min/1.73m² were randomized to receive dapagliflozin 10 mg or placebo daily, on top of standard of care, and followed for a median 2.4 years. We assessed associations among baseline UACR, early change in UACR (baseline to Month 4), and the primary outcome (a 50% eGFR decline, end-stage kidney disease, or kidney death from a CV cause) using multivariable adjusted Cox regression analyses.

Results: Every doubling of baseline UACR was associated with a near doubling of risk: hazard ratio (HR) 1.89 (95% confidence interval [CI] 1.71–2.08) in patients with T2D and 1.84 (95% CI 1.54–2.20) in those without T2D. Dapagliflozin reduced UACR (placebo-adjusted) from baseline to Month 4 by 35.7% (95% CI 29.0–42.5) in participants with T2D (p < 0.001) (81.1%) in those with T2D, with a large between individual variation in both treatment groups. The HR for every 50% decline in UACR from baseline to Month 4 was 0.86 (95% CI 0.79–0.93) and 0.70 (95% CI 0.59–0.83) in participants with and without T2D, respectively.

Conclusions: In patients with CKD with and without T2D, higher baseline albuminuria was associated with a higher risk of progressive kidney disease or cardiovascular death, and early albuminuria reduction was associated with a decreased risk. Because dapagliflozin reduced clinical outcomes in patients with and without T2D but reduced albuminuria to a larger degree in those with T2D, these findings suggest that the clinical benefits gained via dapagliflozin’s albuminuria-reducing effects are more potent among patients with T2D.

Funding: Commercial Support - AstraZeneca

TK-PO1058

Inflammatory Cytokines and Adipokines in Obese Patients with and Without CKD

Sandeep Mahajan, Arunkumar Subbiah. All India Institute of Medical Sciences, New Delhi, India.

Background: Global epidemic of obesity & metabolic disorders are fuelling increasing cases of CKD worldwide. Besides having higher incidence of DM & hypertension, obesity is independent risk factor for CKD. Mechanisms involved are poorly studied, though obesity related inflammation mediated by shift in adipokine and cytokine production towards pro-inflammatory state is implicated. We in this case control study looked at important pro-inflammatory mediators (leptin, IL-6, TNF-α) and anti-inflammatory mediators (adiponectin, IL-10) in obese with & without CKD, non-obese CKD & healthy controls.

Methods: 50 consenting subjects in each group were studied. Besides detailed history, co-morbidity charting, BMI calculation; serum levels of HsCRP, adipokines (leptin & adiponectin) & cytokines (IL-6, TNF-α & IL-10) were assessed using commercially available ELISA kit.

Results: Table shows demographic, clinical & parameters of each group. Patient groups had similar representation of DM & were slightly older than controls. Obese subjects with & without CKD had higher HsCRP, leptin & IL-6 than controls & CKD patients, with obese patients with CKD showing maximum alterations. Adiponectin concentration was higher in patients with obesity alone but suppressed in patients with obesity & CKD.

Conclusions: Inflammation & pro-inflammatory stimuli as evidenced by high levels of HsCRP, IL-6 & leptin and low levels of adiponectin are the important drivers for obesity related complications like CKD. Larger, prospective studies are required to confirm the same.

Funding: Government Support - Non-U.S.
Further, to assess the association between FGF23 levels with respect to time-to-event adverse events of major interest, namely, major adverse kidney events (MAKE), and stage kidney disease (ESRD), ≥50% decline in eGFR, all-cause mortality, and cardiovascular (CVD) mortality, Cox proportional hazard models were used. Competing risk analysis was taken into account while fitting Cox models.

A total of 605 patients with mild to moderate CKD were included in this analysis. Mean age of the CKD patients of age was 48 years, and baseline mean eGFR was 45.8 mL/min/1.73m². Mean (SD) follow up duration of the study was 5.33 (2.37) years with median (IQR) baseline of intact FGF23 as 111 (78, 163) ng/mL. Baseline levels of INT-2 FGF23 were significantly and positively associated in the study period (p=0.02). Unadjusted and adjusted Cox regression models indicated that higher levels of FGF23 were significantly associated with greater risk of MAKE (1.34; 1.15-1.56), 50% eGFR decline (1.25; 1.06 - 1.49) and ESKD (1.35; 1.31-1.62) (table 1).

Results: Among young individuals with mild to moderate CKD, baseline levels of intact FGF-23 are independently associated with the adverse kidney outcomes of CKD.

Funding: Government Support - Non-U.S.

Table 1: Association of FGF23 with Outcomes in CKD patients

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Make</td>
<td>Sub-hazard ratio (95% CI)</td>
<td>Sub-hazard ratio (95% CI)</td>
</tr>
<tr>
<td>≥50% eGFR decline</td>
<td>1.34 (1.15-1.56)</td>
<td>1.15 (1.06 - 1.25)</td>
</tr>
<tr>
<td>End-stage kidney disease (ESKD)</td>
<td>1.35 (1.31-1.62)</td>
<td>1.30 (1.23-1.36)</td>
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<tr>
<td>All-cause mortality</td>
<td>1.35 (1.31-1.62)</td>
<td>1.30 (1.23-1.36)</td>
</tr>
<tr>
<td>CVD mortality</td>
<td>1.25 (1.06 - 1.49)</td>
<td>1.25 (1.06 - 1.49)</td>
</tr>
</tbody>
</table>

TH-PO1062

Association Between Plasma Uric Acid Levels and Mortality and Cardiovascular Outcomes According to Kidney Function Hae Sang Park,1 Ji Eun Kim,2 H Plus Yangji Hospital, Seoul, Republic of Korea; 1Korea University Guro Hospital, Seoul, Republic of Korea.

Background: Plasma uric acid levels rise with worsening renal function, but it is not known whether uric acid levels affect the risk of death and cardiovascular disease according to renal function.

Methods: We conducted a multicenter retrospective observational cohort study based data from the Observational Medical Outcomes Partnership Common Data Model. Adult non-dialysis patients with at least one measurement of serum uric acid levels during study period were screened, and the participants were classified according to their estimated glomerular filtration rate (eGFR) and eGFR < 60 ml/min/1.73m² (low eGFR). Primary outcome of this study was all-cause mortality. And secondary outcomes were the development of myocardial infarction requiring coronary intervention and heart failure.

Results: We included 240197, 84858, and 59044 participants from three centers. In multivariable Cox regression analysis, uric acid level showed J-shaped association with all-cause mortality risk in both high and low eGFR groups. In pooled analysis for three centers, pooled hazard ratios for mortality in uric acid levels > 10 mg/dL compared to uric acid levels 6-7mg/dL were 1.8 (1.36-2.39) and 2.0 (1.51-2.65) in low and high eGFR groups, respectively. The risk for myocardial infarction was neither associated with uric acid levels in low and high eGFR groups from all three centers. The risk for heart failure showed linear association with uric acid levels, especially in high eGFR groups, and this finding was consistent in three centers.

Conclusions: Plasma uric acid levels showed J-shaped association with mortality regardless of eGFR status, while it showed linear association with heart failure in high eGFR participants.
SPARC, urinary SPARC and eGFR could increase the AUC-ROC for kidney fibrosis from 0.86 to 0.90. The diagnostic performance of serum or urinary SPARC were consistent in the validation cohort. In vivo and in vitro kidney fibrosis models also confirmed the upregulation of SPARC expression.

**Conclusions:** Serum and urinary SPARC levels may be potential biomarkers for kidney fibrosis, which may be helpful for the noninvasive diagnosis of kidney fibrosis.

**Funding:** Private Foundation Support

**TH-PO1064**

**Serum Myostatin Is Independently Associated with Endothelial Dysfunction in Non-Dialysis CKD Stages 3 to 5**

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**Background:** Myostatin is known as a negative regulator of skeletal muscle growth and promotes protein breakdown and may have a role in obesity, insulin resistance, cardiovascular disease. However, its relationship with endothelial function in patients with chronic kidney disease (CKD) remains inconclusive. This study aimed to investigate the association between serum myostatin levels and endothelial function in patients with stages 3–5 CKD.

**Methods:** Fasting blood samples were obtained from 136 CKD patients. Serum myostatin levels were determined using the enzyme-linked immunosorbent assay. The endothelial function, demonstrated as a vascular reactivity index (VRI), was measured noninvasively through digital thermal monitoring test. The serum myostatin levels were determined using commercially available enzyme-linked immunosorbent assays. In this study, VRI < 1.0 was used as the poor vascular reactivity, 1.0 ≤ VRI < 2.0 was used as the intermediate vascular reactivity, and VRI ≥ 2.0 was used as the good vascular reactivity.

**Results:** 25 CKD patients (18.4%) were categorized as poor vascular reactivity (VRI < 1.0), 63 CKD patients (46.3%) were categorized as intermediate vascular reactivity (1.0 ≤ VRI < 2.0), and 48 CKD patients (35.3%) had good vascular reactivity. Older age (β = 0.026), higher serum blood urea nitrogen (p = 0.020), creatinine (p = 0.021), plasma myostatin-to-creatinine ratio (UPCR, p = 0.015), and higher serum myostatin level was associated, while lower estimated glomerular filtration rate (eGFR) was associated with poor vascular reactivity. After multivariable forward stepwise linear regression analysis noted that older age (β = −0.331, adjusted R² change = 0.081, p < 0.001), serum creatinine (β = −0.273, adjusted R² change = 0.070, p = 0.001) and log-transformed myostatin level (β = −0.256, adjusted R² change = 0.057, p = 0.002) were significantly and independently negatively associated with VRI values in patients with CKD.

**Conclusions:** Myostatin together with old age and serum creatinine is negatively associated with VRI values and is a potential endothelial function modulator and a valuable biomarker of endothelial dysfunction in patients with CKD.

**TH-PO1065**

**Lower Estimated Glomerular Filtration Rate Is Associated with Cognitive Decline and Longitudinal Structural Brain Changes over Six Years**

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**Background:** Chronic kidney disease (CKD) is characterized by albuminuria and/or reduced estimated glomerular filtration rate (eGFR). CKD is linked to cognitive deficits and structural alterations, such as brain atrophy. The mechanisms connecting decreased kidney function, cognitive impairment, and brain function are not yet fully understood. Here, we examined the correlation between eGFR, cognition, and longitudinal brain structure.

**Methods:** We analyzed a population-based sample of 15,897 participants (53.9 ± 7.5 years old, 49% women) from the CARTaGene cohort in Quebec, Canada. We conducted multivariate linear regressions to explore the relationship between baseline eGFR and cognitive performance. Vertex-based cortical surface analysis was done on the T1-weighted brain MRI scans acquired in 1367 participants six years after baseline to examine whether cortical thickness associated with baseline eGFR adjusting for age, sex, body mass index, vascular risk factors, and white matter lesion volume. Gene set enrichment analysis was done to identify the genetic features of regions where eGFR associated with thickness.

**Results:** Cognitive performance declined with decreasing eGFR after adjusting for age, sex, income, education, smoking, alcohol intake, vascular risk factors, body mass index, and psychopharmacologic medication use (P<0.001). Lower eGFR associated with cortical thinning in frontal and posterior regions and with increases in the temporal and cingulate areas (Figure 1). Brain regions exhibiting lower eGFR-associated thinning were enriched for mitochondrial gene expression, whereas regions with increased thickness were enriched for genes involved in protein-containing complex remodeling, with apolipoprotein E and angiotensinogen being key elements.

**Conclusions:** Baseline eGFR is associated with cognition and longitudinal brain structural changes in regions with specific gene expression characteristics.

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

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**TH-PO1066**

**Kynurenine Metabolism and Neurocognition in CKD: CRIC Study**

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**Background:** Kynurenine metabolites and chronic kidney disease (CKD) are independently linked with neurocognitive dysfunction. We examined the associations between the Tryptophan (TRP) and Kynurenine (KYN) metabolites with neuro-cognitive function in CKD patient in the Chronic Insufficiency Cohort (CRIC).

**Methods:** CRIC participants with data on TRP and KYN metabolites and cognitive tests were included in the analysis. TRP and KYN and its metabolites (kynurenic acid (KYN) and Quinolinic acid (QYN)) were measured at baseline using mass-spectrometry. The neurocognitive tests included Modified Mini Mental State Examination (MMSM), Trail Tests A and B, Buschke Selective Reminding, Category fluency and Boston Naming. Cognitive tests were measured at baseline and then every 2 years thereafter for 10 years. Linear regression and linear mixed models were used for analysis. Model was adjusted for demographics, co-morbidities and eGFR.

**Results:** Among 240 participants, mean age was 62±8 yrs and 66% had CKD stage 3. TRP levels were lower (p<0.001) whereas KYN, KYN and QYN levels were greater (p <0.001) for more advanced CKD stage. In fully adjusted regression model, lower TRP levels were associated with poor performance on the Boston, verbal, MMSE, recall and Trail-A and B tests. In contrast, higher QYN levels were associated with lower MMSE, recall and higher trail-A and trail-B score (Figure). These findings were similar in longitudinal analysis over mean follow-up of 10 years.

**Conclusions:** Our study indicates disturbed metabolism of the KYN pathway in CKD. Low levels of TRP and high QYN levels were related with worse neuro-cognitive function, independent of eGFR. Interventions to modulate the KYN pathway may improve cognition in CKD.
Investigate pancreatic response to incretin hormones in CKD. Secretion and glucose tolerance between CKD and controls.

1032 pM*120min greater GLP-1 (95% CI 74, 1989) and 19103 pm/ml*120min greater GIP tAUC were higher in CKD than controls with a mean of 3420 ± 17 ml/min per 1.73 m² compared to 89 ± 17 ml/min per 1.73 m² (eGFR<60 ml/min per 1.73 m²). We measured total area under the curve (tAUC) of plasma glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) during a 2-hour OGTT. We used linear regression adjusting for demographic, body composition, and lifestyle factors.

Results: Mean age of CKD patients was 64 ± 14 yrs with 51% females versus 61 ± 14 yrs with 44% females among controls. The mean eGFR in CKD participants was 38 ± 13 compared to 89 ± 17 ml/min per 1.73 m² in controls (Table 1). GLP-1 (AUC and GIP AUC were higher in CKD than controls with a mean of 3420 ± 1546 pm*120min (P=0.03), and 79400 ± 38670 versus 53994 ± 28191 pg/ml*120min (P=0.01), respectively (Figure 1). After adjustment, CKD was associated with estimated 1032 pm*120min greater GLP-1 (95% CI 74, 1989) and 19103 pm/ml*120min greater GIP (95% CI 4116, 34090) compared to control. There were no differences in insulin secretion and glucose tolerance between CKD and controls.

Conclusions: CKD is associated with increased incretin hormone levels during OGTT but no difference in insulin secretory response. Further studies are needed to investigate pancreatic response to incretin hormones in CKD.

Funding: NIDDK, Support

Table 1. Participant characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n=70)</th>
<th>CKD (n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>61 (24.4)</td>
<td>63.5 (15.3)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>47 (67)</td>
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<tr>
<td>Race (%)</td>
<td>33 (47)</td>
<td>51 (90)</td>
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<tr>
<td>Black (%)</td>
<td>41 (58)</td>
<td>11 (21)</td>
</tr>
<tr>
<td>Asian/Pacific Island (%)</td>
<td>1 (1)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82.4 (30.6)</td>
<td>88.1 (19.4)</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²)</td>
<td>88.9 (17.1)</td>
<td>72.6 (12.2)</td>
</tr>
</tbody>
</table>

Figure 1. Changes in plasma GLP-1 and GIP in response to OGTT comparing CKD and controls.

TH-PO1068

Choroidal and Retinal Thinning in CKD Are Modifiable with Treatment and Independently Associate with eGFR Decline

Tariq E. Farral, 1 Dan Pugh, 1 Fiona A. Chapman, 1 Peter J. Gallacher, 1, 2 Neeraj Dhaun, 1, 2 The University of Edinburgh Centre for Cardiovascular Science, Edinburgh, United Kingdom; 1Department of Renal Medicine, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom.

Background: Cardiovascular disease is the commonest complication of chronic kidney disease (CKD). As estimated glomerular filtration rate (eGFR) declines, cardiovascular risk increases. There is an unmet need for novel biomarkers that reliably track kidney injury, demonstrate treatment-response, and predict patient outcomes. We investigated the ability of retinal optical coherence tomography (OCT) to achieve these ends.

Methods: Patients with stable, pre-dialysis CKD (including those with a kidney transplant), patients with kidney failure undergoing kidney transplantation, living kidney donors, and healthy volunteers were recruited into a series of prospective, cross-sectional, and longitudinal studies. We used the SPECTRALIS OCT machine to examine retinal thickness, macular volume, and choroidal vascular layer thickness.

Results: Compared to healthy volunteers, macular volume was reduced in CKD patients (health vs. CKD: 8.73±0.36 mm³ vs. 8.44±0.44 mm³, p<0.001). Kidney transplant recipients also had a reduced macular volume compared to health of a similar magnitude to that seen in CKD patients. The choroid was thinner in CKD patients (health vs. CKD, macular locations I, II and III: 234±83mm vs. 197±83mm, 319±93mm vs. 274±93mm, 292±83mm vs. 262±84mm, p<0.01 for each). Conversely, patients with a kidney transplant had choroidal thickesses similar to healthy levels, suggesting reversal of thinning. In those with CKD, the degree of choroidal thinning related to increasing age (r= -0.25, p=0.008), falling eGFR (r= -0.30, p=0.001) and severity of kidney scarring (r=-0.60, p<0.001). Patients undergoing kidney transplantation (n=25) demonstrated rapid choroidal thickening (<10%) that was maintained at 1-year post-transplant. These patients also demonstrated increases in both retinal thickness and macular volume over this period. Conversely, kidney donors (n=22) demonstrated gradual choroidal thinning over 1-year but there were no changes in retinal thickness or macular volume. In patients with CKD (n=28), both retinal and choroidal thickness independently associated with eGFR decline over 2 years.

Conclusions: These observations highlight the potential for retinal OCT to act as a non-invasive monitoring and prognostic biomarker of kidney injury. Larger, longer-term clinical trials are now warranted.

Funding: Government Support - Non-U.S.

TH-PO1069

Disease Progression in Patients with Two APOL1 Variants and Proteinuric CKD from the AASK, CRIC, and FSGS-CT Datasets

Michael Lipkowitz, 1 George Manos, 2 Prasad L. Gawade, 2 Will A. Eagan, 2 Yuan Yang, 2 Ogo I. Egbuna, 2 Glenn Chertow, 3 Georgetown University Medical Center, Washington, DC; 2Vertex Pharmaceuticals Incorporated, Boston, MA; 3Stanford University School of Medicine, Palo Alto, CA.

Background: Two variants in APOL1 (APOL1) lead to proteinuric chronic kidney disease (CKD) referred to as APOL1-mediated kidney disease (AMKD). Disease progression in persons with two APOL1 variants and proteinuric CKD is not well-understood.

Methods: We analyzed data from non-diabetic patients with two APOL1 variants and proteinuric CKD enrolled in the African American Study of Kidney Disease and Hypertension (AASK), Chronic Renal Insufficiency Cohort (CRIC) study, and Focal Segmental Glomerulosclerosis Clinical Trial (FSGS-CT). The analysis included participants in AASK and CRIC with urine protein to creatinine ratio (UPCR) ≥0.7 g/g and participants in FSGS-CT with UPCR ≥1.0 g/g. Baseline age, sex, UPCR, and estimated glomerular filtration rate (eGFR) were determined at enrollment. For each data
set, we derived an annual eGFR slope estimate as related to persistent proteinuria, median time to end-stage kidney disease (ESKD), and proteinuria. The estimated annual time slope in AASK, CRIC, and FG50S-CT was -5.80, -8.55, and -19.08 mL/min/1.73m²/year, respectively. Across all studies, patients had a median time to ESKD of >4 years and a median time to composite clinical outcome of ≥2.14 years.

Conclusions: These results highlight the rapid rate of decline in kidney function in patients with AMRD relative to other glomerular diseases and may inform the design of clinical trials testing the safety and efficacy of APOL1-targeted therapies.

Funding: NIDDK Support, Commercial Support - Vertex Pharmaceuticals Incorporated

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TH-PO1070

Rapidly Increased Pattern of Erythropoiesis-Stimulating Agent (ESA) Resistance Is a Predictor of Poor Renal Prognosis in Predialysis CKD Patients: BRIGHTEN Study Subanalysis

Shinya Kawamoto, Takao Masaki, Shoichi Maruyama, Akane Yamakawa, Tatsuo Narita, Ichiji Nairita, Dokkyo Ika Daigaku Nikko Iryo Center, Nikko, Japan; BRIGHTEN Study, Tokyo, Japan.

Background: As CKD progresses, Hb level becomes sluggish in predialysis patients even though the dosage of ESA increases. We investigated whether renal prognosis can be predicted from transition pattern in ESA resistance as a sub-analysis of the BRIGHTEN study.

Methods: The ESA Resistance Index (ERI) was defined as Darbepoetin (DA) dosage/Hb. After the start of DA administration, ERI measured over time and renal events (dialysis initiation/kidney transplantation) were investigated. The onset relationships were analyzed with Joint linear class models for longitudinal and time-to-event data. The Kaplan-Meier method was used to estimate renal survival curves for each ERI transitional pattern. The patient background was compared.

Results: During an average observation period of 3.5 years in 1625 patients, renal events in 517 dialysis initiation and 18 kidney transplantation were analyzed. ERI transition pattern were divide into 3 classes: ERI unchanged Class A (1237 patients, Hb 9.9±g/dL, Cr 2.6±mg/dL), moderately increased Class B (274 patients, Hb 9.6±g/dL, Cr 3.6±mg/dL), and rapidly increased Class C (114 patients, Hb 9.4±g/dL, Cr 3.8±mg/dL). Class C showed significant poor renal survival curve in 3 groups, and Class B showed intermediate (P=0.0001). The median renal survival time was 1.09 years in Class B, and 0.61 years in Class C. Between Class B and C, though there was no significant difference in Cr levels at the start of DA, Class C showed significant higher ERI throughout all observation period, higher rate of hypertension and ischemic heart disease.

Conclusions: In HD patients, the several studies showed that the ESA resistance is an independent predictor of mortality. On the other hand, in pre dialysis CKD patients, a few reports showed the relationship between ESA resistance and mortality, cardio-renal outcome. The BRIGHTEN study of 1724 Japanese was the largest study and median time to composite clinical outcome based on a decline of ≥30% from baseline in eGFR, the onset of ESKD, or death.

Results: A total of 38 patients from AASK, 47 patients from CRIC, and 27 patients from FG50S-CT were found to have two APOL1 variants, CRK, and proteinuria. The estimated annual time slope in AASK, CRIC, and FG50S-CT was -5.80, -8.55, and -19.08 mL/min/1.73m²/year, respectively. Across all studies, patients had a median time to ESKD of >4 years and a median time to composite clinical outcome of ≥2.14 years.

Conclusions: These results highlight the rapid rate of decline in kidney function in patients with AMRD relative to other glomerular diseases and may inform the design of clinical trials testing the safety and efficacy of APOL1-targeted therapies.

Funding: NIDDK Support, Commercial Support - Vertex Pharmaceuticals Incorporated

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TH-PO1071

Baloxavir Marboxil (BXM) Treatment of Influenza in Renally Impaired Patients: Post Hoc Analysis of CAPSTONE-2

Colleen Collins, Steven E. Cagas, Jian Han, Marie-Laure Delporte, Sylvie Retout, Genentech Inc, South San Francisco, CA; T. Hoffmann-La Roche Ltd, Basel, Switzerland; T. Hoffmann-La Roche Ltd, Paris, France.

Background: Renally impaired patients pts) have a higher mortality rate from influenza vs pts without renal impairment. In the US, oseltamivir (OSL) is used for initial treatment in pts with creatinine clearances ≤30 mL/min. In high-risk pts ≥12 years with influenza, demonstrated the efficacy and safety of prompt single dose BXM treatment: median time to improvement of influenza symptoms (TTIS) was >BXM vs OSL vs placebo (PBO) 73.2 vs 81.0 vs 102.3 h; no new safety signals were identified. This post hoc analysis examined BXM efficacy and safety in renally impaired pts with influenza.

Methods: In CAPSTONE-2, pts received a single oral dose of BXM (40 mg: <30 kg, 80 mg: ≥80 kg). OSL 75 mg twice daily for 5 days or PBO and were to be excluded if CrCl ≤60 mL/min (≤30 mL/min for Japan). At the time of enrolment, a small cohort of renally impaired pts was deemed eligible for inclusion as judged by the PI and were included in the intention to treat infected (ITTI) population. For this study, renal impairment was CrCl ≤55 mL/min. Endpoints were TTIS, time to alleviation of symptoms (TTAS), time to cessation of viral shedding (TCVS) and safety.

Results: Overall, 89/1153 (7.7%) renally impaired Pts were in the ITTI population; 33/384 (6.8%), 23/386 (6.0%), and 33/383 (8.6%) received BXM, OSL vs PBO, respectively. For renally impaired pts, median TTIS was numerically shorter for BXM (61 h [95% CI 29.2–82.6]) vs PBO (92.2 h [44.0–115.9]); p=0.1602 and similarly vs OSL (69.4 h [45.5–123.2]; p=0.2061) with similar results for median TTAS (BXM: 62.4 h [29.2–88.2]; PBO: 92.2 h [44.0–115.9]; p=0.1602, OSL: 78.2 h [48.8–123.2]; p=0.1602). Median TCVS was significantly shorter for BXM (48 h [24–72]) vs PBO (120 h [96–168]; p=0.0016) and OSL (96 h [96–144]; p=0.0029). Overall, 54 (34.2%) pts had ≤1 adverse event.

Conclusions: In this analysis of renally impaired pts (CrCl 21.7 to 54.9 mL/min), there was an increased benefit of BXM with a similar safety profile as well as significantly better median TCVS vs OSL, analysis of the safety data from this small cohort did not identify any new safety concerns.

Funding: Commercial Support - Genentech, Inc.
Conclusions: B/F/TAF was effective and safe with respect to renal outcomes in this real-world study in HIV-positive patients. However, the results show a higher risk of eGFR decline in patients switching to B/F/TAF, supporting use of TAF-based regimens in people with eGFR <60 mL/min/1.73 m².

Background: The aim of this study was to compare the effectiveness and safety of opioid vs. non-opioid analgesics on the risk of end-stage kidney disease (ESKD) and all-cause mortality among patients with chronic kidney disease (CKD) and chronic pain.

Methods: We examined patients with CKD (defined as two or more eGFR <60 or UACR >30) and chronic pain (defined as 2 or more pain scores ≥7, 90 to 365 days apart). Chronic opioid and non-opioid analgesics use was defined as at least one 30-day supply in the one-year period following the second pain score. The association of opioid vs. non-opioid use with ESKD and mortality was examined using Kaplan-Meier estimates and multivariable adjusted Cox proportional hazards models.

Results: The total sample included 16,494 patients, of which 13,631 (82.6%) used non-opioid analgesics and 2,863 (17.4%) used opioid analgesics. Overall, patients were 69.1 years old, 96% were men, and 19% were African American, with a mean baseline eGFR of 32.6 mL/min/1.73 m². Opioid use (vs. non-opioid use) was associated with significantly higher risk of mortality, but not with the incidence of ESKD (Table).

The association of chronic opioid vs. non-opioid analgesics with end-stage kidney disease (ESKD) and all-cause mortality among patients with CKD and chronic pain.

Conclusions: Our study shows that chronic opioid use is associated with higher risk of mortality among patients with CKD and chronic pain. Additional studies are needed to examine whether non-opioid analgesics could be considered as safer agents for chronic pain management among patients with CKD.

Funding: Veterans Affairs Support

Multivariable Adjusted Cox Proportional Hazards Models to Compare the Association of Chronic Opioid vs. Non-Opioid Analgesics with ESKD and All-Cause Mortality Among Patients with CKD and Chronic Pain

<table>
<thead>
<tr>
<th>Model</th>
<th>Opioid Use</th>
<th>Non-Opioid Use</th>
</tr>
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<tbody>
<tr>
<td>Model 1: Unadjusted</td>
<td>1.67 (1.60, 1.74)</td>
<td>1.25 (1.22, 1.28)</td>
</tr>
<tr>
<td>Model 2: Model 1 + Demographic factors</td>
<td>1.34 (1.29, 1.40)</td>
<td>1.05 (1.03, 1.08)</td>
</tr>
<tr>
<td>Model 3: Model 2 + CKD baseline characteristics</td>
<td>1.24 (1.20, 1.29)</td>
<td>1.08 (1.05, 1.12)</td>
</tr>
<tr>
<td>Model 4: Model 3 + 4/5 changes in eGFR</td>
<td>1.31 (1.28, 1.34)</td>
<td>1.06 (1.04, 1.09)</td>
</tr>
<tr>
<td>Model 5: Model 4 + age</td>
<td>1.22 (1.19, 1.25)</td>
<td>1.08 (1.06, 1.10)</td>
</tr>
</tbody>
</table>

Spearman rank correlation used.

TH-PO1074

A Multi-Omics Approach to Renal Epithelial Senescence Urinary Biomarker Discovery

David P. Baird,¹ Maximilian Reck,² Ross A. Campbell,¹ Eoin D. O Sullivan,¹ Marie Docherty,¹ Jamie P. Traynor,³ Patrick B. Mark,² Jeremy Hughes,² Laura Denby,² Bryan Conwy,³ Katie J. Mylonas,¹ David A. Ferenbach,¹ Ferenbach,¹ The University of Edinburgh Centre for Infection Research, Edinburgh, United Kingdom;² University of Glasgow, Glasgow, United Kingdom;³ The University of Edinburgh The Queen’s Medical Research Institute, Edinburgh, United Kingdom.

Background: Epithelial senescence is posited as a driver of kidney fibrosis with senescent cell (SC) depletion improving outcomes. There are no non-invasive biomarkers for quantifying renal SCs. We used samples from patients with kidney disease and cultured human renal proximal tubular epithelial cells (hRPTECs) to identify urinary biomarkers of renal tubular senescence (rSBCs).

Methods: rSBCs was induced in vitro using 10 Gy irradiation. Bulk RNAseq was performed comparing SCs with proliferating controls (n=5/group). Immunofluorescence staining for p21CIP1, Ki67 and tubular markers CD10/CKPAN was performed in human kidney tissue from 131 CKD patients. P21CIP1 (p<0.05) and Ki67 (neg) tubular cells were classified as senescent (expressed as % of all tubular cells). In subgroup 1 (collected in Edinburgh, n=51), LC-MS studies were performed on matched urine samples. Proteins qualified as candidate biomarkers if they predicted the level of histological senescence in multivariate linear regression models alongside baseline eGFR, age and ACR and were upregulated in senescence transcriptionally. Candidate biomarkers were validated in subgroup 2 (collected in Glasgow, matching baseline characteristics to subgroup 1, n=53) that had both urine and kidney tissue available.

Results: In vitro: Irradiation increased mRNA levels of CDKN1A and reduced LMNB1 and MKI67 in keeping with senescence induction. In vivo: rSBCs increased with age (rho = 0.58, p<0.001) and inversely with baseline eGFR (rho = -0.48, p<0.001). 331 proteins were detected by LC-MS. 5 candidate biomarkers were identified; 3 of which remained highly correlated with and predictive of histological senescence in the validation subgroup (fig. 1) [not named pending patent applications].

Conclusions: We have identified and validated 3 urinary biomarkers of senescence. These could aid patient selection for clinical trials of senolytic treatments in kidney disease.

Funding: Government Support - Non-U.S.

TH-PO1075

Prognostic Comparisons of Carbamylated Albumin and Homocitrulline-Two Circulating Markers of Protein Carbamylation in CKD

Ava Awwad,¹ Eugene P. Rhie,² Morgan Grams,² Hernan Rincón-Choles,³ James H. Sondheimer,⁴ Jiang He,⁴ Jing Chen,⁴ Chi-yan Hsu,⁵ Vasan S. Ramachandran,⁶ Paul L. Kimmel,⁷ Anders H. Berg,⁸ James P. Lash,⁹ Mengyao Tang,¹ Sahir Kalimi,¹ Harvard Medical School, Boston, MA;² Massachusetts General Hospital, Boston, MA;³ New York University, New York, NY; ⁴ Cleveland Clinic, Cleveland, OH; ⁵ Wayne State University, Detroit, MI; ⁶ Tulane University, New Orleans, LA; ⁷ University of California San Francisco, San Francisco, CA; ⁸ Kaiser Permanente, Oakland, CA; ⁹ Boston University, Boston, MA; ¹⁰ National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; ¹¹ Cedars-Sinai Medical Center, Los Angeles, CA; ¹² University of Illinois Chicago, Chicago, IL.

Background: Protein carbamylation, a urea driven post-translational protein modification, associates with adverse outcomes in CKD. Circulating markers of carbamylation include carbamylated albumin (C-Alb) and homocitrulline (Hcit, carbamylated lysine), but prognostic comparisons between the 2 have never been made. Demonstrating comparability of the 2 markers could facilitate study comparisons and support HCit use from existing databases (HCit is a common analyte on metabolomic platforms). We thus compared the prognostic performance of C-Alb and HCit in a prospective CKD cohort.

Methods: Baseline C-Alb and HCit levels were assessed using mass spectrometry (Broad Institute Metabolomics Platform for HCit) in 1659 patients with CKD stages
CKD Progression and Complications: Diagnosis, Prognosis, Risk Factors

TH-PO1076
CKD Progression with Remote Pulmonary Artery Pressure (PAP) Monitoring in Heart Failure (HF)
Yale University, New Haven, CT.

Background: CardioMEMS HF system is FDA approved for remote monitoring of PAP in patients with NYHA class III HF to reduce HF hospitalizations. Subgroup analysis of the CHAMPION trial with CKD patients reported a mean estimated glomerular filtration rate (eGFR) change of 1.0a14.48 ml/min/1.73m2 in 6 months in the CardioMEMS group and similar in controls. Limited data is available on the role of remote PAP monitoring on kidney function in a real-world population that includes the CardioMEMS group and was similar in controls. Limited data is available on the role of remote PAP monitoring on kidney function in a real-world population that includes patients with advanced CKD over longer follow up.

Methods: This is a retrospective observational study where we included patients with CKD (eGFR <60 ml/min/m2) for at least 90 days as screened by a nephrologist) and HF who were managed with the CardioMEMS HF system. Patients on dialysis, kidney and heart transplant recipients were excluded. Baseline characteristics were collected at the time of CardioMEMS implant. Outcome characteristics were collected after 2 years. Primary outcome was a composite of >40% decline in GFR, need for dialysis or transplant, and death.

Results: Baseline characteristics are summarized in table 1. Of 42 patients, 73.8% had NYHA Class III HF, 71.4% were diabetic and 90.5% were hypertensive. 20 (47.6%) reached the primary composite outcome. 9 (21.4%) had >40% decline in eGFR, 4 (9.5%) required chronic dialysis and 10 (23.8%) died. While 18 (42.9%) patients developed progression of kidney disease, 17 (40.5%) patients had an improvement in their eGFR. Of those, 10 (23.8%) improved by more than 20%. The median change in eGFR at 2-14.48 yrs was +11.81% (16.88, 34.7). Median number of hospitalizations was 5.0 (3.0, 7.0).

Conclusions: In this cohort of adults at high risk for renal progression at the time of CardioMEMS insertion, we observed an improvement in eGFR despite the expected renal progression. A larger study with a control group is warranted to better understand the impact of remote PAP monitoring on CKD progression.

TH-PO1077
Cytomegalovirus Exposure in Nontransplant, Critically Ill CKD Patients
Max Super Specialty Hospital, Dehli, India.

Background: This study aimed to provide a comprehensive understanding of the incidence, prevalence and to determine whether CMV infection had any significant impact on the clinical course and diagnosis of non-transplant CKD patients in the intensive care unit setting.

Methods: A prospective study involved 94 patients with known cases of CKD stage 3 and above admitted to ICU due to acute illness or comorbidities. CKD Patients who had received corticosteroids, cytotoxic therapy, immunosuppressive medications, or had undergone solid organ or bone marrow transplantation were excluded. In our case, at the end of 3 weeks, the prevalence of CMV infection was defined as the percentage of patients who had the infection at that time, and incidence was defined as the percentage of patients who developed the infection at any point between the time of admission and 3 weeks. At 0, 1, and 3 weeks, a quantitative RT PCR analysis for CMV DNA was conducted. The primary outcome was to evaluate the incidence and prevalence of CMV infection. The secondary outcome was to assess the effect of CMV infection on patient outcomes, hospital stay, and 30-day mortality.

Results: The prevalence of CMV infection was 9.57% with an incidence of 10.63 per 1000 patients. The mean age of CMV-infected patients was slightly higher (58.22 vs 56.9 ± 7.638, p=0.148) compared to CMV non-infected. There was no significant difference in gender or the number of comorbidities between the two groups. The most commonly admitted diagnosis in both groups was sepsis (88.8% and 72.9%). The severity of the disease was higher in CMV-infected patients (p=0.044). CMV infection was associated with longer lengths of ICU stay but did not significantly impact hospital stay or 30-day mortality.

Conclusions: CMV infection is not uncommon among critically ill patients, irrespective of their immune status. It can occur in CKD patients even in the absence of overt immunodeficiency. The acquisition of CMV infection appears to be associated with the severity of illness in the ICU and is linked to higher morbidity. Such studies would provide valuable insights into the relationship between CKD and CMV, shedding light on associated risks and potential interventions.

TH-PO1078
Clinical Utility of Tenasin-C Levels in Patients with CKD
Zhen Yu Z. Lim, Hazirah Mohamad, Gek Cher Chan, Boon Wee Teo.
National University Hospital, Singapore, Singapore.

Background: Tenasin-C (TNC), an extracellular matrix protein, is a novel biomarker associated with kidney fibrosis. Within the kidney, it activates fibroblasts and induces epithelial-mesenchymal transition. Increased levels of TNC have been seen in kidney biopsies of patients with chronic kidney disease (CKD). Current literature lacks studies evaluating TNC and associations with clinical parameters and clinical outcomes.

Methods: We retrieved prospectively collected 24-hour urinary and plasma samples from 126 CKD patients and 99 healthy participants. TNC levels were assayed using IBL Tenasin-C Large (FNHII-B) assay kit. TNC concentration was assessed for associations with serum creatinine, cystatin-C, eGFR albuminuria, and rate of eGFR decline. Other factors evaluated include age, gender and body mass index. Differences in TNC concentration between groups were compared using analysis of variance, chi-squared tests. Univariate analysis was performed to assess correlation between TNC and variables of interest. Multiple regression analysis was performed to identify predictors of eGFR decline/year. Significance was taken at P < 0.05.

Results: CKD patients versus healthy participants: age (59 vs. 42), gender (44% female vs. 51%), non-smokers (78% vs. 81%), BMI (27.7 vs. 24.8), eGFR (45 vs. 100mL/min/1.73m2), serum creatinine (171 vs. 69 µmol/L). 24-hour urinary concentration of TNC is elevated in CKD patients (1.45 vs. 0.32mg/L, p=0.001). It is associated with
serum creatinine levels (p<0.001), serum cystatin-C levels (p<0.001), cGFR (p<0.001) and Diabetes (p<0.001). Urinary TNC concentration is highest in patients with diabetes mellitus (DM, n=52), followed by non-DM (n=43) and healthy controls (n=92). (1.86, 0.93, 0.32 ng/ml, p<0.001). In CKD patients, urinary TNC concentration is associated with rate of eGFR decline/year (p<0.001). Plasma TNC concentration was not associated with eGFR, albuminuria and GFR decline.

Conclusions: 24-hour urinary tenasin C level offers novel clinical utility in management of patients with CKD. Early detection of high risk CKD patients will allow for earlier intervention and may serve to delay ESKD onset.

Funding: Other NIH Support - Pitch For Fund - NIH/NIDDK Research

TH-PO1079
The Effect of Fibrates on Kidney Function: A Systematic Review and Meta-Analysis
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Background: Randomized controlled trials (RCTs) have investigated the effects of fibrates on cardiovascular events. Fibrates are known to cause an acute decline in estimated glomerular filtration rate (eGFR) but their long-term effect on kidney function is unclear. Some trials have indicated that following the acute decline fibrates improve the long-term rate of eGFR decline. We conducted a systematic review and meta-analysis to elicit the impact of fibrates on kidney function.

Methods: This review was prospectively registered on PROSPERO (CRD42023372721) and conducted according to the PRISMA 2020 guidelines. Literature searches were conducted in MEDLINE, EMBASE, CINAHL and Scopus. Inclusion criteria were RCTs in adults comparing fibrates to placebo or active comparator that reported eGFR at least at two timepoints. Screening, data extraction and risk of bias assessments were conducted in duplicate. Random-effects, restricted maximum likelihood, inverse variance meta-analyses were used to pool treatment effects. Primary outcomes included the effect on acute change in eGFR (defined as within the first 4 months), chronic eGFR slope (defined as the eGFR slope following the acute period) and post-washout eGFR. Additional outcomes were change in albuminuria and the incidence of ESRD.

Results: Fifteen (N=16,957) eligible RCTs were included. When compared to controls, fibrates led to an acute decline in eGFR (MD -9.53 ml/min/1.73 m2, 95% CI -12.12 to -6.94) that was present at the end of the study period as well (MD -6.29 ml/min/1.73 m2; 95% CI -14.64 to -2.06). Based on the data available, we were unable to meta-analyze the effect of fibrates on chronic slope. However, two RCTs reported a beneficial effect of fibrates on chronic eGFR slope (-1.19 vs -2.03 ml/min/1.73 m2 per year and -0.27 vs -1.26 ml/min/1.73 m2 per year, p<0.001). Following washout, fibrates improved eGFR as compared to control (MD 3.60 ml/min/1.73 m2; 95% CI 0.02 to 7.17). Fibrates reduced albuminuria (MD -0.17 mg/g; 95% CI -0.25 to -0.10). There was no statistically significant effect on ESRD (HR 0.93; 95% CI 0.71 to 1.22).

Conclusions: Fibrates cause an acute decline in eGFR and an improvement in the rate of eGFR decline thereafter. Further studies are needed to determine the long-term impact of fibrates on renal function.

TH-PO1080
Non-Skeletal, as Opposed to Skeletal, Alkaline Phosphatase Associates with Mortality in Patients with CKD Not Yet on Dialysis
Dieter Smou, 1,2 Hanne S. Joergensen, 1,3 Björn K. Meijers, 1,3 Sander Dejongh, 1 Etienne Cavalier, 1 Mathias Haahrus, 1 Amayrilis H. Van Craenenbroeck, 1 Pieter Smou, 1 and Leo van Craenenbroeck 1,2

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Background: High total alkaline phosphatase (ALP) levels associate with increased mortality in patients with chronic kidney disease (CKD). The underlying mechanisms remain poorly understood. Emphasis has been on the skeletal fraction and its link with accelerated vascular calcification, but intestinal and liver ALP may be implicated given their role in the detoxification of bacterial endotoxins. This study aimed to identify the ALP fraction driving the association with mortality in CKD.

Methods: Demographics, Framingham risk factors, total and bone-specific ALP and parameters of inflammation (CRP) and metabolic endotoxemia (lipopolysaccharide binding protein (LBP)) were assessed in 432 patients with CKD grade 1-5. Non-skeletal ALP levels were estimated as residuals of linear regression (according to Filipowicz et al. CJASN 2013). Statistical significance effect on ESRD (RR 0.93; 95% CI 0.71 to 1.22).

Results: Fibrates reduced albuminuria (MD -0.17 mg/g; 95% CI -0.25 to -0.10). There was no statistically significant effect on ESRD (HR 0.93; 95% CI 0.71 to 1.22).

Conclusions: Non-skeletal ALP drives the association of total ALP with all-cause mortality in patients with CKD not yet on dialysis. We speculate that inflammation and metabolic endotoxemia are implicated in the poor outcomes seen with elevated total ALP.

Funding: Government Support - Non-U.S.

Table 1. Multivariate Cox regression analysis of renal and hospitalization events related to PBUTs

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Renal Events</th>
<th>Hospitalisation Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT(μM)</td>
<td>p Value</td>
<td>p Value</td>
</tr>
<tr>
<td>Unadjusted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A (microalbuminuria)</td>
<td>0.028</td>
<td>0.987 (0.93, 1.04)</td>
</tr>
<tr>
<td>B (A/HSD)</td>
<td>0.006 (0.001 to 0.023)</td>
<td>0.029 (1.00 to 1.01)</td>
</tr>
<tr>
<td>C (HSD)</td>
<td>0.106 (0.001 to 0.023)</td>
<td>0.001 (1.00 to 1.01)</td>
</tr>
</tbody>
</table>

Figure 1. Kaplan-Meier proportion of surviving patients of renal events.
Impact of CKD on Complications of Hypertensive Emergency

Aki S. Kaye,1 Husam El Sharouf,1 Omar Kheder,1 Anish Surapaneni.2

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Background: Hypertension in chronic kidney disease (CKD) is primarily volume-dependent. We sought to examine the impact of CKD on the development of complications in hospitalizations with hypertensive emergency.

Methods: We conducted a retrospective cohort study using the National Inpatient Sample from 2016-2019. We used the International Classification of Disease-10 to identify hospitalizations with hypertensive emergency and then stratified them based on whether they had CKD. We used Chi-square and t-test to compare categorical and continuous outcomes, respectively. Multivariate regression analysis was used to adjust for confounders. Adjusted odds ratios (aOR) were reported with 95% confidence intervals (CI) and results were considered statistically significant if P values <0.05.

Results: Among the 750,595 total hospitalizations with hypertensive emergency 335,805 had CKD. The mean age was 63 (without CKD) VS 61 (with CKD). Of those with CKD, 45% were African Americans and 35% were Caucasians. After adjusting for patient demographics, comorbidities, and hospital characteristics those with CKD had higher odds of developing acute kidney injury (aOR: 2.85; p<0.001, CI: 2.77-2.94), acute pulmonary edema (aOR: 1.94, p<0.001, CI: 1.79-2.09), and retinal hemorrhage (aOR: 1.96, p<0.001, CI: 1.36-2.81). CKD was associated with lower odds of developing aortic dissection (aOR: 0.44, p<0.001, CI: 0.4-0.5), subarachnoid hemorrhage (aOR: 0.34, p<0.001, CI: 0.32-0.35), and acute ischemic stroke (aOR: 0.42, p<0.001, CI: 0.4-0.44). There was no statistically significant difference in the odds of developing acute coronary syndrome (aOR: 1.03, p=0.6, CI: 0.96-1.1) and posterior reversible encephalopathy syndrome (aOR: 1.06, p=0.026, CI: 0.96-1.18).

Conclusions: Among hospitalizations with hypertensive emergency, CKD was associated with higher odds of acute kidney injury, acute pulmonary edema, and retinal hemorrhage.

Logistic Regression

TH-PO1085

Rapid Serologic Response of Patients with Advanced CKD to HepB-CpG Vaccination

Christopher Yang, Anip Bansal. University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Vaccination against Hepatitis B virus (HBV) is recommended in patients with CKD who are at risk for progressive kidney disease due to risk from sporadic outbreaks in hemodialysis units. There are 3 recommended HBV vaccines available in the US: Recombivax-HB, Engerix-B and Hepisav-B (Hep-B CpG). Hep-B CpG has been reported to have improved immunogenicity, especially in groups known to have low responses historically e.g. patients with CKD and ESKD.

Methods: The following retrospective cohort study is an analysis of sero-response rates to Hep-B CpG in the outpatient CKD clinic at the University of Colorado hospital. All patients with documented administration of at least one dose of Hep-B CpG between January 1, 2021 to December 31, 2022 were included in this study.

Results: 96 patients at our clinic received at least one dose of the Hep-B CpG vaccine. Of these 96 patients, 67 had a follow-up hepatitis B surface antibody (HepBsAb) titer measured. Common reasons for non-measurement of follow up titers included death, start of kidney replacement therapy and loss to follow up. Of the 67 patients with measured follow up titers, there was an 80% (53/67) serologic response (HepBsAb > 10 mIU/mL) after 1-3 doses of the vaccine (scheduled to be given at 0, 1 and 6 months). There was similar serologic response between CKD stages (CKD5: 22/27 (81%), CKD4: 22/27 (81%), CKD3b: 7/7 (77%), CKD1-CKD3a: 1/2 (50%). Only 2 of these patients required more than one series for a serologic response. Of the 14 non-responders who received at least two doses of the Hep-B CpG vaccine, 6 patients were solid organ transplant recipients on immunosuppression (5 liver, 1 kidney), 2 patients had active multiple myeloma, and 2 patients had solid organ malignancies.

Conclusions: In our real world clinical experience, Hep-B CpG produces a rapid serologic response in advanced CKD patients requiring less doses compared to the high dose of the traditional HBV vaccines (Engerix or Recombivax-HB). Ongoing immunosuppression and active malignancy were the common causes of response failure.
TH-PO1086

Prevalence and Factors Associated with Hyperkalemia in Outpatients with CKD
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Background: Hyperkalemia (HK) is a frequent complication of chronic kidney disease (CKD), with a prevalence of between 14-20%, which is associated with different factors, such as the use of some antihypertensives (ARA’s, IECA), age, gender, Diabetes Mellitus (DM) to vasoconstriction of the kidney arteries and a consequent reduction in the glomerular filtration rate (GFR). Liver disease further leads to the retention of toxic metabolites that may impair proximal tubular functions. We tested whether cirrhosis is associated with alterations in tubular secretory clearance in patients referred for liver transplantation.

Methods: We recruited 39 outpatients with end stage liver disease undergoing workup for transplantation. We selected 58 control subjects without liver disease, matched to patients with cirrhosis by their estimated GFR (±10 ml/min/1.73m²). We estimated tubular secretory solute clearance based on 24-hour urine and plasma concentrations of endogenous solutes measured by LC/MS. We determined the mean fold-difference in tubular secretory solute clearance based on 24-hour urine and plasma concentrations of many endogenous solutes measured by LC/MS. We determined the mean fold-difference in tubular secretory solute clearance.

Results: HK presented a high prevalence in our population, which increases the risk of death, cardiovascular disease, and hospitalization. An intentional search is necessary from the early stages of CKD, as well as the different associated factors according to the CKD stage.

TH-PO1087

Proximal Tubular Secretory Clearance Is Preserved in Cirrhosis

Background: Cirrhosis promotes substantial changes in the metabolic and circulatory milieu, leading to a decrease in the renal function and a consequent reduction in the glomerular filtration rate (GFR). Liver disease further leads to the retention of toxic metabolites that may impair proximal tubular functions. We tested whether cirrhosis is associated with alterations in tubular secretory clearance in patients referred for liver transplantation.

Methods: We recruited 39 outpatients with end stage liver disease undergoing workup for transplantation. We selected 58 control subjects without liver disease, matched to patients with cirrhosis by their estimated GFR (±10 ml/min/1.73m²). We estimated tubular secretory solute clearance based on 24-hour urine and plasma concentrations of endogenous solutes measured by LC/MS. We determined the mean fold-difference in secretory clearance using regression of log-transformed clearances and adjusted for GFR, age, and sex.

Results: Cirrhosis patients were characterized by a mean Child-Pugh 7.9±1.8 or moderate (B) liver disease, 72% male, age 53.9±9 years, and eGFR 65.6±19.7 ml/min/1.73m². Tubular secretory clearances of most endogenous solutes were equal to or higher in patients with cirrhosis compared to control persons (Fig. 1), which persisted after adjustment for eGFR, age, and sex (Tab. 3). The plasma concentrations of many solutes were substantially lower in cirrhosis (Fig. 2).

Conclusions: In contrast to our hypothesis, proximal tubular secretory clearance is largely preserved or increased in outpatients with cirrhosis. Cirrhosis patients had substantially lower plasma and f(D) of many solutes despite similar kidney function.

Funding: NIDDK Support

TH-PO1088

Perceptions About Influenza and COVID-19 Vaccines Among People with CKD: CRIC Study
Junichi Ishigami,1 Bernard G. Jaar,1 James P. Lash,2 Jing Chen,3 Lawrence J. Appel,1 Deidra C. Crews,1 Kristin Rieckert,1 David W. Dowdy,1 Kunihiro Matsushita,1 Johns Hopkins University, Baltimore, MD; 2University of Illinois Chicago, Chicago, IL; 3 Tulane University, New Orleans, LA.

Background: Vaccine uptake in people with CKD is suboptimal. Understanding reasons for not getting vaccinated (“non-vaccination”) could inform programs seeking to address these concerns.

Methods: In a subset of Chronic Renal Insufficiency Cohort (CRIC) Study participants, we administered a survey on perceptions about influenza and COVID-19 vaccines. Survey development followed the Health Belief Model, including themes of perceived risk, perceived benefits and harms, and cues to action. Response was based on a 5-level Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). The odds of agreeing to each statement in the questionnaire (strongly agree/agree vs. others) were compared between those who did and did not have non-vaccination status, defined as never having received either an influenza vaccine in the last 5 years or a COVID-19 vaccine at any point preceding the survey.

Results: Between July 2022 and March 2023, 199 participants completed the survey (age 71 years, 42% female, 45% Black race, mean eGFR 50 ml/min/1.73m²); 24 (12%) and 35 (18%) had influenza and COVID-19 non-vaccination status. For both vaccines, agreeing that benefits are exaggerated, that people are lied to about the risks of vaccines, and that vaccines cause side effects were associated with higher odds of non-vaccination; whereas agreeing that vaccines prevent people from becoming seriously ill was associated with lower odds of non-vaccination (Figure). Agreeing that the vaccine causes people to get COVID-19, and that people who had influenza do not need the influenza vaccine, were associated with their non-vaccination status.

Conclusions: Among people with CKD, negative perceptions about vaccine safety and benefits were associated with non-vaccination status. Effectively communicating accurate information tailored by vaccine type may be essential to improve vaccination uptake in people with CKD.

Funding: NIDDK Support
TH-PO1089

The Effect of COVID-19 Pandemic on Anxiety in Solid Organ Transplant Recipients
Jad Fadlallah, Ana M. Samudio, Katalin Groe, Mursalj Ahmed, Istvan Muci.
Kidney Health Education and Research Group. University Health Network, Toronto, ON, Canada.

Background: The impact of the SARS-CoV-2 on mental health, specifically on anxiety symptoms may be pronounced among solid organ transplant recipients (SOTRs), who are immunocompromised and at a higher risk of infection. This study assesses the impact of the pandemic on anxiety symptoms in SOTRs.

Methods: Cross-sectional convenience sample of adult kidney, kidney-pancreas, liver and kidney-pancreas transplant recipients, recruited in studies validating PROMIS tools between 1997-2023. Demographic data are self-reported, clinical data is from health records. Patients completed the PROMIS-29 anxiety v2.0 using 4-item SF or CAT, scored on a T-score metric, where higher score indicates more anxiety symptoms. In our primary analysis, we compare anxiety between patients who completed the questionnaires prior to the pandemic (PRE) vs after the onset of the pandemic (POST). In our secondary analysis, we further divide our POST group into those who were transplanted before (POST-B) and those who were transplanted after the pandemic (POST-A), to further delineate the potential association between the pandemic and anxiety symptoms.

Results: Of 682 participants, 422 (62%) were male, mean(SD) age was 53(15) years. In our primary analysis, mean(SD) PROMIS-29 anxiety scores were higher in POST vs PRE (54.9) vs 52.9, p=0.004. POST anxiety scores were significantly higher in the fully adjusted regression model (coefficient[95% CI]; p=290.9,4.9, p=0.007). In our secondary analysis, the fully adjusted regression model showed that the timing of transplant (prior to or after COVID onset) status was associated with anxiety scores (reference: PRE): POST-A (coefficient[95%CI]: 4.20[0.8,7.6], p=0.019), POST-B (2.40[0.6,5.4]).

Conclusions: Anxiety scores collected in this sample of SOTRs were higher after the onset of the pandemic. These findings suggest that mental health support for SOTRs is relevant and important in the context of the post-COVID pandemic. Longitudinal studies can assess the development of anxiety symptoms in the future.

TH-PO1090

Psychological Impact After the COVID-19 Epidemic on Hemodialysis Patients in China: A Multi-Center Cross-Sectional Study
Junru Wang,1,2 Nan Wang,1 1Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, China; 2Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital, Chengdu, China; 3Chengdu Second People's Hospital, Chengdu, China.

Background: Patients on hemodialysis often suffer from anxiety, depression and sleep disturbances. The questionnaire was used to assess the anxiety, depression, insomnia and social support of Chinese hemodialysis patients after the novel coronavirus disease (COVID-19) epidemic period.

Methods: Sent self-questionnaire to hemodialysis patients to record demographic and clinical information and use Generalized Anxiety disorder 7(GAD-7), Insomnia Severity Index(ISI), Patient Health Questionnaire 9(PHQ-9), Percieved social support scale(PSSS) to investigate anxiety, sleep, depression and social support. We used logistic regression to analyses independent factor of anxiety, sleep, depression and social support.

Results: A total of 1044 questionnaires were collected. 480 cases (46.0%) had mild or higher anxiety, 480 cases (46.0%) had mild or higher insomnia, 927 cases (88.5%) had mild or higher depression, and among which 85.1% had suicidal tendency. 1044 cases (100%) had various degrees of social support. Work status, comorbid underlying diseases, COVID-19 vaccination, social support, depression, and insomnia are independent risk factors (p < 0.05) which were further incorporated into the nomogram. The C-statistics were 0.865 and 0.748 in the training and validation sets, respectively. Calibration plots showed that the nomogram accurately predicted the risk of death or transferring to ICU within 28 days in hemodialysis patients with COVID-19. The concordance statistics (C-statistics) and calibration curves were used to assess model performance.

Conclusion: Early identification and intervention is important to prevent the disease progression in these dialysis patients with Covid-19.

TH-PO1092

Incorporation of Chest Computed Tomography Quantification to Predict Outcomes in Hemodialysis Patients with COVID-19
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Background: Patients undergoing maintenance hemodialysis are vulnerable to coronavirus disease 2019 (COVID-19) with a higher risk of hospitalizations and mortality. Early identification and intervention is important to prevent the disease progression in these dialysis patients with Covid-19.

Methods: A total of 186 Covid-19 patients from a hemodialysis center in Shanghai 6th People’s hospital, China were enrolled between March 2021 and June 2021. 70% of patients (n = 130) were randomly selected in the training set for the establishment of a prognostic nomogram. 30% (n = 56) were included for the validation of the predictive model. Artificial intelligence (AI) based parameters of chest computed tomography (CT) were quantitated; demographic features, comorbidities and laboratory examination items were screened using univariate and multivariate Cox regression analyses to construct a nomogram predicting the risk of death or transferring to ICU within 28 days in hemodialysis patients with COVID-19. The concordance statistics (C- statistics) and calibration curves were used to assess model performance.

Conclusion: Our new findings suggest early and dynamic monitoring of Ct values and AI based chest CT quantitative parameters could be helpful to assess the survival and outcomes of hemodialysis patients with SARS-CoV-2 Omicron variant and to explore the risk factors affecting the outcome in these patients.

Funding: Government Support - Non-U.S.
Conclusions: This is the first study to develop a reliable nomogram using clinical indicators and AI based CT image parameters to predict outcome and survival probabilities in hemodialysis patients with COVID-19. This model could be helpful to clinicians in treating SARS-CoV-2 infection, managing serum phosphorus and adjusting the dialysis strategies in these patients to against severe-critical disease progression.

Funding: Government Support - Non-U.S.

TH-PO1093

Safety and Efficacy of Pre-Exposure Prophylaxis with Tixagevimab/ Cilgavimab (Evusheld) in Patients with Glomerular Diseases Who Received Rituximab

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Background: Patients on B-cell depleting agents may have a suboptimal response to vaccination, placing them at a higher risk of contracting SARS-CoV-2 or suffering from a more severe prognosis. Indeed, available data on pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld) in subjects with glomerular diseases (GD) who received rituximab is limited.

Methods: We conducted a prospective study analyzing the safety and efficacy of tixagevimab/cilgavimab for pre-exposure prophylaxis in patients with GD who received rituximab in the previous 12 months. Rate of symptomatic infections and hospitalizations were compared to patients with GD treated with rituximab who refused to receive tixagevimab/cilgavimab.

Results: Tixagevimab/cilgavimab was administered to 22 patients (12 females, mean age 58.4±16.9 years) with GD diagnoses including membranous nephropathy, lupus nephritis, ANCA-associated vasculitis and focal segmental glomerulosclerosis. No patient treated with tixagevimab/cilgavimab experienced symptomatic infection with SARS-CoV-2 during the follow-up (mean observation time follow-up was 112 ± 23 days), while 11 out 28 controls (39.3%) reported a symptomatic infection (p=0.001), requiring hospitalization in 2 cases. Reported adverse events were mild, namely self-limited headache (4), discomfort at the injection site (3), flu-like symptoms/myalgia (3), and fever (1). No serious adverse event, (e.g., cardiac events, anaphylaxis) was reported.

Conclusions: Pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld) seems safe and lowering of about 40% the risk of symptomatic SARS-CoV-2 infection in vaccinated subjects with GD who received anti-CD20 therapy. Possible applications in the subset of patients who need immunosuppressive therapy, especially with Rituximab, in a pandemic setting might be envisaged.

TH-PO1094

Effect of Remdesivir on Long-Term Adverse Cardiac and Kidney Outcomes in Patients with COVID-19 and Impaired Kidney Function

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Background: Patients (pts) who survive COVID-19 are at increased risk for cardiac and kidney sequelae. We sought to determine if the use of remdesivir in pts with underlying kidney impairment who were hospitalized for COVID-19 is associated with differences in long-term cardiac and kidney adverse outcomes.

Methods: We performed a propensity-score matched cohort study to compare the risk of major adverse cardiovascular events (MACE), major adverse kidney event (MAKE), slope of eGFR decline among pts hospitalized for COVID-19 with admission eGFR<60mL/min who received remdesivir versus historical controls admitted prior to EUA for remdesivir (Figure 1). Among pts surviving 30 days and followed up to 18 months, we used Cox proportional hazards model to predict risk of hospitalization/death from MACE and MAKE; we used mixed effect linear model to estimate the eGFR decline slope.

Results: Among the 412 pts who survived >30 days (N=162 for remdesivir-treated cohort, N=250 for historical comparators, variable matching used, Figure1), mean age was 71(SD13), 55% were male, 18% were black, 11% required mechanical ventilation and mean admission creatinine was 1.5mg/dL (1.3 – 2.0). By 18 months, there was no significant difference in MACE or MAKE between the two groups. However, remdesivir use was associated with a significant attenuation of eGFR decline between 30 days to 18 months (-0.77 vs. -2.81 mL/min/year) (Table1).

Conclusions: Among pts with underlying kidney impairment hospitalized for COVID-19 who survived >30 days, remdesivir use was not associated with reduction of MACE or MAKE. However, there was attenuation of eGFR decline in pts treated with remdesivir.

Funding: Commercial Support - Gilead Science

TH-PO1095

Safety and Efficacy of Nirmatrelvir/Ritonavir in Patients with Moderate-Severe CKD with COVID-19: A Real-World Data Study

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Background: Chronic kidney disease (CKD) is a mortality risk factor for COVID-19, predisposing patients to poor clinical outcomes. Nirmatrelvir/ritonavir (Nm/r) is currently the most effective oral antiviral agent for COVID-19, with 89% reduction in hospitalization and mortality. The U.S. Food and Drug Administration advised against Nm/r in severe CKD patients due to lack of study. In this propensity-matched retrospective study, we assess side effects, efficacy, and severity of clinical outcomes in Nm/r-treated moderate-severe CKD patients with COVID-19.

Methods: Patient data was accessed from TruNetX, a platform that aggregates health record data of over 123 million patients. The experimental group consisted of Stage 3-5 CKD patients, with 2 separate eGFR measurements of <60 mL/min/1.73m2, prescribed Nm/r after COVID-19 infection. The control cohort was any non-CKD patient prescribed Nm/r after COVID-19 infection. Nm/r-treated moderate-severe CKD patients were at greater risk of side effects, COVID-19 rebound, and severe outcomes compared to non-CKD high-risk groups even after Nm/r. Providers should counsel patients and monitor the side effect profile and risk of COVID-19 rebound in Nm/r-treated CKD patients.

Funding: Other NIH Support - This project was supported in part by the Clinical and Translational Science Collaborative of Cleveland which is funded by the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Science Award grant, UL1TR002548. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.
Outcomes of Nirmatrelvir-Ritonavir in Patients with Advanced CKD and COVID-19
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Background: Patients with chronic kidney disease (CKD) are vulnerable to severe novel coronavirus-2019 infection (COVID-19). Nirmatrelvir-ritonavir is an effective oral antiviral therapy, but it is not recommended in patients with eGFR < 30 ml/min/1.73m².

Methods: This is a prospective interventional trial that included COVID-19 patients with eGFR < 60 ml/min/1.73m² including dialysis. A 5-day course of nirmatrelvir-ritonavir was prescribed at a modified dosage. The adverse event, viral response and disease rebound were compared between high (> 30 ml/min/1.73m²) and low eGFR (< 30 ml/min/1.73m²). We further compare the treatment failure rate with a cohort treated with molnupiravir.

Results: 59 of the 85 participants had stage 5 CKD and were on dialysis. 9.4% had adverse events, which were comparable between eGFR groups. The viral load significantly reduced on day 5, 15 & 30 (p < 0.001 for all), including the low eGFR group (Fig 1). 10 patients had virological rebound, though was transient and asymptomatic. The rate of adverse clinical outcome was significantly lower compared to molnupiravir users (6.8% vs 21.7%, p = 0.01, Fig 2), and the significance persisted in the multivariate model (odds ratio 0.16, 95% confidence interval 0.04 – 0.71, p = 0.016).

Conclusions: Modified dose of nirmatrelvir-ritonavir is well-tolerated and effective in patients with COVID-19 and CKD including dialysis.

Funding: Private Foundation Support

A Meta-Analysis to Evaluate the Safety of Remdesivir in Patients with Reduced Renal Function
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Background: Remdesivir is approved by the U.S. FDA for treating coronavirus disease-2019 (COVID-19). However, the clinical trials assessing remdesivir’s efficacy did not include patients on dialysis and those with an estimated glomerular filtration rate (eGFR) of <30 ml/min/1.73 m². Sulfobutylether-β-cyclodextrin (SCEBD), the solubilizing excipient used in intravenous formulations could accumulate in renal tubules causing further renal dysfunction. We performed a meta-analysis to find the safety profile of this therapeutic agent.

Methods: We systematically searched PubMed, Google Scholar, EMBASE, Cochrane, Web of Science and Clinical trials.gov from inception to January 2023 to identify studies with CKD and ESRD patients over 18 years of age with COVID-19 who received Remdesivir therapy. Using a random effects model, proportional effect sizes were calculated. The heterogeneity between study-specific estimates was assessed by the I² statistics. The primary outcome were the pooled rates of liver failure, renal failure and serious adverse effects. Secondary outcomes assessed were requirements of oxygen, mechanical ventilation, and mortality rate.

Results: Eighteen studies (764 patients) met the inclusion criteria. 58.3% (95% CI: 49.5-66.6; I² = 76.9%) were males. 82.6% (95% CI: 65.3-92.3; I² = 87.7%) were ESRD on dialysis. Severe liver failure occurred in 1.6% (95% CI 0.6-3.9; I² = 0%). The rate of renal failure in eGFR of <30 mL/min/1.73 m² was 8.9% (95% CI 4.6-16.5; I² = 0%). The pooled proportion of all serious adverse effects due to remdesivir was 2.9% (95% CI:1.3-6.4; I² = 7.8%). 17.7% (95% CI: 13.0-23.7; I² = 62.5%) were on mechanical ventilation. The mortality rate in CKD and ESRD patients treated with remdesivir was 26.8% (95% CI: 21.1-33.5; I² = 65.4%).

Conclusions: The use of remdesivir in CKD and ESRD is relatively safe from our meta-analysis. Randomized clinical trials are needed to further evaluate the safety and other adverse effects of remdesivir in this population.
Conclusions: Use of Remdesivir in patients with kidney disease was not associated with renal function deterioration. Contrary to concerns there was rather an overall significant improvement in eGFR, degree of albuminuria and acid-base balance after treatment regardless of their disease severity and its use in patients on hemodialysis have not shown any detrimental impact on mortality.

TH-PO1099
COVID-19-Associated C-ANCA Vasculitis
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Introduction: Anti-neutrophil cytoplasmatic antibody (ANCA) associated vasculitis is a group of systemic vasculitides that causes inflammation and destruction of the small and medium-sized blood vessels and can cause acute renal failure. SARS-CoV-2 (COVID-19) has been shown to increase the risk for autoimmune diseases. We present a case of C-ANCA vasculitis a few weeks after COVID-19 infection which was successfully treated with steroids and Rituximab.

Case Description: 87-year-old female with hypertension presented with generalized weakness, malaise, and myalgias. She had COVID-19 infection with bronchitis symptoms a few weeks before the presentation. She has no history of kidney disease; labs showed creatinine of 2.99 mg/dl, BUN of 36 mg/dl with eGFR of 14. Urine dipstick showed 3+ proteinuria and 3+ hematuria. Labs showed serum Anti-proteinase-3 antibody titer of 1/946, C-ANCA titer of 1:1280, and myeloperoxidase, P-ANCA were negative. Renal biopsy showed necrotizing and crescentic glomerulonephritis. Immunofluorescence: granular mesangial and capillary loop staining with 3+ staining for IgG, IgM, C3, kappa, and lambda. Infection-related crescentic vasculitis was considered and ruled out with negative blood and urine cultures. She was given pulse dose steroids and four weekly doses of Rituximab. Prednisone was tapered to 10 mg daily over 8 weeks. She had significant improvement with her general weakness, anemia, and myalgias. Even though her eGFR recovery (17) was marginal, proteinuria and hematuria resolved completely and ANCA titer improved which indicates improving vasculitis activity.

Discussion: A few cases of COVID-19-associated ANCA vasculitis has been reported but data regarding management is scarce. Our case highlights the safety and efficacy of prompt Rituximab and steroid therapy in patients with COVID-associated ANCA vasculitis.

TH-PO1100
A Case of Newly Diagnosed Systemic Lupus Erythematosus and Lupus Nephritis After COVID-19 Infection
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Introduction: Systemic Lupus Erythematosus (SLE), the most common form of lupus, is a chronic autoimmune inflammatory disease with clinical manifestations affecting any organ. Kidney involvement is seen in about 50% of patients, leading to CKD or ESKD. The year 2019 brought on a pandemic caused by the virus Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Here we illustrate a case of SLE and lupus nephritis with clinical manifestations discovered after COVID-19 infection.

Case Description: A 39-year-old Hispanic male presented to our institution with abdomen pain associated with nausea and vomiting, recurrent skin rash, hematuria, weight loss of 40 pounds over the past several months and joint pains. Prior to this admission, he had multiple visits to the hospital for abdominal pain, general malaise, and joint pains that started about 9 months after a 5-day course of COVID-19 infection; and subsequently diagnosed with urticarial vasculitis with colitis during one of his hospital admissions. Physical examination was notable for tenderness to the epigastic and periumbilical region, and multiple umbilicated papules of the elbows and palms and tense bulla of the left third digit. His laboratory findings revealed elevated creatinine, anemia and urinalysis showed hematuria. Previous autoimmune workup was positive for ANA, ds-DNA, Sjogren’s antibodies and low C3 and C4 complements. His CT abdomen without contrast showed a thickened terminal ileum with inflammatory changes consistent with colitis. Skin biopsy findings were consistent with small vessel vasculitis. Subsequent renal biopsy confirmed immune complex – mediated glomerular nephritis with full house tubular inclusions and subepithelial deposits consistent with membranous lupus nephritis. He was treated with IV methylprednisolone, PO prednisone, with plans for starting Cyclophosphamide.

Discussion: The link between lupus and colitis is rare in the literature. Similarly, the link between lupus and COVID-19 is also rare with only case reports of both scenarios currently existing. This and other case reports in the literature hopes to spark the discussion and later the investigation as to the possible reasons for both occurrences.

TH-PO1101
COVID-19 Vaccination (VAX) and Infection (INF)-Related Glomerular Diseases (GNs)
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Background: There have been numerous reports of GNs associated with both COVID-19 VAX and INF. We performed a systematic review per PRISMA involving reported COVID-19 VAX and INF-associated GN cases to explore for supportive evidence of a cause-and-effect rather than a fortuitous relationship.

Methods: We searched LEMBE, EMBASE, and the World Health Organization COVID-19 database for case reports and series, and observational studies for reported VAX or INF-associated GNs.

Results: Of 1261 articles identified, 117 articles were included. Fifty-eight articles pertained to infection- and 59 to vaccine-related GNs. Among vaccine-related GNs, the top 3 diagnoses were IgA nephropathy (IgAN, 35 out of 111 cases, 31.5%), anti-neutrophil cytoplasmatic antibody-associated GN (ANCA, 23 out of 111, 18.9%), and minimal change disease (MCD, 23 out of 111, 18.9%). Among infected patients, the top 3 were focal segmental glomerulosclerosis (FSGS, 90 out of 162, 55.6%), ANCA-associated GN (34 out of 111, 30.5%), and IgAN (12 out of 111, 10.8%). The immune perpetuating factors present in COVID-19 real associated GNs were associated with proteinuria and INF differ significantly compared with that in the pre-COVID era, where excluding diabetic glomerulosclerosis, the top 3 GNs globally were FSGS 17.4%, IgAN 16.5%, and MN 12.1%.

Conclusions: Based on the pathogenesis of GNs and systemic immune response to COVID-19 VAX and INF and the observed differences in GN patterns among pre-COVID era, VAX, and INF-reported GN cases, we suspect that the relationship between VAX and INF-reported GNs were directly causal rather than coincidental.

TH-PO1102
Impact of COVID-19 Infection in a Glomerular Disease Unit
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Background: COVID-19 infection poses a significant global health challenge, yet its impact on glomerular disease patients (GDP) remains understudied. This research aims to investigate the mortality and chronic renal replacement therapy (CRRT) rates among GDP, identify predictive factors, and explore the influence of proteinuria on the evolution of essential glomerular filtration rate (eGFR). Methods: This retrospective study compares the annual eGFR changes in GDP before and after COVID-19 infection. The study period spans from January 10, 2020, to July 28, 2022. Proteinuria was defined as a urine protein/creatinine ratio exceeding 0.2 mg/mg.

Methods: Among the 302 GDP included, 64 (21%) contracted COVID-19. The mean age was 47 years. Sex: Females 31 (48%) patients. Infection rates were 9% in 2020, 28% in 2021, and 63% in 2022. Of the infected patients, 12 (19%) either died

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Glomerular diseases reported following COVID-19 vaccination and infection in non-transplant patients.
Background: Relapse cases of membranous nephropathy (MN) and other glomerular diseases have been reported after the infection of COVID-19. The risk factors for MN disease progression after COVID-19 infection need to be clarified.

Methods: A retrospective study were conducted from November 11th, 2020 to February 22nd, 2023 on 656 consecutive patients with biopsy-proven primary MN who had been treated and followed up for more than 6 months. Logistic regression analyses were performed to identify the risk factors.

Results: 555 (84.6%) patients underwent COVID-19 infection. Among them, 112 (20.2%) patients experienced urinary protein aggravation > 50% from the baseline, including 30 (5.4%) patients with relapse of nephrotic syndrome. 16 (2.9%) patients got immune relapse with antibody reoccurrence. Ten (1.8%) patients got kidney aggravation with the increase of anti-PLA2R levels and five (0.9%) patients got immune aggravation with the increase of anti-PLA2R levels and five (0.9%) patients got immune aggravation with the increase of anti-PLA2R levels and five (0.9%) patients got immune aggravation with the increase of anti-PLA2R levels and five (0.9%) patients got immune aggravation with the increase of anti-PLA2R levels.

Conclusions: The findings proposed an active anti-virus treatment and no or shorter duration of immunosuppressants withdrawal for a better prognosis of kidneys on the clinical practice of MN patients with COVID-19 infection.

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TH-POI107
Series of Glomerular Diseases Developed After COVID-19 mRNA Vaccination
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Introduction: The coronavirus disease 2019 (COVID-19) vaccine has been proven effective in preventing severe COVID-19 infection. Meanwhile, many vaccine-related adverse events have been reported with the increasing use of messenger RNA (mRNA) COVID-19 vaccines. In fact, cases of vaccine-related new-onset and relapsing glomerular diseases, including minimal change disease (MCD), anti-neutrophil cytoplasmic autoantibody-associated vasculitis, immunoglobulin (Ig)G4-related disease, and IgA nephropathy (IgAN), have been reported. Here, we report 40 patients who developed glomerular diseases after COVID-19 mRNA vaccination.

Case Description: We evaluated the clinical characteristics, vaccine types, and clinical outcomes of 40 patients whose urinalysis indicated proteinuria and/or occult blood after COVID-19 mRNA vaccination. For a definitive diagnosis, we performed a renal biopsy and evaluated their histological findings. Out of 43 patients, 30 patients were treated with an adaptive immune response to display its protective effect, which may stimulate a hyperinflammatory condition. Further studies are necessary to elucidate the underlying biological mechanisms and identify the exact causal relationship.

TH-POI108
The Severity of Microscopic Hematuria in IgA Nephropathy Correlates with the Incidence of Gross Hematuria Following SARS-CoV-2 mRNA Vaccination

Background: Since the initiation of a global vaccination program against the COVID-19 pandemic, numerous cases of newly diagnosed or worsening immunoglobulin A nephropathy (IgAN) with gross hematuria have been reported following SARS-CoV-2 mRNA vaccination. Recent case studies have indicated a possible link between baseline urinary findings and the appearance of gross hematuria following SARS-CoV-2 mRNA vaccination.

Methods: Outpatients with biopsy-proven IgAN aged 18 years or older were included in this study. The association between pre-vaccination microscopic hematuria (urine sediment < 5 HPF) or proteinuria (< 0.3 g/gCr) and post-vaccination gross hematuria was retrospectively analyzed.

Results: A total of 417 IgAN patients (mean age, 51 years; 56 % female; eGFR, 58 mL/min/1.73 m²) were included. The frequency of post-vaccination gross hematuria was higher in patients (20/123; 16.3%) with pre-vaccination microscopic hematuria than in patients (5/294; 1.7%) without pre-vaccination microscopic hematuria (p < 0.001). There was no association between pre-vaccination proteinuria and post-vaccination gross hematuria. After adjustment for potential confounders such as gender (female), age group (< 50 years), eGFR category (≥ 60 mL/min/1.73 m²), and prior tonsillectomy or corticosteroid therapy, microscopic hematuria was still associated with post-vaccination gross hematuria (OR 8.98, p < 0.001). Notably, the severity of pre-vaccination microscopic hematuria increased, the incidence of post-vaccination gross hematuria increased (Figure 1).

Conclusions: These results suggest that baseline microscopic hematuria predicts gross hematuria after SARS-CoV-2 mRNA vaccination in patients already diagnosed with IgAN. The correlation between the severity of pre-vaccination microscopic hematuria and the incidence of post-vaccination gross hematuria suggests that IgAN disease activity is involved in this association.
Elucidating the Mechanism of Gross Hematuria in IgA Nephropathy: Analysis of the Biomarkers in Patients with Gross Hematuria After COVID-19 Vaccination

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Background: Gross hematuria (GH) is observed shortly after an upper respiratory tract infection in 30–40% of the patients with immunoglobulin A nephropathy (IgAN), however, its mechanism is unclear. Recently, several reports showed the cases with GH after vaccination against coronavirus disease 2019 (COVID-19) in patients with IgAN. Here, we sought to clarify the mechanism of GH in IgAN by detailing the clinical characteristics and measuring serum and urinary galactose-deficient IgA1 (Gd-IgA1), which are known to be associated with development of IgAN, in patients with GH after COVID-19 vaccination. We conducted a prospective cohort study of 82 patients with presented after GH after COVID-19 vaccination.

Methods: All the patients visited either Juntendo University Hospital or Juntendo University Urayasu Hospital between May 11, 2021, and July 31, 2022. We collected the serum and urine samples at the time of the first presentation to the hospital with GH (GH 0) and six months after GH (GH 6). Gd-IgA1 were measured by enzyme-linked immunosorbent assays.

Results: We found that majority of patients who developed GH after COVID-19 vaccination were females (58 patients, 71%). GH was observed after the second or subsequent vaccinations in most patients (75 patients, 92%). Among the 82 patients, 22 had already been diagnosed with IgAN or IgA vasculitis (IgAV) prior to vaccination. In the remaining 60 patients, 42 performed kidney biopsies, who were all diagnosed with IgAN or IgAV. Although serum Gd-IgA1 were comparable throughout the observation period (GH 0: 5135.7 ng/mL; interquartile range [IQR] 3730.3–6914.4 ng/mL vs. GH 6: 5354.8 ng/mL; IQR 4288.5–7973.9 ng/mL; p<0.019), urinary Gd-IgA1 was increased at the time of GH (GH 0: 42.7 ng/mL; IQR 2.1–110.1 ng/mL vs. GH 6: 31.7ng/mL; IQR, 12.8–93.9 ng/mL; p=0.030). These data suggest that deposition of Gd-IgA1 in the glomeruli was enhanced by COVID-19 vaccination by a mechanism other than increasing serum Gd-IgA1.

Conclusions: Our cohort study suggests that GH in IgAN is triggered by some alternations in glomerulus itself that facilitate the deposition of Gd-IgA1. Increased incidence of GH after COVID-19 vaccination in females and after the second or subsequent vaccinations may help to clarify the mechanism of GH in detail.

Collapsing FSGS in a Patient with Post-COVID-19 Infection

Poster/Thursday

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Introduction: Focal segmental glomerulosclerosis accounted for about one sixth of cases of nephrotic syndrome prior to the COVID pandemic. This disease is focal, involving some glomeruli, and segmental, involving part of the glomerulus. Patients may present with either nephrotic or nephritic syndrome. This abstract describes a 40-year-old Caucasian female who presented post-COVID pandemic with nephrotic range proteinuria after being asymptomatic for the past 14-years. Renal biopsy revealed collapsing glomerulopathy. This case demonstrates CKD patient post-COVID that presented with nephrotic range proteinuria, however non-uremic and not on dialysis despite worsening laboratory findings. Kidney failure in the form of COVID associated nephropathy (COVAN) is associated with increased morbidity and mortality. Few large cohort studies of kidney biopsies from patients with COVID-19 have been completed to-date.

Case Description: A 40-year-old Caucasian female with a history of hypertension and underwent emergency C-section due to fetal distress. Postoperative vaccinations were closely monitored post vaccination without event. The antibody response to vaccination could not be tested.

Discussion: Concurrent administration of COVID-19 vaccine with anti complement therapy poses special clinical challenges due to lack of conclusive data and guidance. SARS-CoV-2 virus, mRNA and adenovirus vaccines have shown to trigger Microangiopathic Hemolytic anemia (MAHA) and CM-TMA. Additionally, inconclusive data exists regarding the use of Eculizumab in the treatment of COVID-19. Data regarding strength of immune response after vaccination while on therapy is also limited. Due to increasing use of anti-complement therapies, we call for further research to aid development of guidelines for timing of covid vaccination. Such data will not only be useful in timely administration of preventive vaccination but also guide further management of complement mediated disorders.

Risk Factors for Post-COVID-19 Incident CKD in the National COVID Cohort Collaborative

Poster/Thursday

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Background: COVID-19 has been associated with accelerated GFR decline in hospitalized patients (pts), but prior studies are limited by cohort sizes, duration of follow-up and geo-specificity. Moreover, characterization of incident CKD in non-hospitalized patients with COVID is lacking.

Methods: Electronic health record data were obtained from 77 health systems in the United States in the National COVID Cohort Collaborative. Adults diagnosed with COVID between Mar 1, 2020, and Oct 1, 2022, and without pre-COVID CKD, were evaluated for incident post-COVID CKD until Dec 31, 2022. CKD was identified via outpatient eGFR measurements or diagnosis (dx) codes. Multivariable (MV) models were applied to analyze risk factors like pre-existing comorbidities (age, sex, race/ethnicity, and hospital region (Midwest, Northeast, South, West), hospitalization, AKI, and a reported diagnosis (I09.9) of long-COVID (PASC).

Results: Among 3,776 pts, 76% (2%) had incident post-COVID CKD. Of these pts, 55% (73%) were not assigned a CKD dx code but met requirements for eGFR-based CKD. Data regarding strength of eGFR-based CKD. In MV models, incident CKD was associated with older age, male sex, and Black and Native Hawaiian or Pacific Islander race (compared to White). Compared to pts never hospitalized during follow-up, event rates for incident CKD for pts hospitalized during follow-up were significantly higher (11.4 vs 28.7 /1000 patient yrs [pt- yrs]). Among hospitalized pts, those with AKI (vs no AKI) had an even higher rate of incident CKD (98.3 vs 21.2 /1000 pt- yrs). In MV analyses, when compared to pts never hospitalized, those hospitalized during COVID with AKI had much higher incidence of

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CKD (hazard ratio [HR] 1.32, p < 0.001). The adjusted odds ratios for incident CKD were higher in the West (1.32, p < 0.001) and South (1.03, p < 0.001) and lower in the Northeastern regions (0.94, p < 0.001) compared to the Midwest. In a sub-cohort of 1.5mpts evaluated at U09.9-reporting sites, PASC was associated with a moderately higher HR for incident CKD (1.41, p < 0.001).

**Conclusions:** In one of the largest studies on this topic, we observe that incident CKD in pts with COVID was underdiagnosed and influenced by geographical region, hospitalization and AKI. Pts with PASC had higher rates of CKD compared to those without.

**Funding:** NIDDK Support, Other NIH Support - This work was supported by National Center for Advancing Translational Sciences, (NCATS) Grant / Award Number: U24 TR002366 (YIT, SK, RAM, FMK), as well as the National Institute for Diabetes & Digestive & Kidney Diseases (Office of the Director, KJW), as part of the N3C program.

**FR-PO001**

A Network-Based View of AKI and CKD at Cell Subtype and Spatial Niche Resolution

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**Background:** Understanding functional relationships between genes and their regulators and how they are altered in acute kidney injury (AKI) and chronic kidney disease (CKD) is a crucial challenge. New computational methods are necessary to elucidate disease-specific gene regulation and function in spatial context.

**Methods:** We develop a computational framework to integrate spatial transcriptomics with single cell multi-omic data (Table 1) and infer disease-associated gene networks at spatial niche and cell type resolution. We identify spatial niches using a biological knowledge-informed matrix decomposition method, align single-cell multiome data with spatial transcriptome data, and infer functional regulatory relationships between genes using an integrated Bayesian framework.

**Results:** Using glomerular identification as an example, the spatial transcriptome-based niche pattern is concordant with image-based digital pathology. We build functional regulatory gene networks for ~50 kidney cell subtypes for each disease state. Focusing on the adaptive pro ximal tubule (pT) network, ~13000 gene ontology terms based on their differential network connectivity between disease states. The terms with highest differential connectivity include regulation of neutrophil tubule epithelial cell differentiation (CKD vs AKI), phospholipase A2 inhibitor activity (reference vs AKI), and regulation of kidney size (CKD vs reference). The regulatory networks mediated by HNF4A and NFkB1 in pT cells are further validated on independent single cell data (Lake et al 2023). These disease-associated cell type networks are aligned to spatial niches, enabling a spatially-resolved, cell-type specific characterization of molecular pathways in kidney disease.

**Conclusions:** Our framework provides a network-based view of molecular differences between kidney disease states, cell subtypes, and spatial niche patterns.

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

Table 1. Number of biopsies for each disease state.

<table>
<thead>
<tr>
<th>Data type</th>
<th>AKI</th>
<th>CKD</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
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<td>6</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>Single cell RNA-seq</td>
<td>2661</td>
<td>2972</td>
<td>25274</td>
</tr>
<tr>
<td>Spatial metabolite</td>
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</tbody>
</table>

**FR-PO002**

Integrative Metagenomic, Metabonomic, and Deep Immune Profiling to Reveal Coordinate Effects on Host-Microbe Interactions in CKD

I-Wen Wu,1,2 Cheng Gung Memorial Hospital, Keelung, Keelung, Taiwan; 2Chung Gung University College of Medicine, Taoyuan, Taiwan.

**Background:** Perturbation of gut dysbiosis is present in chronic kidney disease (CKD) and associated with a sophisticated milieu of metabolic and immune dysregulation. However, the underlying host-microbe interaction is unclear.

**Methods:** We performed multi-omics measurements, including systems-level gut microbiome, targeted serum metabolome, and high-dimensional immunotyping, in a cohort of 72 CKD patients and 20 controls.

**Results:** Our analyses on functional profiles of gut microbiome showed that loss of renal function decreased the diversity and abundance of carbohydrate-active enzyme (CAZyme) genes, but increased the abundance of antibiotic resistance, nitrogen cycling enzyme, and virulence factor genes. Models generated using measurements of circulating metabolites (amino acids, bile acids, and short-chain fatty acids) or immunotypes were predictive of renal impairment but less so than many of the taxonomic or functional profiles derived from gut microbiota, with the CAZyme genes being the top performing model to accurately predict early stage of diseases. Correlation analyses among different omics parameters revealed coordinated host-microbe relationships in CKD. Specifically, significant correlations were identified with circulating metabolites by several taxonomic and functional profiles of gut microbiome, while immune profile features were only moderately associated with the abundance of microbiome-encoded metabolic pathways and serum levels of amino acids.

**Conclusions:** Our multi-omics integration revealed signatures of the systems-level gut microbiome in robust associations with host-microbe co-metabolites and renal function, highlighting potential etiological and diagnostic implications in CKD.

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

**Integrated image:** Integration of the multi-omic experiment (A) The types and sample sources of omics analyses. (B) α- and β-diversity among the groups. (C) t-SNE plot detected by the flow cytometer. (D) PBMCs abundances densities from the groups. (E) Correlations between multi-omic data types and renal function.

**FR-PO003**

Developing a Kidney Genetics Registry Within an Electronic Medical Record

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**Background:** Dynamic patient registries within the electronic medical record (EMR) can provide security in a clinical setting by using existing tools to automate database compilation, reducing the time burden required to painstaking documentation whilst maintaining the accuracy of patient lists and data entry. A kidney genetics registry within the EMR facilitates decision-making that directly affects clinical care whilst concurrently contributing to a better understanding of disease processes and therapeutic approaches. We present our approach to the development of an EMR-embedded kidney registry in a tertiary pediatric setting highlighting the implementation challenges of amalgamating clinical data from multiple platforms.

**Methods:** An encounter-based EPIC registry was designed and created in collaboration with the Centre of Health Analytics for all patients referred to the Kidney Genetics clinic at the Royal Children’s Hospital, Melbourne from February 2016 to present. Metrics for data capture included demographic information, growth parameters, clinical diagnoses, non-genetic diagnostic test results (including imaging and histopathology), and surveillance (including clinical parameters, hematological and biochemical test results). Triggers for genetic re-evaluation or clinical intervention were included. A subsequent validation study was performed with a manually collated cohort of patients.

**Results:** The complete registry consisted of 516 patients (median age at presentation of 24 months). Challenges included the identification of appropriate patients, inclusion of genetic results from external laboratories, manual validation of non-machine-readable genetic reports, and the concurrent use of paper-based family genetic files. Sequencing was undertaken in the form of a clinical exome or whole exome sequencing with or without microarray depending on clinical indication. A genetic diagnosis was found in 88/212 (41.5%), variants of uncertain significance in 16/212 (7.5%), and incidental findings in 212 (0.94%).

**Conclusions:** Obtaining a genetic diagnosis can instigate a precision medicine approach, aiding risk stratification, tailored surveillance, initiation of disease-modifying therapies, and transplant planning. Combining genetic results with real-time monitoring of patients has the potential to streamline and automate this process.

**Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.**
ADPKD Predictor: A Cloud-Based Prognostic Tool for Autosomal Dominant Polycystic Kidney Disease

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Background: Total Kidney Volume is accepted by FDA and EMA as a prognostic biomarker for ADPKD and is currently used to select patients eligible for drug treatment. We developed ADPKD Predictor, a user-friendly cloud-based tool for fast and accurate estimation of disease classification and progression, based on advanced image processing techniques.

Methods: The tool was designed on Microsoft Azure Cloud to facilitate the use of a MATLAB algorithm to automatically detect kidneys and cysts contours from MRI data (Figure 1). TKV is automatically calculated and ADPKD Imaging Classification, eGFR, GFR Category, eligibility for drug treatment and estimated effect are obtained (Figure 2).

Results: The proposed solution is extremely fast and precise compared to manual segmentation (absolute mean error 2.4% ± 2.7%), and more accurate than ellipsoid-based method, resulting in a manifold reduction of misclassification error (2.5%). No numerical expertise, software or hardware is required since computations run remotely in the cloud.

Conclusions: ADPKD Predictor provides a fast and reproducible assessment of risk classification and disease progression. It is extremely useful to researchers and clinicians for effective stratification of patients, hence supporting correct therapy administration.

Using Deep Learning to Determine Kidney Function Decline in Patients with ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with progressive kidney cyst growth, eventually leading to kidney failure in many patients. The current risk stratification tool uses height-adjusted total kidney volume (TKV) by age. However, it does not include clinical or other imaging features that may contribute to kidney function decline. In this study, we developed a deep learning classifier that integrates clinical and imaging features to predict rapid estimated GFR (eGFR) decline in patients with ADPKD.

Methods: We included 120 patients with confirmed ADPKD with at least one MRI scan and at least 3 serial eGFR measures. An eGFR decline of 4 mL/min/1.73 m² per year or greater was defined as rapid progression. We tripled the sample size by extracting the largest manually segmented 2D MRI slice and its two neighbouring slices for each patient and assigning the corresponding clinical features. Pixel-level and spatial-level transformations were applied to the images to enhance our deep model’s generalizability and robustness. The model consisted of three components: 1) EfficientNet-B2, 2) FuseNet, and 3) Classifier with the train:validation:test split of 63:17:20. The EfficientNet-B2 extracted 1000 features from each MRI slice. The FuseNet performed feature fusion on 1.5 clinically relevant features associated with ADPKD. The feature maps obtained from both models were concatenated and fed into the Classifier. Weighted-average F1 and AUC scores and the confusion matrix were used to assess the model’s performance.

Results: The mean age of the study cohort was 46 years (SD 14), 54% were male, 95% were non-Black, hypertension prevalence was 79%, the median eGFR was 67 ml/min/1.73 m² (IQR 45-99), height-adjusted TKV was 940 mL/m² (IQR 542-1373), tolvaptan use was 53%, and the Mayo Imaging Class was 8%, 17%, 40%, 23%, 10%, and 2% for 1A, 1B, 1C, 1D, 1E and class 2, respectively. The weighted-average F1 and AUC scores and the true positive and true negative values were 0.88, 0.88, 0.88, and 0.88 on the validation set, respectively and 0.83, 0.83, 0.86, and 0.80 on the test set.

Conclusions: Our study demonstrates that a deep learning approach which integrates clinical information with MRI features can successfully classify patients at risk for rapid eGFR decline. Further validation in an external cohort is required.

In Silico Drug Repurposing of Aquaporin 1

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Background: Drug repurposing is the identification of new therapeutic targets for existing licensed medicinal compounds. We have developed protocols and programs for an in silico high-throughput repurposing screen using structural modelling, docking, and molecular dynamics (MD). Uniquely our approach uses a bespoke interface on Google Colab for graphic processing units (GPUs) to run the MD simulations. We describe its application to human aquaporin 1 (AQP1).

Methods: The library of British National Formulary listed compounds was obtained from NCBI PubChem. I-TASSER was used to generate monomeric structural models and Modeller for assembling oligomers. PLANTS was used for docking simulations. CHARM-GUI and bespoke software were used to prepare membrane-bound systems to run in GROMACS using GPUs in Google Colab. 20 nanosecond simulations were undertaken (300 Kelvin and 1 bar) to discriminate between binding and non-binding events.

Results: Complete monomeric and tetrameric structural models of human AQP1 were obtained incorporating chains of water molecules traversing the pores. Docking studies of 1002 drug compounds at the cytoplasmic opening of AQP1 identified 200 compounds binding in the pore. 45 compounds exhibited a higher calculated binding energy higher than the known binder furosemide and underwent further testing using
MD. The 20 nanosecond MD simulations distinguished the compounds which were not binding and elucidated the dynamics of the binders. A noteworthy finding was that furosemide induced a conformational change in the cytoplasmic chain.

Conclusions: We have developed a robust docking-MD protocol for high throughput repurposing screening. We have demonstrated that shorter simulations than previously published can reliably detect active binding conformations and identify compounds that could interact with human AQP1. Several commonly used medications exhibited stable interactions including furosemide, gabapentin, pregabalin, pravastatin and esmolol.

FR-PO011
Histopathological Prediction of CT-Based Radiomic Imaging Biomarkers in Native Kidney Biopsies
Ji Eun Kim, Kiijo Kim. Inha University Hospital, Incheon, Republic of Korea.

Background: In recent years, there has been a growing interest in radiomics as a quantitative approach for image analysis. This study aims to explore the relationships between radiomic features extracted from CT scans and histological findings obtained from kidney biopsies.

Methods: We retrospectively enrolled participants who underwent abdomen CT scan within 7 days before native kidney biopsy. Three-dimensional kidney segmentation was performed in two different methods; the entire kidney parenchyma and isovolumetric cortical area. We extracted various radiomics features such as shape, first-order, and texture features from the CT images. The histological findings were assessed using a semiquantitative scoring system, which assigned severity grades to various parameters including interstitial fibrosis (IF), tubular atrophy (TA), glomerulosclerosis (GS), interstitial inflammation (II), and arterial intimal thickening (IT).

Results: Total of 124 patients were included in the main analysis. The ROC curve analysis of the extracted radiomic features revealed higher AUC values for moderate IF, TA, and II in both the total kidney parenchyma and cortex. However, the ability to distinguish GS and IT was relatively lower. The most discriminatory features extracted from total kidney for IF and TA were GLCM IDMN (LLH-wavelet) and GLCM IDN (HLH-wavelet), with the AUCs of 0.84-0.88. For the kidney cortex, GLRLM RV (HLH-wavelet) and GLRLM DE (HLL-wavelet) had distinguish GS and IT was relatively lower. The most discriminatory features extracted from total kidney for IF and TA were GLCM IDMN (LLH-wavelet) and GLCM IDN (HLH-wavelet) with the AUCs approximately 0.83. For the kidney cortex, GLRLM GLNU (HLL-wavelet), GLRLM GLN (HLL-wavelet), GLRLM DE (HLH-wavelet), and GLRLM RV (HLH-wavelet) had the texture features with the highest AUCs for IF and TA, with the AUCs of 0.84-0.88. Texture features extracted from kidney cortex showed higher correlation with histologic features. We found that CT-based texture features consist of volume-dependent and independent components. Volume-independent texture features extracted from kidney cortex showed more a higher degree of correlation with chronic histologic scores.

Conclusions: In conclusion, our findings suggested the potential of CT-based radiomics in predicting chronic histological findings in kidney biopsies.

Figure 1. The association between interstitial fibrosis scores and representative texture features with high ROC-AUC values. (A) and (B) from the entire kidney parenchyma, (C) and (D) from cortical area. The associations between IF scores and (A) textureVision_HLGLNU_Circularity (B) textureVision_HLGLN_Circularity (C) textureVision_HLGLMRV_Circularity (D) textureVision_HLGLMRV_Circularity

FR-PO012
Assessment of Hemodialysis Arteriovenous Shunt (AV Shunt) Sounds by Using a Novel Electronic Stethoscope and Machine Learning Techniques

Background: Hemodialysis AV shunt management is performed by listening for auscultatory sounds. However, determining stenosis with a stethoscope requires skill, and it is difficult to make assessment objectively and quantitatively. We linked the echo findings of AV shunt to audio data obtained from a novel electronic stethoscope (Togo Medikit Co., Ltd., Japan) and used these data to train AI, and then developed software that estimated two labels with AI. In this study, the usefulness of this software in clinical settings was examined by comparing the rating of trained staffs and AI for auscultatory sounds.

Methods: The quality and intensity of the shunt sounds were evaluated in six levels by trained staffs just before and after dialysis by auscultation mainly just above the shunt creation site. At the same time, 20 seconds of shunt sound data were electromagnetically recorded from each patient by a novel auscultation device. The sound quality rating by the staffs was 0–3 as bad, 4–5 as good, while the electromagnetically recorded sound data was rated as normal or abnormal using the developed software. Match rate, sensitivity, and specificity by both evaluation methods were calculated.

Results: We compared the ratings of trained nurses and AI for 191 auscultatory sounds. The matching rate between the two was 66.0%. 83.3% of the subjects were classified as normal by AI, when trained staff judged as “bad”. 94.1% of the subjects were judged “good” by trained staff, when AI calculated as normal. Contrary to expectations, the rate of AI judging as normal was higher after dialysis than before, even though the intensity of the shunt sound was weaker after dialysis. When echo examination showed shunt blood flow reduction, it was more likely to be judged as abnormal by AI compared to the judgment by the staff.

Conclusions: In this study, AI rating for AV shunt sounds was considered to be at an acceptable level for clinical use. However, there are differences between trained staffs and AI for “normal” results. This reason for this may be that the AI label is based on the echo. This evaluation method using a new device is expected to become more useful with additional AI learning.

FR-PO013
eGFR Trajectories Among Children with CKD Using a Multi-Institutional Electronic Health Record Database
Jarcy Zee,1,2 Caroline A. Gluck,1 Mitchell Malenfant,2 Amy Goodwin Davies,2 Ryan Webb,2 Miranda J. Higginbotham,3 Elana Dickoco,2 Vikas R. Dhamdhere,2,3 Keith A. Marsolo,2 Priya S. Verghese,2 Rebecca Ruebner,2 Dorey A. Glenn,2 Alicia Neu,2 Michelle Denburg,2 1University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 2Children’s Hospital of Philadelphia, Philadelphia, PA; 3Penn clinically Observational Research Network, a computable phenotype was implemented to identify children ages 1-18 years old with CKD stage 2-3A. Over half were in stable or improving eGFR trajectories, and only a small proportion exhibited steep decline. These subgroups provide the basis for further research on the factors that predict these trajectories.

Methods: Using electronic health records from 16 healthcare institutions within PCORnet, a computable phenotype was implemented to identify children ages 1-18 years old with CKD stage 2-3A. Over half were in stable or improving eGFR trajectories, and only a small proportion exhibited steep decline. These subgroups provide the basis for further research on the factors that predict these trajectories.

Results: N=17,168 children with CKD were grouped into four eGFR trajectory classes [Figure]. Class 1 (“steep decline”) contained N=499 (2.9%) patients with mean eGFR at cohort entry of 66.4 and a moderate, nonlinear decline in eGFR. Class 2 (“moderate decline”) had N=6,661 (38.8%) patients with mean entry eGFR of 59.2 and a moderate, nonlinear decline. Class 3 (“stable”) had N=7,999 (46.6%) patients with mean entry eGFR at cohort entry of 66.4 and a steep, nonlinear decline in eGFR. Class 4 (“moderate nonlinear decline”) had N=6,661 (38.8%) patients with mean entry eGFR of 59.2 and a moderate, nonlinear decline. Class 3 (“stable”) had N=7,999 (46.6%) patients with mean entry eGFR of 59.2 and a moderate, nonlinear decline. Class 4 (“moderate nonlinear decline”) had N=6,661 (38.8%) patients with mean entry eGFR of 59.2 and a moderate, nonlinear decline.

Conclusions: Four distinct classes of eGFR trajectories were identified among children meeting criteria for CKD stage 2-3A. Over half were in stable or improving eGFR subgroups, and only a small proportion exhibited steep decline. These subgroups provide a real-world, multi-institutional characterization of eGFR trajectories among children with mild-moderate CKD.
FR-PO014
Regulation of the Adaptive Proximal Tubule Cell State by ELF3, KLF6, and KLF10
Debora L. Gisch, Blue Lake, CA; Jeaninne M. Basta, Michelle Pherson, Ying-Hua Cheng, Ricardo Melo Ferreira, Daria Barwinska, Mahla Ashghar, Tarek M. El-Achkar, Shamin Mollah, Jonathan Himmelfarb, Matthias Kretzler, Pierre C. Dagher, Sanjay Jain, Michael I. Rauchman, Michael T. Eadon.
KPM. Indiana University School of Medicine, Indianapolis, IN; 2 San Diego Institute of Science, Altos Labs, San Diego, CA; 3 Washington University in St Louis School of Medicine, St Louis, MO; 4 Saint Louis University, Saint Louis, MO; 5 University of Washington, Seattle, WA; 6 Michigan State University, East Lansing, MI.

Background: Gene regulatory regions modulate gene expression and maintain cell function. In response to injury, the proximal tubule (PT) undergoes adaptation, including differentiation or epithelial to mesenchymal transition, resulting in successful or failed repair. Single-cell multisite, whole genome bisulfite sequencing (WGBS), and CUT&RUN were used to study the regulatory control of the PT as it undergoes this adaptation.

Methods: Single-cell multisite with ATAC-seq data was generated and analyzed for 12 kidney tissue samples. TRIPOD and scMEGA were used for analysis. Celloracle in silico perturbation tested DEG changes after the knockout of transcription factors (TFs). scMEGA was used to map TF activity in spatial transcriptomics samples (N=3). Regulatory relationships were characterized by WGBS and CUT&RUN. The overall performance of the segmentation algorithm for all classes in the training set was 91.78 ± 0.02 Dice scores for the glomerulus, healthy tubules, necrotic tubules, and tubules with cast. The highest Intersection over Union and the Dice coefficient are obtained for the segmentation in injury in mouse PAS-stained samples. In the segmentation model for four structures, the Dice score was 91.78 ± 0.12 for the glomerulus, 91.65 ± 0.14 for tubules, 91.78 ± 0.02 for necrotic tubules, and 91.78 ± 0.02 for tubules with cast. A segmentation model was developed for acute tubular injury using deep learning models.

Conclusions: ELF3, KLF6, and KLF10 contribute to the PT’s adaptive response to injury as a regulatory network, specifically localized to the PT.

Funding: NIDDK Support

FR-PO015
Evaluating the Impact of a Tailored Electronic Medication Management System on Anemia Management in Outpatient Hemodialysis Patients
Xiaohui Sheng, Niansong Wang. Department of Nephrology, Shanghai Sixth People’s Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Background: The prevalence of Medication-related problems (MRPs) in outpatient hemodialysis patients, especially in anemia management, is high. We developed a tailored electronic medication management system for outpatient hemodialysis (the New System) and evaluated its impact on anemia management.

Methods: The New System was collectively developed by our hospital and Spectrum Healthcare, building on the existing electronic information system. We compared the percentage of patients with hemoglobin, ferritin, transferrin saturation within the KDIGO recommended range, and cardiovascular events six months before (control period) and after (study period) the implementation of the New System.

Results: Using the New System, physicians perform evaluations and prescribe medications based on patients’ lab reports. After patient payment and pharmacist review, medications are auto-allocated to a virtual pharmacy in the Hemodialysis Center. The New System then generates a medication form before each dialysis session for nursing staff. On dialysis days, the system displays the predetermined prescriptions. After administration by nurses, the system auto-deducts the used medication. The control period included 285 patients (190 males and 95 females, aged 62.4±13.2 years), and the study period included 278 patients (193 males and 85 females, aged 62.8±13.2 years). Compared with the control period, the percentage of patients at the study period with hemoglobin (40.2% [887/1710] vs 47.8% [977/2068], P<0.001), ferritin (31.2% [176/557] vs 39.0% [217/556], P=0.016), transferrin saturation (56.6% [334/570] vs 64.7% [360/556], P<0.034) within the KDIGO recommended range was higher. The occurrence of cardiovascular events during the study period was 11.2% (31/278), which was lower (P=0.043) compared to the control period where it was 16.5% (47/285).

Conclusions: The implementation of the New System in the Hemodialysis Center improves anemia management in outpatient hemodialysis patients. The study hints that an electronic medication management system tailored for outpatient hemodialysis holds potential in addressing partial MRPs.

Funding: Government Support - Non-U.S.

FR-PO016
Deep Learning Model for Evaluating Histopathology of Acute Renal Tubular Injury

Background: Acute tubular injury is the most common cause of acute kidney injury (AKI). Histopathological diagnosis may help distinguish between the different types of acute kidney injury and aid in treatment. Currently, no studies have utilized deep learning models to assist in the histopathological diagnosis of acute kidney injury. The aim of this study is to perform histopathological segmentation to identify the four structures of acute renal tubular injury using deep learning models.

Methods: We use a segmentation model (glomerulus, healthy tubules, tubules with cast, and necrotic tubules) to classify tubule-specific injuries after cisplatin treatment. A total of 45 whole slide images with 400 generated patches are used in the segmentation model and 27,478 annotations are created for four classes, namely glomerulus, healthy tubules, necrotic tubules, and tubules with cast. A segmentation model was developed utilizing the DeepLabV3 architecture with the MobileNetv3-Large backbone to accurately identify four histopathological structures associated with acute renal tubular injury in mouse PAS-stained samples. In the segmentation model for four structures, the highest Intersection over Union and the Dice coefficient are obtained for the segmentation of the “glomerulus” class, followed by “necrotic tubules,” “healthy tubules,” and “tubules with cast” classes.

Results: The overall performance of the segmentation algorithm for all classes in the test set includes an Intersection over Union of 0.7968 and Dice coefficient of 0.8772. The Dice scores for the glomerulus, healthy tubules, necrotic tubules, and tubules with cast are 91.78 ± 11.09%, 87.37 ± 4.02%, 88.08 ± 6.83%, and 83.64 ± 20.39%, respectively.

Conclusions: The utilization of deep learning in a predictive model has demonstrated promising performance in accurately identifying the histopathological structures of injured renal tubules. These results may provide new opportunities for applying the proposed methods to more effectively evaluate renal pathology in the future.

Funding: Other U.S. Government Support
FR-PO017
Proximal Tubule Neighborhood in AKI, CKD, and Healthy Control Kidney Tissue Using Spatial Transcriptomics
Mahalia Asghar,1 Michael Yoshifumi and Image Processing Is a Novel Method to Reveal Therapeutic Targets
Capturing Spatial Transcriptomics Around Cysts with Deep Learning
FR-PO018
Proximal Tubule Neighborhood in AKI, CKD, and Healthy Control Kidney Tissue Using Spatial Transcriptomics
Mahalia Asghar,1 Ricardo Melo Ferreira,1 Ying-Hua Cheng,1 Debora L. Gisch,1 Daría Barwinka,1 Angela R. Sabo,1 Matthias Kretzler,1 Jonathan Himmelfarb,3 Pierre C. Dagher,1 Seth Winnick,1 Sanjay Jain,1 Tarek M. El-Achkar,1 Michael T. Eadon,1 KPMP, Indiana University School of Medicine, Indianapolis, IN; 2University of Michigan, Ann Arbor, MI; 3University of Washington School of Medicine, Seattle, WA; 4University of Nebraska Medical Center, Omaha, NE; 5Washington University in St Louis School of Medicine, St Louis, MO.

Background: The interaction of proximal tubules (PTs) with neighboring immune, stromal, and endothelial cells may impact their physiological functions. Using spatial transcriptomics (ST), we sought to establish the spatially anchored microenvironments of the PT across kidney samples in chronic kidney disease (CKD), acute kidney injury (AKI) and healthy human kidney biopsy samples.

Methods: We interrogated 23 samples from the HuBMAP, Kidney Precision Medicine Project (KPMPP) and Biopsy Biobank Cohort of Indiana with Vismum ST. Cell labeling was performed using a transfer score methodology of the publicly available snRNAseq atlas. Label score vectors were utilized to cluster and identify niches in R. Pathway analysis was performed in PathfinDEG analysis of Barcoded spots in these areas. A list of histopathology-related genes was obtained DEG analysis of Barcoded spots in these areas. A list of histopathology-related genes was obtained in 23 samples from the HuBMAP, Kidney Precision Medicine Project (KPMPP) and Biopsy Biobank Cohort of Indiana with Vismum ST. Cell labeling was performed using a transfer score methodology of the publicly available snRNAseq atlas. Label score vectors were utilized to cluster and identify niches in R. Pathway analysis was performed in PathfinD

FR-PO019
Interactive Visualization of Kidney Structural Segmentations and Associated Pathomic Features on Whole Slide Images
Mark Keller,1 Nicholas Lucarelli,2 YiJiang Chen,3 Bangchun Wang,4 Charles E. Alpers,5 Andrew Janowczyk,5 Jeffrey B. Hodgkin,6 Samuel Border,5 Sayat Mimara,5 Ahmed Nugali,7 Nikki Bondoch,7 Ulysses G. Balis,7 Jonathan Himmelfarb,3 Matthias Kretzler,3 Laura Bartisomi,4,11 Nils Gehlenborg,1 Pinaki Sarwar,1 The Kidney Precision Medicine Project (KPMPP).1 Harvard Medical School Department of Biomedical Informatics, Boston, MA; 2University of Florida Department of Biomedical Engineering, Gainesville, FL; 3Case Western Reserve University Center for Computational Imaging and Personalized Diagnostics, Cleveland, OH; 4Duke University Department of Pathology - Division of AI and Computational Pathology, Durham, NC; 5University of Washington Department of Laboratory Medicine & Pathology, Seattle, WA; 6Emory University Department of Biomedical Engineering, Atlanta, GA; 7University of Michigan Department of Pathology, Ann Arbor, MI; 8University of Florida Department of Medicine - Quantitative Health, Gainesville, FL; 9University of Michigan Department of Medicine - Division of Nephrology, Ann Arbor, MI; 10University of Washington Kidney Research Institute, Seattle, WA; 11Duke University Department of Medicine - Division of Nephrology, Durham, NC.

Background: The Kidney Precision Medicine Project (KPMPP) is a collaborative study generating histology images and spatial molecular data from patient biopsies. To enable seamless study of whole slide images (WSI) and derived data, it is important to integrate solutions for navigation and visualization into computational pipelines.

Methods: We built a pipeline to (a) apply previously developed segmentation models of kidney structures on KPMPP PAS-stained WSIs, including for globally/non-sclerotic glomeruli, arteries/arterioles, tubules, peritubular capillaries (PTC), interstitial fibrosis and tubular atrophic (IFTA), and the cortical interstitial fractional space (Ginley et al., bioRxiv 2023); (b) extract quantitative features from these structures; and (c) load these data in Vitessce (http://vitessce.io), a web-based framework for visualization and analysis of biomaging data.

Results: Segmented KPMPP WSIs linked to corresponding extracted features are visualized using quantitative colormaps and statistical plots such as histograms, violin plots, and bar charts. As a use case, we explore the spatial relationship between different structures and associated features (i.e., aspect ratio of PTCs in IFTA and non-IFTA regions).

Conclusions: Image analysis methodologies paired with web-based visualization tools allow for the interactive examination of renal morphometry. These tools enable KPMPP investigators and a broader public to exploit WSI-extracted data for integration with other omics data and hypothesis generation and testing.

Funding: NIDDK Support
Vitesses showing WSI data overlaid with segmentations of multiple kidney structures and statistical plots of quantified features such as area, cell thickness, or luminal fraction (of tubules) associated with those structures.

FR-PO020
Self-Supervised Learning Applied to Kidney Histomorphology in Whole Slide Images
Krutika Pandit,1 Nicolas Coudray,2 Adalberto Claudio Quiros,2 Aditya L. Surapaneni,1 Avi Z. Rosenberg,2 Katalin Susztak,2 Morgan Grams,2 Aristotelis Tsiiris.3 1 New York University, New York, NY; 2 University of Glasgow, Glasgow, United Kingdom; 3 Johns Hopkins University, Baltimore, MD, USA.

Background: Current approaches to characterize medical imaging data typically use some degree of supervision, relying heavily on expert annotation. Pathologist reads can have high inter-observer variability. A supervised model built on these reads will mimic the idiosyncrasies of the expert and may perpetuate inter-observer inconsistencies. Supervised approaches also require time-consuming and meticulous labeling on the input images. Given the limitations, supervised learning may not be optimal for unbiased and generalizable characterization of histologic patterns in the kidneys, which are complex.

Methods: Histomorphological Phenotype Learning leverages the latest advances in self-supervised learning (SSL), the Barlow-Twins method, to learn representations of image tiles that are later clustered by the Leiden method, a state-of-the-art community detection algorithm. This strategy was used to discover de novo clusters of histologic patterns across sets. Clusters that were visually indicative of disease were linked to gene expression and metabolic processes.

Results: Visual inspection of representative tiles from clusters revealed comparable histologic patterns across sets. Clusters that were visually indicative of disease were positively correlated with fibrosis; clusters representing healthy tissue were negatively correlated with fibrosis (Figure 1). The best-performing elastic net model used 17 clusters to predict percent fibrosis (R² in test set = 0.81).

Conclusions: In this study, we demonstrated the application of SSL to characterize WSIs of the kidney. Features extracted from this approach were associated with and demonstrated good prediction of expert-provided histology scores. Subsequent work will link clusters to gene expression and metabolic processes.

Funding: NIDDK Support

FR-PO021
Diverse Immune, Stromal, and Vascular Niches Along the Cortico-Medullary Axis of the Human Kidneys by Integrating 10 Different Modalities Performed on the Same Tissue Block
Seth Winfree,1 Blue Lake,2 Ricardo Melo Ferreira,2 Anthony A. Fung,2 Angela R. Sabo,3 Madhirema Kaushal,4 Daria Barwinka,2 Bo Zhao,5 Joseph Gnat,5 Kun Zhang,5 Lingyan Shi,5 Michael T. Eadon,5 Tarek M. El-Achkar,6 Sanjay Jain.7 HuBMAP.1 University of Nebraska Medical Center, Omaha, NE, USA; 2 Altos Labs Inc, Redwood City, CA; 3 Indiana University School of Medicine, Indianapolis, IN; 4 University of California San Diego, La Jolla, CA; 5 Washington University in St. Louis School of Medicine, St. Louis, MO.

Background: Methods to delineate cell types and microenvironment using multiple modalities (DNA, RNA, protein and metabolites) across cortico-medullary axis and that are applicable in a clinical setting are needed to understand cellular basis of kidney disease.

Methods: Multimodal assays were performed on same or sequential sections using an innovative freezing and processing method on prechilled metal blocks: 1) 10X multimodal (snRNAseq and snATACseq on same cell, 280µm), 2) Light microscopy (5µmH&E, SUPMPS), 3) 10X VISIUM and H&E (spatial transcriptomics, 10µm), 4) CODEX (40plex antibody panel for nephron, immune, endothelial, stromal and kidney injury, 10µm) and H&E, 5) Label free imaging with Stimulated Raman Scattering (SRS) microscopy on the same section as CODEX to generate lipids, extracellular matrix and pseudo-H&E data. Integration of modalities used molecular, cellular, and morphological bridges across kidney functional tissue units (FTUs).

Results: The tissue processing pipeline was feasible with multiple omic and spatial technologies from the same block at multiple institutions with passing QC for each assay. 10X multimodal (snRNAseq and snATACseq on same cell, 280µm) yielded more than 25 million unique, 20 stromal and 20 endothelial cell identities with clear zonation along the cortico-medullary axis. Novel niches of several fibroblast and immune cells were identified using VISIUM integrated with CODEX where 3.9 million cells (5 donors, 30 cell types based) on protein markers showed distinct zonation and higher protein-to-lipid ratio and increased lipid saturation in podocytes and mesangial cells versus distal tubules were seen in CODEX-SRS mapping.

Conclusions: This work outlines the collection and construction of a multimodal atlas of the human kidney from same tissue by 1) Integrating multimodal single cell and FTU spatial map using less than half depth of a kidney biopsy is feasible and compatible in a clinical setting, 2) Identifying zonation of interstitium and vascular cell diversity along the cortico-medullary axis by multiple modalities, 3) RNA-protein-lipid-ECM-histology mapping in millions of cells, neighborhoods and FTUs.

Funding: NIDDK Support

FR-PO022
Accuracy of Bayesian Improved First Name Surname Geocoding (BIFSG) for Race and Ethnicity Imputation in a Kidney Care Management Program to Assess Racial Disparities
Liana D. Bruce, Christopher S. Krasniak, Cliff S. Eddings, Brandon Phan, Bassem Mikhael, Joe Kimura. Somatus, McLean, VA.

Background: Self-reported race and ethnicity data are ideal for classifying race and ethnicity to improve equity and close health outcome disparities, but these data have low response rates, typically <20%. Our goal was to validate race and ethnicity imputed using the BIFSG algorithm against self-reported data in a kidney care management program.

Methods: Patients and responses are classified into six Office of Management and Budget standardized combined categories. We applied RAND’s indirect estimation method to generate estimates based on first names, surnames, and ZIP Codes. Accuracy, specificity, sensitivity, and positive predictive value (PPV) were then calculated to compare BIFSG-imputed values with self-reported values in a validation subsample.

Results: 53,695 (16%) of 326,679 patients self-reported race/ethnicity. BIFSG predicted 269,354 (82%) of the overall population, including 44,964 of the self-report cohort. After imputation, 278,085 (85%) of patients had non-missing race/ethnicity. Overall imputed value accuracy compared to self-report was 99%. PPV was highest for Hispanic and lowest for American Indian or Alaskan Native, while accuracy was highest for Native and lowest for White.

Conclusions: Imputation of race/ethnicity can improve analyses of health disparities in kidney disease. The BIFSG imputation model obtained highly accurate (99%) predictions of race and ethnicity in a large chronic kidney disease population, increasing coverage of racial identity from 16% to 85%. The BIFSG algorithm could be supplemented with additional sources eg, historical records to impute residual missing data. Incorporating additional data and advanced machine learning models will improve predictions to better track health disparities.

Funding: Commercial Support - Somatus

<table>
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<tr>
<th>Metric</th>
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TP: True Positives, FP: False Positives, FN: False Negatives, TN: True Negatives

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO023
Prediction of Individual Educational Attainment in ESKD Patients Using Zip Code-Derived Measures
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Background: Social determinants of health (SDOH) are associated with various health outcomes. Area-level SDOHs based on patients’ zip codes or census tracts have been commonly used in research instead of individual SDOH. Previous work showed that zip code-derived SDOH measures were inaccurate in highly heterogeneous urban neighborhoods. Therefore, we aimed to predict individual SDOH by using machine learning.

Methods: We used data from ESKD patients ≥25 years old enrolled in two studies at Mount Sinai in NY. All patients completed a questionnaire regarding the highest level of education, age, gender, and race/ethnicity. We used data from the American Community Survey to achieve the zip code-derived education based on the patient’s zip code, gender, and race/ethnicity. We tested several machine-learning algorithms, including Naïve Bayes, decision tree, and random forest (RF). We then developed three multi-class prediction models to predict individual educational attainment. Model 1 used only zip code-derived education. Model 2 included model 1 + demographic variables and comorbidity. Model 3 included model 2 + neighborhood SDOHs (GINI and dissimilarity indices). The model was divided into 75/25 training and test sets, and 5-fold cross-validation was employed.

Results: A total of 603 ESKD patients were identified. The mean age was 58±12 years. 55% of patients attained less than high school, 32% completed high school, and 13% had a bachelor’s degree or higher. Only 31% of zip code-derived education accurately matched actual education. The RF model has the best overall performance. Using RF, model 1 enhanced accuracy to 51% with an AUROC of 0.62 (95% CI 0.53 to 0.67). Model 3 demonstrated the highest accuracy (59%) and AUROC (0.71; 95% CI 0.63 to 0.77) (Figure 1).

Conclusions: Combining zip code-derived educational attainment with demographic data and neighborhood SDOH measures can improve the prediction of individual education in ESKD patients. This may improve the performance of models that incorporate SDOH as a feature.

Funding: NIDDK Support

FR-PO025
Exploring the Diversity of Clinical Profiles and Outcomes in Kidney Transplant Recipients with Limited Education Using Clustering Analysis
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Background: Education level has been identified as a potential predictor of post-transplant outcomes for kidney transplant recipients. However, there is a lack of research focusing on recipients with lower education levels and their unique clinical characteristics. Therefore, the objective of our study was to utilize unsupervised machine learning techniques to cluster kidney transplant recipients with lower education levels.

Methods: We performed consensus clustering analysis on 20,474 kidney transplant recipients with education levels below college/university using recipient, donor, and transplant data from the OPTN/UNOS database (2017-2019). We identified significant clinical characteristics for each cluster and compared posttransplant outcomes.

Results: Most recipients had completed high school (86%) and were non-white (64%). We identified four clusters: Cluster 1 comprised young, non-diabetic patients receiving kidneys from young, non-hypertensive, non-ECD deceased donors with lower KDPI. Cluster 2 included preemptive or early dialysis initiators, predominantly white, receiving kidneys from living donors. They showed better outcomes. Cluster 3 consisted of young kidney re-transplant recipients with higher PRA and fewer HLA mismatches. Cluster 4 involved older, diabetic patients receiving kidneys from lower-quality donors. Cluster 2 exhibited the best outcomes, while clusters 1, 3, and 4 had higher risks of graft failure and patient mortality.

Conclusions: Unsupervised machine learning successfully clustered kidney transplant recipients with lower education levels into four distinct groups, each with unique clinical profiles and varying posttransplant outcomes. Cluster 2 demonstrated the best outcomes, while clusters 1, 3, and 4 had higher risks of graft failure and patient mortality. These findings have implications for personalized care and risk stratification in kidney transplant recipients with lower education levels.

FR-PO024
Uncovering Subgroups of Diabetic Deceased Donor Kidney Transplant Recipients with Differing Outcomes Using Consensus Cluster Analysis
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Background: Diabetic donor kidney transplants have inconsistent clinical outcomes, possibly due to population heterogeneity. This study aimed to use an unsupervised machine learning technique to cluster kidney transplant recipients with lower education levels.

Methods: The study analyzed recipient-, donor-, and transplant-related characteristics of 3,176 recipients of diabetic deceased donor kidney transplants from 2010 to 2019 in the OPTN/UNOS database. Consensus cluster analysis was performed to identify important clinical backgrounds of AKI patients in each cluster, compared with annotation by three nephrologists.

Results: One hundred and twelve patients (18.2%) had at least one AKI episode. We created a dataset from the electronic medical records (EMR) of 616 patients who received ICI therapy at the Kyoto University Hospital from July 2014 to September 2022. AKI was defined by serum creatinine changes more than 1.5× the baseline without any known acute kidney injury guideline. We developed a gradient-boosting decision-tree-based machine learning (ML) model continuously predicting AKI within 7 days from each time point, using 287 clinical variables obtained from EMR as input features. We noted that the temporal changes in individual predictive reasoning in AKI prediction models represented the key features contributing to each AKI prediction, and clustered AKI patients based on the pattern of features with high predictive contribution quantified in time-series by SHapley Additive exPlanations (SHAP), a model interpretation framework. We searched for common clinical backgrounds of AKI patients in each cluster, compared with annotation by three nephrologists.

Results: One hundred and twelve patients (18.2%) had at least one AKI episode. They were clustered per key features and their SHAP value patterns, and the nephrologists assessed the clusters’ clinical relevance. Receiver operating characteristic analysis revealed that the area under the curve was 0.880. Patients with AKI were categorized into four clusters with significant prognostic differences (p=0.010). The leading causes of AKI for each cluster, such as hypovolemia, drug-related, and cancer cachexia, were all clinically interpretable, which conventional approaches cannot obtain.

Conclusions: Our results enabled us to clarify the background of AKI development in ICI-treated patients with complicated AKI risks and suggested the potential for applying ML prediction models as interpretable artificial intelligence to medical care, which had been a challenge to explainability.

FR-PO006
Interpretable Machine Learning-Based Individual Analysis of AKI in Immune Checkpoint Inhibitor Therapy
Minoru Sakuragi1,2, Eiichiro Uchino,1,2 Noriaki Sato,1,2 Takeshi Matsubara,3 Ryo Suzuki Kojima,1 Motoko Yanagita,1 Yasushi Okuno,1 Department of Biomedical Data Intelligence, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 2Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 3Institute for the Advanced Study of Human Biology (ASHBi), Kyoto University, Kyoto, Japan.

Background: Acute kidney injury (AKI) is a critical complication in immune checkpoint inhibitor (ICI) therapy. Since the etiologies of AKI in cancer therapy vary among patients, clarifying AKI causes in individuals is critical for optimal cancer treatment. Although it is essential to individually analyze ICI-treated patients for underlying pathologies existing behind each AKI onset occurring at different times, these analyses have not been realized with conventional clinical research methods.

Methods: We created a dataset from the electronic medical records (EMR) of 616 patients who received ICI therapy at the Kyoto University Hospital from July 2014 to September 2022. AKI was defined by serum creatinine changes more than 1.5× the baseline. The model was divided into 75/25 training and test sets, and 5-fold cross-validation was employed.

Results: One hundred and twelve patients (18.2%) had at least one AKI episode. They were clustered per key features and their SHAP value patterns, and the nephrologists assessed the clusters’ clinical relevance. Receiver operating characteristic analysis revealed that the area under the curve was 0.880. Patients with AKI were categorized into four clusters with significant prognostic differences (p=0.010). The leading causes of AKI for each cluster, such as hypovolemia, drug-related, and cancer cachexia, were all clinically interpretable, which conventional approaches cannot obtain.

Conclusions: Our results enabled us to clarify the background of AKI development in ICI-treated patients with complicated AKI risks and suggested the potential for applying ML prediction models as interpretable artificial intelligence to medical care, which had been a challenge to explainability.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO027

Development, Implementation, and Outcome of Telemedicine to Improve Access to Renal Health During the COVID-19 Pandemic at the National Kidney and Transplant Institute (NKTi)

Melchor A. Atilliero, National Kidney and Transplant Institute, Quezon City, Philippines.

Background: With health care facilities becoming high risk places during the COVID pandemic, NKTi has developed adjustments in the provision of healthcare for outpatient consultation during the pandemic. This study aims to describe the development, implementation and outcome of telemedicine among service renal patients of Adult Nephrology Department in NKTi Out-Patient Service (OPS).

Methods: A hybrid model of telemedicine and ambulatory visits was utilizing synchronous video consults integrated with electronic medical records (EMR). Data were collected from the NKTi-OPS and Adult Nephro System including e-survey forms to assess patient satisfaction.

Results: Comparing with pre-pandemic, a 29% decrease in the mean service renal patient consultation/month was noted, with 28% and 50% reduction in GN and KT respectively. During the 4-month dry run of the program, the GN telemedicine utilization was only 4% while 27% for KT. With the full operation by October 2020, an increase of telemedicine usage was observed for both GN and KT with a high percentage among KT 68% vs 34% in GN patients. Majority of patients who utilized telemedicine were within 30-40 age group with comparable demographics between sex. Telemedicine was used by patients in almost all regions in the Philippines. Over-all patient satisfaction rate was 95.2%.

Conclusions: Delivering telehealth consultation to renal patients in our Institute during the COVID-19 pandemic demonstrated that it is feasible and well accepted alternative in augmenting patient care.

FR-PO028

Using Telemedicine Compared with Face-to-Face Visits for Outpatient Management in CKD Patients

Nichapat Apibankurukit, Anan Chuauswan. Bhumibol Adulyadej Hospital, Bangkok, Thailand.

Background: In the recent past, Coronavirus disease 2019 (COVID-19) was a pandemic. Telemedicine is thought to be used for outpatient management in chronic kidney disease (CKD). We aim to set up a virtual management for CKD patients because we want to reduce hospital visits and congestion in CKD clinic to decrease the risk of COVID-19 infection in CKD patients. This study aimed to compare the effectiveness of telemedicine with face-to-face visits for outpatient management in CKD patients.

Methods: A non-inferiority, non-randomized open-label controlled trial in a CKD clinic at Bhumibol Adulyadej Hospital, Bangkok, Thailand from January 2022 to January 2023. The patients were divided into 2 groups, using telemedicine and face-to-face visits. The primary outcome was to compare the percentage change of eGFR-EPI between the two groups.

Results: There were 32 patients in both the telemedicine and face-to-face visits group. The majority were male 60.9%. The mean age was 72.2 ± 11.2 (SD) years. CKD KDIGO stage 4 was the majority by 56.2% and mean eGFR-EPI was 24.6 ± 9.9 (SD) ml/min/1.73 m². The eGFR increased by 2.1% in the telemedicine group and decreased by 2.1% in the face-to-face visits group (p = 0.374). There was no difference between the two groups in all-cause mortality, hospitalization, emergency department visits, renal replacement therapy initiation rate, co-morbidities and CKD complications controlled, adherence, and satisfaction with the service. Telemedicine had higher quality of life, measured from the EQ-5D scales (69.5 vs 58.4 scores, p = 0.009), and used shorter timing in the visit (52.5 vs 189.5 minutes, p = 0.001) than the face-to-face visits group.

Conclusions: Compared to face-to-face visits, telemedicine for outpatient management in CKD patients is not inferior in the percentage change of eGFR, co-morbidities, and CKD complications. Telemedicine tends to have a better quality of life, shorter the timing of the visit, and lower travel costs to the hospital.

Funding: Government Support - Non-U.S.

The difference in change of eGFR between the telemedicine group and face-to-face visits groups at 2, 4, and 6 months in follow-up times.

FR-PO029

Integration of CODEX and Brightfield Histology for Cell Type Segmentation and Classification Using Deep Learning

Nicholas Lucarelli,1 Seth Winfree,2 Angela R. Sabo,1 Samuel Border,1 Daria Barwinska,1 Zoltan G. Laszik,3 Michael T. Eadon,1 Tarek El-Achkar,1 Sanjay Jain,1 Pinaki Sarder,1 University of Florida Department of Biomedical Engineering, Gainesville, FL; 2University of Nebraska Medical Center Department of Medicine, Omaha, NE; 3Indiana University Department of Medicine - Division of Nephrology and Hypertension, Indianapolis, IN; 4University of California San Francisco Department of Pathology and Laboratory Medicine, San Francisco, CA; 5Washington University in St Louis Department of Medicine Division of Nephrology, St. Louis, MO; 4University of Florida Department of Medicine - Quantitative Health, Gainesville, FL.

Background: Cell types in a biopsy provide information on disease processes or organ health. Multiplex imaging technologies like CODEX provide spatial context to protein expression and detect cell types in a tissue sample. New CODEX workflows allow for hematoxylin and eosin (H&E) staining on the same sections. Deep learning can automate the process of image analysis, saving time. We seek to segment and classify cell nuclei from renal tissue sections using deep learning with CODEX generated cell labels as a ground truth.

Methods: Images consisted of brightfield H&E whole slide images (WSIs) from two institutions, collected from human reference kidneys. Nuclei were segmented using deep learning, and CODEX markers were measured for each nucleus. Cells and their markers were clustered in an unsupervised manner and assigned labels according to upregulated markers and biological priors. Cell types included: proximal tubules, distal tubules connecting tubules and collecting ducts, thick ascending limb, podocytes, endothelium, vessels, and immune cells. Cell maps were used to train a Deeplab V3+ semantic segmentation model. Classification was assessed in hold-out slides from CODEX generated sections.

Results: Two segmentation models were trained on WSIs from each institution. For the model trained on 3 sections containing ~3.9M cells, we achieved a balanced accuracy of 0.68, and for the model trained on ~350k cells from 11 sections, we achieved 0.75.

Conclusions: We were able to automatically segment and classify nuclei from various cell types directly from H&E stained WSIs. In future work, we seek to extend these segmentations to typical WSIs in renal pathology, with no prior molecular interrogation.

Funding: NIDDK Support, Other NIH Support - R21DK128668, OT2 OD033753, R01 DK114485

Images consisted of brightfield H&E whole slide images (WSIs) from two institutions, collected from human reference kidneys. Nuclei were segmented using deep learning, and CODEX markers were measured for each nucleus. Cells and their markers were clustered in an unsupervised manner and assigned labels according to upregulated markers and biological priors. Cell types included: proximal tubules, distal tubules connecting tubules and collecting ducts, thick ascending limb, podocytes, endothelium, vessels, and immune cells. Cell maps were used to train a Deeplab V3+ semantic segmentation model. Classification was assessed in hold-out slides from CODEX generated sections.

The difference in change of eGFR between the telemedicine group and face-to-face visits groups at 2, 4, and 6 months in follow-up times.
FR-PO030

Comparison of a Deep Learning Model with Human Expert Annotations for Segmentation of Kidneys, Tumors, and Cysts in Routine CT Imaging Exams


Background: This study explores if a deep learning model for automatic kidney, tumor, and cyst segmentation from abdominal CT images can match interrater agreement.

Methods: A deep learning model was developed to segment the kidneys, tumors, and cysts from abdominal CTs. The training/validation set consisted of 1003 images from 479 unique subjects. A urologic oncologist with expertise in renal tumor evaluation and treatment (reference standard) and two radiology residents with experience in general abdominal CT imaging manually segmented 30 images, a held-out test set subset. Segmentation overlap between the reference standard and residents, or AI segmentations was assessed via the Dice coefficient. Confidence intervals (CI) for the probability the Dice coefficient between the reference standard and AI segmentation was larger than the with the residents based on a Mann Whitney U equivalence test were generated for left kidney, right kidney, tumor, and cyst.

Results: The mean and standard deviation of the Dice coefficients between reference standard and residents (AI) were 0.91±0.03 (0.93±0.03) for left kidney, 0.92±0.02 (0.94±0.02) for right kidney, 0.80±0.23 (0.86±0.18) for tumor mask, and 0.24±0.35 (0.42±0.37) for cyst mask, 0.81±0.24 (0.83±0.23) (see Figure 1). The 90% CIs tended to be greater than 0.5 in all cases but the tumor masks (see Table), suggesting the AI is often performing within expected interrater agreement.

Conclusions: A fully automated kidney, tumor, and cyst segmentation algorithm was trained and evaluated against three independent readers. The AI algorithm was found to compare similarly to interrater agreement.

FR-PO031

Development and Evaluation of a Vision Transformer-Based Machine Learning Model for Improved Nephron Segmentation in Kidney Disease Analysis


Background: Impacting over 20 million globally, kidney diseases mostly stem from nephron lesions. Nephrons’ complex tubular structure complicates 3D pathology assessment. We’ve created a workflow merging optical clearing and AI to automate and improve this process. Optical clearing transfer samples transparent for accurate nephron mapping. Light-sheet microscopy visualizes these structures, but precise segmentation is required for measurements like tubule volume. Our proposed vision transformer-based machine learning model automates these measurements, assisting diagnosis and offering gene expression insights. This adaptable method extends to other tubular tissues, promising wider benefits.

Methods: We collected 36 quarter-mouse-kidney light-sheet microscopy images, each 2048x2048 pixels, with a depth range of 700-1200 pixels. Images are split into blocks and individually segmented. Each block is treated as a 2D image series. Adjacent images’ local features and segmentation results are encoded using a convolutional neural network. The transformer encoder/decoder processes high-level contextual representations, while the convolutional decoder recovers spatial dimensions and generates a tubule probability map. The final segmentation mask is derived from a normalized output probability map, and blocks are reassembled into an original-size image. Segmentation results can be visualized and validated using VR.

Results: Amid ongoing data annotation, preliminary tests of our model on a synthetic dataset of 6000 images showed promising results. After ten epochs of training on 4800 images, it demonstrated an IoU score (Intersection over Union, a measure of the overlap between the predicted segmentation and the ground truth) of 93%, Binary Accuracy (percentage of correctly predicted data points out of all predictions) of 98%, and F1 Score (100% indicates a more robust prediction) of 96% on a validation set of 1200 images.

Conclusions: Despite synthetic data’s simplicity, our model’s promising performance implies its potential with real-world data. We’ll keep refining the model and, once enough real-world data is annotated, we’ll test and compare it with baseline models like the Classical 3D Convolutional Neural Network. At that point, we’ll release the model’s structure, code, annotated data, and performance results.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO032**

**Automated Pipeline for Peritubular Capillary Inflammation Scoring**

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**Background:** Antibody-mediated rejection (AMR) can occur after kidney transplantation and is characterized by immune cell-mediated microvascular injury in response to donor-specific antibodies (DSA) and results in progressive graft survival and function. Using dual immunostaining for endothelium (anti-CDS4) and leukocytes (anti-CD45), we identified peritubular capillaries (PTCs) and intracapillary leukocytes to determine the inflamed peritubular capillary ratio (iptcr), a quantitative Microvascular Inflammation (MVI) score that in a previous study correlated with renal graft failure and DSA strength.

**Methods:** Initially, we selected our stain vectors through QuPath. Used them to implement color deconvolution to separate CD34 (Red) (PTCs) and CD45 (DAB) (leukocytes). Thresholding and noise removal techniques were applied to each WSI to segment PTCs and leukocytes. The iptcr was determined by the ratio of total leukocyte (+1 cell) containing PTCs to total PTCs. Automated iptcr scores were compared to ground truth iptcr from manual scoring.

**Results:** There was a high correlation between pathologist and automated iptcr score (R-square: 0.83). Perhaps even more important automated iptcr was 4X faster versus manual pathologist scoring for each WSI.

**Conclusions:** Our automated approach based on using a relatively simple analytical pipeline (intensity transformation/enhancement, texture analysis, binarization, and morphological processing) makes iptcr scoring feasible. Our early results demonstrate the potential of the iptcr score pipeline as an efficient supplementary tool for improved AMR evaluation to replace the current discontinuous scoring system in place. Further validation and exploration of larger cohort are warranted.

**Funding:** NIDDK Support

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**FR-PO033**

**Multimodal Data Analysis with Spatial Transcriptomics**

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**Background:** Spatial transcriptomics (ST) methods have provided researchers the ability to link morphological observations in histology with molecular mechanisms. This expanded view has great potential in a clinical setting towards improving patient stratification and treatment design. However, it is difficult for a human to handle all of these data. Machine Learning (ML) methods are specially equipped to handle dense datasets, exhibiting high performance on image-related tasks. ML can be used to provide stratification and treatment design. However, it is difficult for a human to handle all of the data. Our training data without substantial augmentation. Predictions made on a patch-level were converted into heatmaps for visualization of cell type localization.

**Results:** FUSION is deployed on the web for public access. SpotNet achieved a Mean Absolute Error (MAE) of 6.4±3.2%, 10.1±1.8%, 1.2±1.16%, 11.9±4.2% on prediction of 6 cell types and 4 cell states for glomeruli and 12 cell types and 4 cell states for tubules respectively. Predicted cell localizations overlapped well with ground truth.

**Conclusions:** We present a method for interactive viewing of ST data and a novel ML model for prediction and interpretation from images. Integration of this model into our visualization platform will enable highly granular analysis of histology.

**Funding:** Other NIH Support - TO2 OD033753

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**FR-PO034**

**The Acceptability and Usability of My Kidneys & Me, a Digital Self-Management Health Intervention for CKD**


**Background:** The use of digital health interventions (DHIs) to provide education and support has rapidly increased, especially in the post-COVID era, due to potential cost-effectiveness and ease of equitable delivery. We co-developed My Kidneys & Me (MK&M), an educational self-management DHI for CKD. Here we report the usage metrics of MK&M during a 20-week evaluation.

**Methods:** As part of a randomized trial, participants at 26 UK sites were given access to MK&M for 20-weeks. MK&M provided online education sessions (underpinned by behaviour change theory), and digital applications to track goals, symptoms, physical activity, and clinical measures. Access to and usage data of MK&M were collected, alongside perceived usefulness (scored from 0 (not useful at all) to 10 (very useful)). Frequency analysis identified the frequency and length of time spent on MK&M sessions.

**Results:** 281 patients received MK&M (age 60.8±12.8 years, 58% male, eGFR 38.9±18.5 ml/min/1.73m²). 205 (73%) used MK&M at least once. The median number of login per person was 10.0 (IQR 6.0–20.0). The median time per login was 12 mins (IQR 7-25 mins). ‘The kidneys’ was the most accessed session (n=152 participants). Table 1 displays top three sessions by the total number times accessed and total duration spent on session. All sessions scored ≥7/10, with ‘Kidney disease and general health’ considered the most useful session (8.7/10). Goal setting was considered the most useful tracker (8.5/10) and symptoms the least (6.7/10).

**Conclusions:** MK&M was well received and utilised by participants. Our findings show that people with CKD are capable and willing to use DHIs for kidney health. Identification of real-life use and usability issues will help refine MK&M, improving the content and delivery before clinical implementation.

Top three sessions by the total number of times session accessed and total duration of time spent on the session per participant.

<table>
<thead>
<tr>
<th>Session title</th>
<th>Median time</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managing my symptoms</td>
<td>13</td>
<td>15-11</td>
</tr>
<tr>
<td>How to return to and be active</td>
<td>13</td>
<td>13-19</td>
</tr>
<tr>
<td>Treatment options available</td>
<td>13</td>
<td>13-15</td>
</tr>
</tbody>
</table>

Table 1: Total duration of time spent on sessions per participant.

NB. IQR: interquartile range

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

Underline represents presenting author.

414
FR-PO035

Tracking the 3D Architecture of Hundreds of Nephrons and Peritubular Capillaries in Health and Disease Using Light Sheet Microscopy and Deep Learning
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Background: Until recently, it has been practically impossible to study whole kidney nephrons and peritubular capillaries throughout the many millimeters of tissue necessary to examine them in their entirety. This technical limitation has obscured correlations and causal relationships between different parts of the same nephron, and between nearby nephrons and vasculature in cases of injury. Our study will use recent technical breakthroughs in 3D imaging, tissue clearing, and artificial intelligence to study thick specimens and process large datasets. We aim to establish a 3D connectivity map of hundreds to thousands of nephrons and study the coupling of injuries between glomeruli, tubules, adjacent nephrons, and peritubular capillaries at different stages of chronic kidney disease.

Methods: We used in vivo antibody labeling and solvent-based clearing to uniformly stain and clear whole mouse kidneys, which were then imaged on a custom-built lightsheet microscope with sub-cellular spatial resolution. We processed the 3D fluorescence data using a human-in-the-loop AI method, a deep-learning-based supervised image segmentation that allows for scaling up to large volumes and segmenting many nephrons at a time.

Results: From a single fluorescence label, our deep learning segmentation model traced hundreds of whole nephrons in 3D. We also used vasculature labeling to visualize and quantify the characteristics of the peritubular capillary network around the nephrons. So far, we have generated 3D renderings of nephrons and connectivity maps, and performed associated morphometrics (length, volume, tortuosity) for nephrons in healthy kidney.

Conclusions: We have developed a pipeline using 3D imaging and artificial intelligence to extract relevant 3D features in hundreds of whole nephrons and capillaries in the same tissue. We will apply this framework to study the spatial correlations of injuries at various timepoints in models of chronic kidney diseases, such as focal segmental glomerulosclerosis and ischemia-reperfusion injury.

Funding: Private Foundation Support

FR-PO037

ToxIPedia: A Website Research and Education Tool on Uremic Toxins
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Background: Mounting evidence suggests that current understanding of uremic toxicity is limited. As many different uremic toxins are being identified there is a need for research tools to better study, classify and analyze the different molecules implicated in uremic toxicity, their origin, chemical structure, metabolism, and ill effects. ToxIPedia, is an encyclopedic free access website, to be used as a tool to store all information on each toxin, its effects, chemical structure, metabolic, proteomic, and toxicological classifications, and other pertinent information. It may also provide a continuously updated resource for researchers to study and analyze uremia. The clinical impact of uremic toxins will also be retrievable. The website aims to serve as an educational and research tool to improve renal replacement therapies that eliminate these toxins, improve the quality of life, and reduce morbidity and mortality.

Methods: The website is designed with a website generator to allow physicians and researchers to easily contribute to it. An advisory committee will validate the project to provide independent guidance and expert advice to improve the project before it is completed, along with a peer review process for every page. As new data on uremic molecules develops researchers can update and revise relevant pages to keep the website up to date.

Results: Online free access catalogue of Uremic Toxins allows retrieving all relevant information on Uremic Toxins.

Conclusions: This website may close current knowledge gaps and improve the accessibility of information on uremic toxins. It will also provide a much-needed resource to organize the large mass of emerging data on the uremic syndrome, causes, mechanisms, and complications. It is hoped that ToxIPedia will contribute to more knowledge and better treatment of uremic toxicity.

FR-PO036

Data-Driven Disease Detection: A Learning Health System
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Background: Achieving pre-clinical diagnosis in time to change the course of disease is the promise of data analytics and genomic medicine. Our Kidney Genomics Clinic (KGC) showed a high diagnostic yield for Alport syndrome (AS) in a pediatric cohort with persistent microscopic haematuria. Early diagnosis of AS in childhood offers an opportunity to start treatment and delay progression. Large studies of variant databases have shown heterozygous pathogenic variants in COL4A5 in 1 in 2320. Despite guidelines and education, patients have shown heterozygous pathogenic variants in COL4A3/COL4A4 are present in 1 in 415 and pathogenic variants in COL4A5 in 1 in 2320. Despite guidelines and education, referral rates remained static and follow up rates were low. We created a digital health solution using data analytics of the electronic medical record (EMR) to identify children with an incidental finding of microscopic haematuria and offer early genomic diagnosis to those at risk of AS.

Methods: EMR databases were interrogated using Microsoft SQL to identify patients with incidental findings of microscopic haematuria and no prior or subsequent results below the threshold (20 RCC). Patients were stratified according to levels of haematuria and those with pyuria excluded. Patients were contacted with a letter outlining the need for repeat testing utilising bulk communication and ordering functions within the EMR. All those with persistent microscopic haematuria were offered genomic sequencing for repeat testing utilising bulk communication and ordering functions within the EMR. All those with persistent microscopic haematuria were offered genomic sequencing for repeat testing utilising bulk communication and ordering functions within the EMR.

Results: Figure 1

Conclusions: Direct patient contact through the EMR is feasible and acceptable demonstrating how digital health strategies can be employed to solve problems in healthcare. Response rates using postal contact are poor; alternate modes of communication may improve uptake. Lessons learned from this will be utilized to develop a prospective strategy automating the process for recall of future findings of microscopic haematuria.
FR-PO038
Perceived Value of Advance Care Planning Documents in the Electronic Health Record: A Qualitative Study of Chief Medical Information Officers, Clinicians, and Patients with CKD
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Background: Older adults with advanced chronic kidney disease (CKD) are at high risk for hospitalization, serious complications, cognitive decline, and death. Despite this, advance care planning (ACP) remains low among this population. Barriers to ACP completion and the impact of ACP availability in the electronic health record (EHR) are not well understood.

Methods: Qualitative study using semi-structured interviews (March 2022-March 2023) with purposively sampled patients (CKD stage 4-5 patients, age ≥50), chief medical information officers (CMIOs), and clinicians. Participants discussed EHR-related barriers and facilitators to ACP completion and accessibility. Audio recordings were transcribed verbatim and a thematic analysis was conducted.

Results: 72 participants (29 clinicians, 11 CMIOs, 33 patients) completed interviews. Among clinician and CMIO participants, 33% were women and 43% were from the Northeast. Among patients, 36% were women, 39% identified as Black, and mean age was 70 ± 9 years. Four themes with subthemes emerged: 1) Challenges to ensuring patient autonomy (document ownership, evolving patient preferences, ensuring preferences are actionable); 2) Valuable ACP requires interoperability (lack of standardized ACP protocols, variable access across settings, limited infrastructure and incentives, policies for improving interoperability); 3) Complexity of timing (in-the-moment decisions, clinical triggers for intervention and options for workflow); and 4) Consequences of inconsistent ACP protocols (discordant care, overconfidence that patient wishes are known).

Conclusions: The perceived value of ACP is negatively impacted by inconsistent access to ACPs across settings. Recommendations for increasing the reliability of ACP at the time of need include encouraging patient ownership of ACP documents, ensuring revisions occur regularly and are reconciled in the EHR; institution-level training on storage and documentation of ACP in the EHR; employing available EHR tools such as trigger messages; and introducing financial incentives for sharing across institutions.

Funding: Private Foundation Support

FR-PO039
Implementing a Supportive Information System for the Vaccination Program of CKD Patients: Project from the Regional Nephrology Program, Military Hospitals, Taif Region, Saudi Arabia
Najlaa AlMalki, Hichem Abdi.1 Al Hada Armed Forces Hospital, Taif, Saudi Arabia.

Background: Vaccination rates remain particularly low in chronic kidney disease (CKD) patients, with diminished immune responsiveness due to delayed vaccination. Based on an in-depth review of vaccination-related processes, this project aimed at ensuring CKD patients timely receive all recommended vaccines, while boosting vaccination culture among healthcare providers, and implementing information system support for smoothly shared documentation through the continuum of care.

Methods: An in-depth review of national and international guidelines related to the vaccination of CKD patients was undertaken. Existing local policies were reviewed in comparison. Additionally, real-life practices were scrutinized to understand the level of adherence to policies, physicians’ vaccination culture, prescription and administration of vaccine processes, and the information systems that underlay them.

Results: Standardizing and centralizing electronic vaccine prescription and documentation was one of the specific objectives of the project. Different, non-linked supports -electronic and paper- were used in the different nephrology units, which resulted in siloed in-unit data, that was impossible to be shared instantly or consulted remotely. The absence of a defined process in the clinics hindered vaccine prescribing for outpatients. Prescribing was standardized by adding vaccines to the regular medication form on the electronic medical record (EMR). To standardize documentation, the EMR native pediatric vaccination form was upgraded to hold adult vaccines. A reminder -that would pop up whenever the EMR is opened- was added to the system to help staff carry out planned vaccination. The preventive medicine (PM) vaccination clinic was linked to the information system to support the vaccination of nephrology outpatients. The clinic was mapped with an individual code, allowing for referral and booking, and for full access of the PM nurses to the prescription information and to the newly created vaccination form for documentation.

Conclusions: A coherent information system, that allows for readily available and smoothly shared information, is an essential component to support the development of a comprehensive vaccination program for chronic kidney disease patients through their continuum of care.

FR-PO040
Have You Googled Your Kidney? Interpretation of Google Trends Data During World Kidney Day
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Background: World Kidney Day (W KD) is a global campaign conducted yearly in March to raise awareness of the importance of kidney disease. Analysis of the public’s online interest may provide insight into the effectiveness of such awareness efforts.

Methods: We performed a retrospective study looking at relative search volumes (RSVs) of terms related to kidney disease from January 2006 to April 2023 in the USA. The search terms’ RSVs during March of each year were compared to the other months of the year. Pearson correlation coefficient was used to determine the statistical significance of the change in the RSV of W KD and its related search terms such as “Kidney Disease”, “Chronic Kidney Disease”, “Kidney damage”, “Acute Kidney Injury”, and “Diagnosis”.

Results: Throughout the years, an upward trend was observed in the RSVs of W KD and its associated terms. However, no consistent statistically significant correlation was found between the RSVs of W KD and related terms during March compared to the other months of the year. There were isolated statistically positive correlations found in March 2023 between RSVs for W KD, “dialysis,” and “kidney disease” (p=0.04 and p=0.019, respectively), as well as an isolated positive correlation in March 2019 with the terms “kidney disease” (p=0.006). Siddiquy, the workflow, and the workflow (p=0.039) between W KD and “Kidney Failure” for all the years analyzed.

Conclusions: Studies with similar designs have shown solid statistical correlations between the public’s online queries and the Pink October campaign for breast cancer and the Go Red campaign for heart disease. The interpretation of these findings suggests that these campaigns have successfully raised public awareness. Our study found an inconsistent positive correlation between W KD and specific terms over the years within our study period. Moreover, a negative correlation was noted with “Kidney Failure” for all the years. Further research emphasizes the need for more studies on creating and executing awareness campaigns for kidney disease that can achieve the same success as those for other similarly burdensome illnesses.

Funding: NIDDK Support

FR-PO041
Characterizing the Genetic Architecture of Rare Glomerulonephropathy Disease: The Landscape of RNA Binding Protein Dysregulation
Tessa A. Marvin,1 Aviya Litman,2 Chen Wang,2 Chandra L. Thesfeld,1 Laura H. Mariani,1 Krzysztof Koryluk,2 Matthias Kretzler,2 Olga Troyanskaya,3 CureGN Genetics,1 Princeton University Princeton Center for Quantitative Biology Lewis-Sigler Institute for Integrative Genomics, Princeton, NJ; 2Columbia University Vagelos College of Physicians and Surgeons, New York, NY; 3University of Michigan Department of Internal Medicine, Ann Arbor, MI; 4Princeton University, Princeton, NJ.

Background: The majority of primary glomerular nephropathy (GN) cases present with either immunoglobulin A nephropathy, focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease. Despite overlapping pathologies, each diagnosis may represent many distinct disease subtypes with unique etiologies. Even as most disease risk is concentrated in a small number of genes, most patients do not carry syndromic mutations in GN-associated genes. Regulatory mutations that alter the magnitude or spatiotemporal aspect of expression may contribute to the genetic architecture of disease. RNA binding proteins (RBPs) regulate the life cycle of the RNA molecule (e.g. alternative splicing). Here we employ a genome-wide analysis of >67 million mutations in WGS of GN patients from the Cure Glomerulonephropy (CureGN) cohort using a set of RBPs and their target sites to characterize the role RBPs play in the genetic architecture of GN.

Methods: To assess the pathogenic contribution of RBP dysregulation to GN, we identified the functional impact of GN patient variants on RBP binding profiles using Seqweaver, a deep learning framework for predicting variant dysregulation for over 200 known binding protein models with single nucleotide sensitivity. To determine if there are global signals of RBP dysregulation across the CureGN cohort, we identified trends in RBP disease impact scores across the patient variants. A pipeline was designed to select high-importance variants that are disease specific to identify mechanisms of disease. Beyond looking at individual RBP and variants in isolation, we utilized a network-based approach to nominate active disease processes at a pathway level.

Results: We observed genes enriched for predicted high-importance variants from different patients (e.g. FAM5), and together, the rare variants associated with GN GWAS had signatures for average disease impact than control variants associated with all other genes. Importantly, we also observed significant enrichment of RBP impact in kidney cell types. Seqweaver variant predictions provide hypothesis for biochemical mechanisms that explain GWAS association signals.

Conclusions: These findings suggest that RBP regulatory mutations of known kidney disease genes may harbor substantial disease risk.

Funding: NIDDK Support
FR-PO042
Vascular Calcification Heterogeneity Evaluated by Deep Radiomics Based on Chest Radiography
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Background: Vascular calcification (VC) is regarded a systemic pathology involving most arterial segments. Recent studies suggest that calcification heterogeneity exists, meaning that VC involves different wall components and locations, indicating diverse calcification patterns. We previously established a chest radiography-based radiomic approach for identifying VC. In this study, we aimed to evaluate whether radiographic calcification heterogeneity existed, in the form of different VC distributions between those with and without chronic kidney disease (CKD).

Methods: We devised a classification method using the attention mechanism of a deep learning neural network, whose architecture was first trained in a large chest radiography dataset, and then used as an initialization for the target domain with fine-tuning. We divided substrate images into subdivisions with grids and numeric values showing the radiomics features guided by deep learning attention mechanism. Boxes were used to indicate regions more significantly affected in patients with at least stage 3b CKD comparing to those in non-CKD populations. We visualized the attention of the network and extracted attentional areas.

Results: We analyzed chest radiography images from 11,106 general population (3.3% with VC) and 59 stage 3b or higher CKD patients (61% with VC). We examined the differentially attentioned areas between CKD and non-CKD patients after deep learning (Figure 1A, overlapping images). Activated areas, or differentially calculated areas in CKD patients included the ascending aorta, carotid vessels, and inter-diaphragmatic areas of thoracoabdominal aortas (Figure 1B). Quantitative analysis revealed inter-diaphragmatic areas exhibited the highest radiomic feature values, followed by carotid vessels and ascending aorta region (Figure 1C).

Conclusions: Using deep radiomics, we demonstrated specific aortic segments and branch arteries to be more significantly affected by VC among CKD patients than those without. Calcification heterogeneity can be detected using deep radiomics.

FR-PO043
Automated Detection of Renal Contrast Phases

Background: Renal contrast phases are vital for evaluating renal function, assessing pathology, detecting abnormalities, and formulating treatment plans. In this study, we utilized a combination of deep learning (DL) and regression techniques to identify contrast agents in CT scans and determine the specific stages of contrast-enhanced (CE) renal imaging. Initially, DL was employed to differentiate between CE and non-CE scans. For scans with administered contrast agents, a random forest regression model was trained to predict the complete range of values associated with the contrast phases. This approach allows for a more precise analysis of the continuous chronological sequence of contrast phases, rather than relying on predefined categories like classification.

Methods: The DL model is trained using a ConvNeXt-Fento architecture to classify CE and non-CE renal imaging. We used 3033 CT scans from 1017 patients with renal cell cancer. Using a segmentation model the left and right kidney were segmented. We selected 5 two-dimensional slices of the kidneys for classification: the middle slice based on the right kidney, two slices above, and two slices below. This simplified the input data while leveraging renal image characteristics. Features extracted from DL were used as input for a regression task using random forest to associate a value with each contrast phase based on chronological sequence aspects of renal enhancement. We employed five-fold cross-validation for training, using a sixth fold as the test set.

Results: The models performed well both in contrast detection and phase association tasks. The DL achieved an accuracy of 98% in classifying CE versus non-CE. For predicting other contrast phases, the model had a mean absolute error (MAE) of 0.34 on the test set. The model effectively associates numerical values with the eight contrast phases from “early corticomedullary” to “late pyelectographic”, enabling characterization of renal contrast enhancement patterns.

Conclusions: Coupling DL and regression, proved to be highly effective in automating the detection of contrast agents in CT scans and accurately determining the specific stages of CE in renal imaging. This approach enables comprehensive analysis of the continuous chronological sequence of contrast phases, surpassing the limitations of predefined categories typically used in classification.

Funding: Other NIH Support - National Human Genome Research Institute (NHGRI)

FR-PO044
Characterizing Urinary Tract Infections and Their Treatment Pathways EHR
Ning Shang, Katherine Xu, Krzysztof Kiryluk. Columbia University, New York, NY.

Background: UTIs are one of the most common infections worldwide. UTI epidemiology studies show a 27% recurrent rate in women within 6 months after the first UTI. Hence UTI early diagnosis and systematic treatment are very important. This project studies antibiotics treatment pathways (medication usage sequence) using big data.

Methods: We developed an electronic UTI phenotype identifying UTI by having at least 1 diagnosis/positive urine culture. It can further subgroup UTI as having a single episode of UTI or recurrent UTIs using 1-week time window to define each episode. UTI treatment pathways were analyzed for those who had at least one antibiotic in EHR. The patient had to have at least a 1-year of data in the database before the first UTI occurrence to be included. The medications were defined by ingredients using RxNorm and were grouped to drug class using ATC. The medications were extracted, and then ordered by first exposure. The sunburst plots were generated to visualize the pathways.

Results: Analyzing 5-M CUMC EHR spanning back to 1980s, we identified 176,533 UTI patients (71% single vs 29% recurrent), consistent with prior reports. Among them, 112,126 patients qualified for this analysis. Recurrent UTIs patients were younger than single UTI patients (48 vs 53 years). The prevalence of female UTI was significantly higher than male UTI (female in overall 83%, in single UTI 82%, in recurrent UTI 87%). The five most commonly used antibiotics were nitrofurantoin monohydrate (24%), cephalaxin (23%), nitrofurantoin/tetracaine (22%), ceftriaxone (18%), sulfamethoxazole/trimethoprim (17%) (Fig 1).

Conclusions: We designed a new electronic phenotype to detect single and recurrent UTI events. This algorithm can be useful for big data approaches to studies of UTI epidemiology and treatment patterns.

Funding: Other NIH Support - National Human Genome Research Institute (NHGRI)

FR-PO045
A Machine Learning Approach to Differentiating Between Typical Diabetic Nephropathy (DN) and Atypical DN with Podocytosis in Periodic Acid-Schiff (PAS)-Stained Whole Slide Images of the Kidneys
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Background: Diabetic nephropathy (DN) is a leading cause of end-stage kidney disease. Other podocytopathies may occur in the setting of diabetes, leading to atypical presentations and potential responsiveness to immunosuppressants. Differentiation between typical and atypical cases is infeasible with light microscopy alone. We show that atypical DN with other podocytopathy can be differentiated from typical cases by uncovering clusters in a 2D projection of quantitative morphological features of glomeruli.

Methods: 99 PAS-stained whole slide images of DN kidney biopsies (91 typical; 8 atypical) were fed into a deep learning model to segment glomeruli, from which
315 morphological features were quantified. Features were categorized according to compartment: glomerular, PAS-positive (P), luminal (L), nuclear (N), both P & L, both P & N, and both L & N. They were further categorized according to type: morphological, size, color, radial, relative distance, textural. Points representing cases in a 315-dimensional hyperplane (1 dimension per feature) were projected onto 2D while preserving high-dimensional clusters using uniform manifold approximation and projection (UMAP) method.

Results: Points representing typical DN cases clustered separately from atypical cases (top of projection). See Fig. 1.

Conclusions: Since some podocytopathies in the setting of DN respond to immunosuppressants, our approach could inform treatment in DN cases with suspicion of co-occurring podocytopathy. Given the infrequency of atypical cases and the overwhelming background diabetes, data are scarce. Future research may identify features that contribute to the clustering and to understand how morphology can inform diagnosis.

Funding: NIDDK Support

Fig. 1: Two-dimensional uniform manifold approximation and projection (UMAP) of 315 morphological image features of glomeruli from 99 cases of diabetic nephropathy (DN). (91 typical, 8 atypical). Points representing typical DN cases (blue points) occupy the greater part of the projection and clustered separately from atypical cases (orange points; top of projection). This illustrates that atypical DN cases with dense cortex could overlap with typical DN cases. UMAP projects high-dimensional clusters onto 2D while preserving high-dimensional structure.

FR-PO046
Symptom Trajectories in the Electronic Health Record During the Transition to Dialysis
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Background: How symptoms recorded in the electronic health record (EHR) change during the transition to dialysis has not been fully explored.

Methods: Using Optum’s de-identified Integrated Claims-Clinical Dataset, we identified individuals with CKD stages 4-5 who transitioned to dialysis. We searched clinical notes for symptoms, identified by natural language processing, recorded across weekly intervals in the 6 months before and after dialysis initiation. We estimated changes in the odds of a symptom being recorded with an interrupted time series analysis using segmented logistic regression.

Results: The cohort comprised 728 individuals (mean age 67.7 ± 13.1 years, 44.0% women, 55.9% White and 29.9% Black). During the 6 months prior to dialysis initiation, 83.3% were recorded as having fatigue, 68.4% had fatigue/weakness, 66.3% had shortness of breath, 60.6% had nausea/vomiting, and 37.1% had difficulty concentrating. Before initiation, odds of a symptom being recorded as having fatigue/weakness increased (OR 0.95 per week, 95% CI 0.94 – 0.97). Patterns for shortness of breath, nausea/vomiting, and difficulty concentrating were similar to those of fatigue/weakness.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The CANVAS/CREDENCE trials evaluated the effects of the SGLT2i canagliflozin on cardiorenal outcomes in patients with type 2 diabetes at high cardiovascular risk or with CKD. We validated the Klinrisk model for prediction of CKD progression, defined as greater than 40% decline in eGFR or kidney failure. The model applies results from complete blood cell counts, chemistry panels, comprehensive metabolic panels, and urinalysis. Model performance was assessed up to 3 years (median follow up 2.4 years) with the area under the receiver characteristic operating curve (AUC). Brier scores, and calibration plots of observed and predicted risks. We compared performance of the model to standard of care using eGFR (G1-G4) and urine ACR (A1-A3) KDIGO heatmaps categories.

**Results:** Among 14,464 patients in CANVAS/CREDENCE, we found the Klinrisk model provided excellent discrimination for CKD progression (696 events at 2 years), with an AUC of 0.81 (95% confidence interval 0.78 – 0.83) for prediction of the outcome at 1 year, increasing to 0.88 (0.86 – 0.89) at 3 years. Brier scores were 0.020 (0.018 – 0.022) at 1 year, increasing to 0.056 (0.052 – 0.059) at 3 years. Calibration was satisfactory, with minor overprediction in patients randomized to canagliflozin. Compared to the KDIGO heatmap, the Klinrisk model had improved performance at every interval (Table 1).

**Conclusions:** The Klinrisk machine learning model using routinely collected laboratory features was highly accurate in its prediction of CKD progression in the CANVAS and CREDENCE trials.

<table>
<thead>
<tr>
<th>Time frame, years</th>
<th>AUC (95% CI)</th>
<th>Brier score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.81 (0.78 - 0.83)</td>
<td>0.020 (0.018 - 0.022)</td>
</tr>
<tr>
<td>2</td>
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<td>3</td>
<td>0.80 (0.78 - 0.82)</td>
<td>0.044 (0.042 - 0.050)</td>
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**FR-PO050**

**Overview and Outcomes of the Kidney STARS Program**

Lili Chan,1 Leticia Rolon,2 Molly Rubin,3 Keisha L. Gibson,4 Ursula C. Brawer,5 Robert S. Hoover,6 Stephen M. Sozio.7 *Icahn School of Medicine at Mount Sinai, New York, NY; 1University of California San Francisco School of Medicine, San Francisco, CA; 2American Society of Nephrology, Bethesda, MD; 3University of North Carolina Wilmington, Wilmington, NC; 4Yale School of Medicine, New Haven, CT; 5Tulane University, New Orleans, LA; 6Johns Hopkins University, Baltimore, MD.

**Background:** The ASN Kidney Students and Residents (STARS) program was founded to increase interest in Nephrology careers. In addition to tailored events and networking opportunities, this program provides travel support and complimentary registration to attend the Annual Meeting during ASN Kidney Week. Understanding the impact of Kidney STARS participation on recruitment of trainees into the nephrology workforce is critical.

**Methods:** We tracked medical students (MS) and residents (PGY) STARS participants from 2009-2017 using Doximity, ABIM, and ABP by searching for the participants’ first and last names. Two reviewers validated the search results. MS began to be accepted into the program in 2010. Those that participated multiple times were logged in their first year of participation only. Participating who were still in training at the time of tracking (e.g., MS or PGY), were international participants, or were unable to be validated by the reviewers were excluded from final analysis. Starting in 2010, assessment of participant interest in nephrology pre- and post-participation was obtained via a post-Kidney Week survey.

**Results:** There have been 1,624 STARS participants over those nine years, of which 1,128 were included in our tracking metrics. MS made up 26% of the participants while PGY constituted 74%. 52% of participants completed a fellowship in nephrology (Figure 1A). A larger proportion of PGY participants chose a career in nephrology compared to MS participants (64% vs. 18%, P<0.001) (Figure 1B) with significantly higher odds (OR 8.9, 95% CI 5.8-11.2). While MS had lower pre- and post- interest than residents (Pre 6.2 vs. 7.7, P<0.001 and Post 7.4 vs. 8.9, P<0.001), relative change in interest was higher in MS (19 vs. 15.3, P=0.007) (Figure 1C).

**Conclusions:** The ASN Kidney STARS program has been adapted to include diverse levels of learners, has built programs in mentorship, and has refined its tracking metrics. The program has been successful with more than half of participants in the STARS program completing a fellowship in nephrology. Continued investment into the Kidney STARS program is critical to attracting trainees into nephrology.

**Funding:** NIDDK Support

**FR-PO049**

**The KIDNEE Club: An Acceptability and Feasibility Study of a Preclinical Medical Student Experience in a Pediatric Dialysis Unit Pilot Program**

Sarah Couset, Lisa E. Herrmann, Robin Hurdle, Meredith P. Schuh. Cincinnati Children’s Hospital Medical Center, Cincinnati, OH.

**Background:** Recently, concerns have developed over the sustainability of the pediatric nephrology workforce. Studies indicate that preclinical exposure may impact medical students’ interest in field specialization. Seeking to provide early pediatric nephrology exposure to medical students, we implemented an educational intervention to pair preclinical students with pediatric dialysis patients, called the KIDNEE (Kids In Dialysis, Nephrology Exposure and Education) club. We aimed to study the acceptability and feasibility of this pilot intervention for the students, patients, and unit staff.

**Methods:** For the 2022-23 academic year, seven first year medical students were paired with pediatric dialysis patients. Students met with their “match” once weekly during dialysis sessions. We distributed surveys to participants six months after program implementation. Surveys included acceptability and acceptability of this pilot program. Surveys, based on a previously published Likert scale tool assessing student and parent impression of a preclinical exposure program, were iteratively revised after review by medical education experts. Surveys were distributed via REDCap to the medical students, staff, and patients/families who participated in the program.

**Results:** From October 2022-April 2023, the 7 medical students spent ~173 hours in the dialysis unit. All (100%) students, 8 of 24 (33%) dialysis staff, and 2 of 7 (28%) patients/families responded to the survey. Students reported increased interest in caring for children with kidney disease after participation in the KIDNEE Club. Staff and patients/unanimously reported students were helpful to patients and played an important role in patient’s overall happiness. They all reported that they would recommend the KIDNEE club to other families. One parent reported that the program “improved my child’s mood and maybe made it easier for the necessary care to take place because he was more cooperative/motivated.”

**Conclusions:** Preliminary data suggests the KIDNEE club pilot was both feasible and acceptable for students, staff, and patients/families. As our results are limited by small sample size given the nature of the program, future study is needed with program expansion and longitudinal assessment of the impact on students’ career trajectories.

**FR-PO051**

**Reimagining Safety in the Learning Environment: A Grounded Theory Exploration of Identity Safety in Clinical Medical Students**

Justin L. Bullock,1 Javed Sukhera,1 Amira del Pino Jones,1 Timothy G. Dyster,2 Jonathan S. Ilgen,1 Tai M. Lockspieper,3 Pim Teunissen,2 Karen E. Hauer.1,2,3

1University of Washington, Seattle, WA; 2Universiteit Maastricht, Maastricht, Netherlands; 3Harford HealthCare Institute of Living, Hartford, CT; 4University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; 5University of California San Francisco, San Francisco, CA.

**Background:** Trainees in nephrology who identify as underrepresented in medicine and/or international medical graduates are at high risk for identity threats such as stereotype threat and microaggressions. Identity threats impair learning and erode well-being. In contrast to identity threat, less is known about how learners experience feelings of safety regarding their identity. This exploratory study aims to develop a theory of identity safety in the clinical learning environment.

**Methods:** This multi-institutional, qualitative interview study was informed by constructivist grounded theory and critical pedagogy. Participants were clinical students at three US medical schools. Investigators purposively sampled interviewees based on their responses to an 11-item survey with an open-ended question soliciting students’ personal identities and their scores on the racial/ethnic and gender Stereotype Vulnerability Scales. The investigator interviews were recorded, transcribed, completed sampled based on the data, and coding in alignment with grounded theory. The team engaged in critical reflexivity throughout the analytical process to enrich data interpretations.

**Results:** Sixteen diverse students were interviewed. We organized their identity salient experiences into identity safety, identity threat, and threat mitigation. Identity safety occurred when learners existed as their authentic selves without feeling the need to monitor others’ perception of their identities. This arose when: 1) learners demonstrated agency to leverage their identities for patient care, 2) others upheld their personhood and saw them as unique individuals, and 3) learners felt they belonged. Participants experienced identity threat when they experienced stereotype threat or interpersonal threat. Threat mitigation occurred when someone intervened against an identity threat, dampening but not eliminating the impact of the identity threat.

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FR-PO052
Building Diagnostic Schemas Improves Resident Confidence in Managing AKI
Colton Jensen, Varun Agrawal. University of Vermont, Burlington, VT.

Background: The complexity of nephrology has been identified as a major contributing factor as to why fewer resident physicians are pursuing it as a career. Improving resident comfort and knowledge about nephrology topics, particularly acute kidney injury (AKI), is imperative to decreasing resident perception of their difficulty. There is a paucity of data on effective teaching methods for AKI for resident physicians. Therefore, we designed and tested a workshop where interns build an AKI diagnostic schema to see if that improved their comfort with the topic.

Methods: The workshop took place during dedicated didactic time for interns at an academic hospital’s internal medicine residency. They received a pre-workshop survey that explored their perceived knowledge of AKI etiology, diagnosis, and management as well as their comfort level with explaining AKIs to patients and medical students. Interns were briefed on how to use diagnostic schemas and together constructed one for AKI (pre-renal, intrinsic, and post-renal causes). They then underwent didactics on pathophysiology, clinical manifestations, diagnostic work up, and management of AKI using this schema. Finally, the group used the schema to map out a general approach for a patient presenting with an AKI and answered practice questions. Finally, they took a post-workshop survey with the same questions as the pre-survey.

Results: 12 interns completed the pre-workshop survey and 15 completed the post-workshop survey. In the pre-survey, only 25% of the interns “agreed” or “strongly agreed” they felt comfortable working up and managing a patient with an AKI and only 16% had an organized approach compared to 80% of interns in the post-survey for both responses. 8% and 16% of interns felt comfortable explaining AKIs to patients and medical students, respectively, which improved to 73% and 57% after the workshop.

Conclusions: Internal medicine interns felt more confident diagnosing and managing AKI as well as discussing it with their patients and medical students after building and practicing with a diagnostic schema. Though this study was limited by study size and lack of control group, it serves as a first in collecting data and exploring effective teaching methods for common nephrology topics, with the crucial goal to increase resident comfort level with kidney disorders and bolster interest in nephrology.

FR-PO054
Career Development in Nephrology: A Pilot Fellowship Mentorship Program

Background: Mentorship programs can improve career enhancement for trainees and mutually benefit the mentor. Structured mentorship programs in graduate medical education have been shown to enhance the training experience and are met with high satisfaction. We implemented a structured 2-year mentorship program in the nephrology fellowship at the University of Pennsylvania from 2021-2023.

Methods: Between 2021 and 2023, nephrology faculty volunteered as mentors. Faculty created career and special interest profiles. Fellows reviewed faculty profiles and ranked mentor preferences, which program leadership used to create mentor-mentee pairs. Pairs met quarterly throughout the academic year and participated in professional development sessions (Figure). End of year feedback was obtained using anonymous surveys to assess satisfaction and effectiveness of the program using Likert scales (1-6, extremely dissatisfied to extremely satisfied, extremely ineffective to extremely effective). This program was deemed exempt by the University of Pennsylvania IRB.

Results: 34 mentor-mentee pairs were created between 2021-2023. 22 fellows (65%) and 22 faculty (65%) responded to anonymous surveys. Average overall program satisfaction score among fellows was 5.0/6.0 (SD 1.1), and among faculty was 3.9 (1.2). Fellows were satisfied with support of their professional aspirations (avg 5.3, SD 1.1). Faculty were satisfied with mentor resources (avg 4.3, SD 1.1). Perceived effectiveness of mentorship among fellows was satisfactory across all domains (Table).

Conclusions: The nephrology fellowship mentorship program at the University of Pennsylvania was met with active participation and high overall satisfaction. Limitations include survey response rates and assessment of attitudes rather than professional outcomes. Based on the pilot program, we will continue to evolve the professional development sessions and faculty resources to meet the needs of the fellows.

FR-PO055
Creation and Validation of a Formative Assessment Tool for Nephrology Fellows' Clinical Reasoning in a National Cohort
Suzanne Boyle,1 James R. Martindale,2 Andrew S. Parsons,3 Stephen M. Sozio,4 Rachel Hilburg,4 Jehan Z. Bahrainwala,5 Lili Chan,5 Lauren D. Stern,6 Karen M. Warburton.1 Lewis Katz School of Medicine at Temple University, Philadelphia, PA; 2University of Virginia School of Medicine, Charlottesville, VA; 3Johns Hopkins Medicine, Baltimore, MD; 4University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 5Icahn School of Medicine at Mount Sinai, New York, NY; 6Boston University School of Medicine, Boston, MA.

Background: Deficits in clinical reasoning are common among graduate medical learners. We created and validated an instrument to assess clinical reasoning in a national cohort of first-year nephrology fellows and established performance thresholds for remedial coaching.

Methods: Experts in nephrology education and clinical reasoning remediation designed an instrument to measure clinical reasoning through a written patient-encounter note from a web-based, simulated AKI consult (https://sites.temple.edu/rene/case-2/). The instrument measured clinical reasoning in three domains (Problem Representation, Contextual Understanding, and Network Construction). The instrument was designed to identify patterns consistent with intermediate and advanced levels of clinical reasoning. The instrument was then administered to a larger cohort of first-year nephrology fellows to establish performance standards for coaching using a two-way random effects agreement intraclass correlation coefficient (ICC) model. The instrument was then administered to a larger cohort of first-year fellows to establish performance standards for coaching using the Hofstee method.

Results: Both the pilot cohort (n=15 fellows; 4 training programs) and study cohort (n=61 fellows; 20 training programs) were representative of first-year nephrology fellows nationwide. The ICCs for Problem Representation, Differential Diagnosis, and Diagnostic Plan were 0.90, 0.76, and 0.50. Passing thresholds (% total points) in Problem Reasoning

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The simulated consult measures three domains, which map to a part of the linear clinical reasoning pathway.

**FR-PO056**

A Qualitative Analysis of Advanced Training in Glomerular Diseases: Results from a Program Directors' Survey

Kenar D. Jhaveri,1 Insa M. Schmidt,2 Jun Oh,3 Laurel J. Damashek,4 Koyal Jain.5 International Glomerular Diseases Society Education Committee. Donald and Barbara Zucker School of Medicine at Hofstra/ Northwell, Hempstead, NY; 2University of Cincinnati, Cincinnati, OH; 3Boston University, Boston, MA; 4The University of North Carolina at Chapel Hill, Chapel Hill, NC; 5Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 6International Society of Glomerular Disease, Boston, MA.

**Background:** Several centers around the world offer either an advanced year of training in glomerular disease (GD) or focus on specialized GD training during nephrology fellowship. Data on the successes and limitations of advanced fellowship programs or focused training in GD is scant.

**Methods:** As part of the education committee of the International Society of Glomerular Disease (ISGD), we conducted a 10-question survey of all program directors that offer an advanced year in GD training. Open-ended questions were used to evaluate measures of success and challenges of each program and data were analyzed using thematic content analysis.

**Results:** 15 programs responded to the survey (>90% response rate). 6/15 programs had GD specific training for over 15 years; and the remaining ranged from 5-15 years. The majority of the programs were in USA (10/15) and 5/15 programs were located in Europe. 11/15 program graduates entered academia. All had a renal pathologists. The majority (9/15) of programs did not have a formal fellowship curriculum. Fig 1 and Fig 2 discuss success and challenges programs faced with GD fellowships. Success was noted as having departmental resources, multidisciplinary teams and local expertise in GD and protected time for research. Challenges included funding, interest in nephrology, visa issues, lack of resources for patient education in GD.

**Conclusions:** There is a lack of GD focused training programs in nephrology. Data from this study can help to inform the development of new guidelines and educational curricula for trainees and highlight the need to foster international collaborations that can provide peer support, aid with funding, and promote GD research.

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

Underline represents presenting author.
FR-PO060

Institute of Nephrology
Mihir V. Nalivay,1,2 Mackenzie Cecil,1 Tim Medcalf,1 Adam J. Weinstein.1
1DaVita Inc, Denver, CO; 2Louisiana State University, Baton Rouge, LA.

Background: Home dialysis has shown to have potentially positive clinical and lifestyle impacts for many patients such as preserving residual kidney function or flexibility with schedules when compared to in-center hemodialysis (ICH). However, peer-reviewed research suggests that nephrologists receive inadequate exposure to home dialysis during their fellowships, creating a barrier to increasing the use of home dialysis. Moreover, use of home dialysis in the US is lower than in many other developed countries. It is therefore crucial to improve nephrologists’ competence in home dialysis as a way to improve patient care and access. We are addressing these challenges with a new virtual educational platform for nephrologists, advanced practice providers and nephrology fellows: the Institute of Nephrology (IoN).

Methods: IoN offers online courses on a variety of home dialysis topics, selected based on numerous interviews and surveys of practicing nephrologists. Content is self-paced to accommodate physicians’ busy schedules and aligns with skills preference for interactive, case-based content. Nationally-recognized home dialysis experts developed the content on subjects such as mitigating peritoneal dialysis (PD) peripheral edema, peritoneal dialysis prescription optimization, embedded PD calcium interruption (DI) content in critical care nephrology (60%), 50% in hypertension (38% new, 50% established) compared to fellows (41% and 25%, respectively). While 45% of current fellows rank dialysis modalities within their top three areas of interest, nearly half feel unprepared to manage peritoneal dialysis patients, and this only increases to 79% for home hemodialysis patients. Interestingly, despite encouragement within the industry to transition more dialysis patients to home modalities, new and established physicians show greater interest in other topics. Perspectives on Nephrology fellows need for new therapeutic agents to treat specific conditions also differ by tenure. AKI is perceived as having a greater unmet need by 64% of established nephrologists, compared to 27% of new nephrologists and 41% of fellows. Within glomerular diseases, newer practitioners perceive a greater unmet need for IgA nephropathy (39% fellows, 41% new), while only 10% of established nephrologists share the same sentiment. KDIGO guidelines are followed more closely by fellows, 91% of whom report that they always reference them when making treatment decisions. Establishing new nephrologists instead rely more heavily on their own clinical experience.

Conclusions: As a nephrologist’s career progress, their interests become narrower and more specialized based on clinical experience. Nephrology fellows often express more innovative views but many report feeling ill-prepared for the movement of dialysis and more specialized based on clinical experience. Nephrology fellows often express more innovative views but many report feeling ill-prepared for the movement of dialysis patients to home modalities.

FR-PO062

Insights from the ASN Kidney Week 2022 Point-of-Care Ultrasound Precourse
Abhilash Koratana,1 Nathanial C. Reisinger.2 1Medical College of Wisconsin, Milwaukee, WI; 2University of Pennsylvania, Philadelphia, PA.

Background: A multi-organ point of care ultrasound (POCUS) precourse was offered at the ASN Kidney Week in November 2022 with the objective of introducing core POCUS concepts and image acquisition techniques to practicing nephrologists and trainees, co-chaired by the authors. We share some insights from the course.

Methods: The course was limited to 80 registrants and had full attendance. It was conducted in hybrid format consisting of on-demand virtual content and an in-person hands-on workshop. The virtual content consisted of 60 lectures listed in the Figure, which were provided to the registrants prior to workshop. The in-person workshop consisted of a refresher lecture and hands-on practice on healthy subjects. 2 identical scanning rooms (40 attendees per room) were set up with 8 stations each teaching a predefined sonographic application (see Figure). We conducted anonymous pre- and post-course surveys to assess the impact of the training on participants’ knowledge, confidence, and satisfaction.

Results: The pre- and post-course surveys were answered by 60 and 46 registrants respectively (response rate of 75% and 57.5%). The mean % of correct answers on the pre-course survey (image interpretation) was 51.9 ± 20.4, which significantly increased to 81 ± 13.1 on the post-test (p<.001). Similarly, the self-reported confidence in image acquisition improved from 3.56 ± 0.4 to 6.66 ± 0.7 on a scale of 1-10 (p<0.001) after completing the course.

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4 hrs/week (IQR 2.25, 5.75) to effectively fulfill their role, regardless of program size. 90% of nephrology fellows during clinical rotations; 85% gave lectures; 85% attended conferences; 95% did fellow evaluations. 73% of APDs and 56% of faculty assisted in fellow remediation. 90% participated in recruitment; 85% mentored scholarly work; 80% mentored quality/safety training. APDs commonly managed rotations (62%) and were involved in 20% of APDs and 20% of faculty were at high risk for emotional exhaustion, reporting feeling “burned out from my work” daily or a few times a week.

Conclusions: APDs and core faculty have little protected time for program administration/didactic teaching, despite contributing substantially in these areas. About 40% have none. They estimate needing 4-5 hrs/week to effectively do their work, regardless of program size. The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.

FR-PO061

AKI Education of Internists: A Needs Assessment
Sahil P. Sanghani,1 Michael Heung,2 Patricia F. Kao.3 1Washington University in St Louis John T Milliken Department of Medicine, Saint Louis, MO; 2University of Michigan Michigan Medicine, Ann Arbor, MI; 3Washington University in St Louis, St Louis, MO.

Background: Acute kidney injury (AKI) is one of the most common complications of hospitalized patients. The pooled incidence in North America is estimated to be 22.3%, and the rate of AKI has been increasing. Many patients with AKI are managed by internists during and after hospitalization. As the Society of General Internal Medicine (SGIM) and the Society of Hospital Medicine (SHM) are major internal medicine meetings focusing on high-yield education for internists, we examined the prevalence of AKI-related education at their annual meetings.

Methods: This is a retrospective review of SGIM Annual Meeting session titles, session agendas, and accepted abstracts, and SHM approved abstracts from 2018-2022. SHM session titles and agendas are not publicly available. Any session title or description, or abstract containing keywords “kidney,” “renal,” or “nephrology” was manually reviewed by authors for relevance to: A) prevention of AKI, B) treatment of AKI, C) post-AKI care. Descriptive analysis was performed.

Results: Among 5203 research abstracts presented at SGIM and SHM national meetings from 2018-2022, a total of 259 (5.0%) abstracts contained one or more keywords. Of the keyword positive abstracts, 57 (1.1% of the total abstracts) were related to AKI (Figure). Of those, 38 abstracts (67%) were related to prevention of AKI, 7 abstracts (12%) were related to treatment of AKI, and 12 abstracts (21%) explored post-AKI care. Among the 1022 sessions at SGIM and their descriptions in that timeframe, only 2 contained the keywords, neither of which were directly related to prevention, management or treatment of AKI.

Conclusions: Despite the clinical importance of AKI and the fact that patients with AKI are frequently managed by internists, we identified no SGIM Annual Meeting sessions dedicated to AKI education over a 5-year period. Between SGIM and SHM, only 1% of accepted abstracts over the last 5 years were related to AKI, with a nominal decline in number since 2019. These findings suggest a substantial need to increase AKI education opportunities for internists.

Funding: Clinical Revenue Support
the workshop. 41.9% of the post-course survey respondents felt that the course met their expectations whereas 51.2% reported it exceeded their expectations. Most attendees reported lack of protected time, inadequate expert supervision and limited availability of ultrasound machines as barriers to continued POCUS practice at their institutions.

Conclusions: The POCUS course led to significant improvement in the knowledge and confidence of the participants. Nonetheless, as we cannot expect anyone to master physical examination by attending a one- or two-day workshop, same applies to POCUS and continued hands-on practice is the key to achieving mastery.

FR-PO063

Nephrologist-Led Cardiac Point-of-Care-Ultrasound (POCUS) Workshop Using High-Fidelity Simulation: Insights and Observations
Abhilash Kerketta, Hari R. Paudel, Kevin R. Regnier. Medical College of Wisconsin, Milwaukee, WI.

Background: Cardiac point-of-care-ultrasonography (POCUS) is an integral component of bedside volume status assessment. We sought to explore the effectiveness of a short simulation-based POCUS workshop for medical students taught by a nephrologist.

Methods: Workshops were conducted for two different groups of 4th year medical students with a total of 25 attendees. The workshop consisted of a 1-hour lecture followed by 15 minutes of cardiac anatomy simulation and a 2-2.5-hour hands-on session in the simulation laboratory [Fig 1]. An anonymous pre-course survey comprising of 10 questions assessing the interpretation of common greyscale POCUS findings encountered in patients with undifferentiated hypotension was performed. A post-course exam and feedback survey were also administered.

Results: 23 and 20 students answered the pre- and post-course surveys, respectively. The mean total score on the pre-test was 63.8% ± 13.6%, which significantly increased to 91.5% ± 10.5% on the post-test (P<.001). 90% of the respondents strongly agreed that the hands-on simulation enhanced their confidence in interpreting anatomy. 75% strongly agreed that the hands-on simulation enhanced their confidence in image acquisition and interpretation. 70% said they would choose nephrology elective if POCUS training was integrated with it [Fig 2].

Conclusions: A Nephrologist-led diagnostic POCUS workshop using simulation techniques is effective may increase medical student interest in Nephrology elective rotations

Funding: Private Foundation Support

FR-PO064

Simulation of Ultrasound-Guided Renal Biopsy Using a Novel Custom-Made Training Model
Ji Hwan Kim, Jinha Jang, In Soo Kim, Jung Nam An, Jwa-kyung Kim, Sung Gyun Kim, Hyungseok Lee. Hallym University Sacred Heart Hospital, Anyang, Gyeonggi-do, Republic of Korea.

Background: Kidney biopsy is a critical procedure in nephrology fellowship training, necessitating extensive simulation to prevent biopsy-related complications. There’s a need to practice optimizing ultrasound imaging and guiding the biopsy needle to target points in real-time images. We introduce a novel, cost-effective renal biopsy training model.

Methods: We developed a model using Konjac jelly and soft-boiled chicken or duck eggs to simulate ultrasound-guided renal biopsy. The soft-boiled eggs' yolk and egg white were distinctly depicted in grayscale images due to their differences in echogenicity, resembling the renal sinus and corticomedullary area of the kidney's lower pole (Figure 1A). Trainees were instructed to sample the egg white selectively. The biopsied yolk and egg white samples were easily distinguishable with the naked eye (Figure 1B), allowing trainees to verify if the sample was successfully obtained from the target with immediate feedback. The materials were readily available, and the model was easy to construct and reproduce. Trainees were able to simulate the operation of biopsy devices, optimize ultrasound imaging, and guide the biopsy needle in real time.

Results: Nephrology fellows underwent the simulation training using the model before performing kidney biopsies on patients. After implementing this curriculum, a total of 186 kidney biopsies were performed from March 3, 2022, to May 20, 2023. Biopsies were conducted with a 16-gauge needle under ultrasound guidance. There were no failed procedures. Complications included three minor hematomas that resolved with bed rest and one arteriovenous fistula that was treated with coil embolization. In pre- and post-training surveys, trainees' confidence levels in performing renal biopsies significantly improved.

Conclusions: This novel model may assist nephrology fellows in familiarizing themselves with biopsy procedures and enhancing their skills before commencing renal biopsies in a clinical setting.

Figure 1.A. A duck egg embedded in Konjac jelly (white arrow: the egg white, yellow arrow: the yolk, black arrow: biopsy needle). B. The yolk (left) and egg white (right)

FR-PO065

Virtual Nephron: Assessment of a Virtual Reality (VR) Educational Tool
Elias Bassil,1 Ali Mehdi,1 Susana Arrigain,2 Jesse D. Schold,2 John R. Sedor,1 Joseph V. Nally,1 John F. O’Toole,3 S. Beth Bierer,1 Jonathan J. Talliercio,1 Georges Nakhoul.1 Cleveland Clinic, Cleveland, OH; 2University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Recent technological advancements within the VR sphere have allowed for the development of innovative technological tools. Using funding from ASN’s Bennett Clinical Scholars Program, we developed a 3D VR physiology course and assessed its efficacy on learners’ knowledge gains.

Conclusions: This novel model may assist nephrology fellows in familiarizing themselves with biopsy procedures and enhancing their skills before commencing renal biopsies in a clinical setting.
Methods: Internal medicine PGY1 residents were randomized into 2 groups: a VR group (exposed to the VR session) and a traditional group (received a printed script of the VR learning course). The VR session consisted of a 3D review of water and electrolyte transport across the nephron and of the mechanism of action of diuretics. Within a week of the intervention, both groups underwent a 2-hour seminar on physiology of solute/water transport and diuretics. Knowledge acquisition and retention were assessed with a test administered immediately after the conclusion of the 2-hour seminar and repeated within 6-12 weeks. The 40-question test was issued using the secure platform RedCAP. Tests were anonymous, thereby preventing paired test comparisons. We used independent t-tests to compare the number of correct answers and the percent correct between the VR and traditional groups. Initial and follow up tests were evaluated separately.

Results: Of the 188 PGY1 residents who were scheduled and randomized to participate, 117 completed the initial testing. Sixty-four were randomized to the VR group and 53 were randomized to the traditional group. 51.3% of participants were males and average age was 27.3 ± 2.0 years old. Initial test results showed higher scores among VR compared to the traditional group (76.5% correct vs. 68.8%, Table 1). Seventy-eight PGY1s participated in the follow up testing (46 VR group vs. 32 traditional group). Results of the follow up test showed no significant difference in test results. Test score results are summarized in Table 1.

Conclusions: The 3D VR platform appeared to have improved short-term learning but without improving long-term retention. A larger student cohort with longer term follow up will help assess the long-term impact of VR technology and its effect on transfer of learning.

Table 1. Test results by group participation

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<th>Overall</th>
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<th>Traditional</th>
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<tr>
<td>Score out of 40</td>
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<td>Correct Mean ± SD</td>
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<td>Percent Correct Mean ± SD</td>
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FR-PO066
Success of Virtual Patient Simulation at Improving Management of CKD-Associated Pruritus
Amy Larkin, Donald Blatherwick. Medscape Education, New York, NY.

Background: We sought to determine if online, virtual patient simulation (VPS)-based and comprehensive medical education (CME) can improve performance of nephrologists and primary care physicians (PCPs) related to comprehensive management of chronic kidney disease associated pruritus (CKD-aP).

Methods: The intervention comprised two different patients presenting at a given time points in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments similar to actual practice. Tailored clinical guidance (CG), based on current evidence, was provided after each decision, followed by the opportunity to modify the decision. Decisions were collected post-CG and compared with each user’s baseline (pre-CG) using a McNemar’s test to determine P values. The activity posted September 2022; initial data were collected through December 2022.

Results: 281 nephrologists and 234 PCPs completed the activity (all decisions within at least 1 case) and were included. Case 1: 15% increase of nephrologists (67% pre-CG vs 80% post-CG; P<.001) and 11% increase of PCPs (76% pre-CG vs 87% post-CG; P<.01) who ordered a patient health questionnaire-9 (PHQ-9) assessment 28% increase of nephrologists (56% pre-CG vs 84% post-CG; P<.001) and 29% increase of PCPs (45% pre-CG vs 74% post-CG; P<.01) who diagnosed CKD-aP 46% increase of nephrologists (6% pre-CG vs 52% post-CG; P<.001) and 45% increase of PCPs (0% pre-CG vs 45% post-CG; P<.01) who ordered difelikefalin for a patient with CKD-aP 37% increase of nephrologists (11% pre-CG vs 48% post-CG; P<.001) and 39% increase of PCPs (10% pre-CG vs 48% post-CG; P<.01) who ordered an antileptic agent for a patient with CKD-aP. Case 2: 24% increase of nephrologists (51% pre-CG vs 75% post-CG; P<.001) and 30% increase of PCPs (47% pre-CG vs 77% post-CG; P<.001) who diagnosed CKD-aP 38% increase of nephrologists (16% pre-CG vs 54% post-CG; P<.001) and 34% increase of PCPs (13% pre-CG vs 48% post-CG; P<.001) who treated CKD-aP.

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to comprehensive management of CKD-aP.

Funding: Commercial Support - Developed through an independent educational grant from CSL Vifor

FR-PO067
Providing Patient-Centric Education in Type 2 Diabetes and CKD: The “YOU” Project™
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Background: Recently, we have seen many new and impactful therapeutic options to treat Type 2 Diabetes (T2D) and Chronic Kidney Disease (CKD). Clinicians are challenged to educate patients with T2D and CKD during a limited appointment time. To address this, we created a simple patient-centric education tool to help them understand the factors impacting their disease, treatment guidelines, and medication options to positively impact disease progression. We assessed how the tool impacted patient knowledge.

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

5 = Strongly Agree, 4 = Agree, 3 = Neither or N/A, 2 = Disagree, 1 = Strongly Disagree. Note: It is very likely that patients overestimated their knowledge base when being asked pre-test questions. 43 patients agreed that the “YOU” educational tool improved their comprehension and understanding of kidney disease.
FR-PO068
EMR-Based CKD Patient Education and Decision Support in Primary Care Improves Patient Satisfaction
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Background: We pilot-tested an EMR-based CKD patient education and decision support tool in primary care. Systems engineering optimized seamless integration into clinical workflow.

Methods: With input from patients and providers we developed an EMR-based patient education and decision support tool called an Encounter Decision Intervention (EDI). The EDI was designed to be used during primary care encounters when patients and providers discussed a CKD diagnosis and decided on management steps. Patients were enrolled into an intervention (received EDI) or control group (did not receive the EDI) using a prospective, cross-sectional design. Measurement of outcomes occurred after patient visits via validated surveys of patient perceived and objective kidney disease knowledge, CKD-specific stress, and satisfaction. Chi-square tests, t-tests, and Kruskal-Wallis were used to detect associations between outcomes and measured characteristics, as appropriate.

Results: Seventy-four patients completed the pilot study (37 per group). There were no statistically significant differences in patient characteristics between groups, nor were there statistically significant differences in overall kidney objective knowledge (mean (SD) of 67 % correct (15)), perceived knowledge (mean (SD) out of 4 total, 3.0 (2.1)) or CKD-specific stress (1.9 (0.7)). Satisfaction scores were associated with visit communication, care, and providers themselves were all significantly higher in the intervention group:

The proportion of participants rating satisfaction with visit communication as all 5’s (scale 1-5), showed n= 16 (43%) in usual care and 30 (81%) in the EDI group, p=0.0016. For satisfaction with care, 26 (70%) in usual care and 35 (95%) in the intervention group rated all 5’s, p=0.012. The proportion of patients rating all 5’s for satisfaction of providers themselves were 29 (78%) in the usual care group and 36 (97%) in the EDI group, p < 0.028. All three satisfaction scores remained statistically significant in multivariate analyses. The difference in mean (SD) of overall kidney education was (4.4 (1.3) vs. 4.4 (0.6), p<0.001).

Conclusions: The EDI was seamless to care delivery and associated with more patients who were very satisfied with provider communication, overall care, and the primary care provider themselves.

Funding: NIDDK Support

FR-PO069
A Pilot Plant-Based Cooking Class to Improve CKD Patient Education

Background: Diet has a crucial role in chronic kidney disease (CKD) management, but patients experience barriers such as limited knowledge, cooking skills, and conflicting dietary restrictions with other comorbidities. We previously designed and implemented a plant-based cooking class for nephrology providers to unify counseling to the updated Kidney Disease Outcomes Quality Initiative dietary guidelines. We adapted feedback from the provider classes to design and pilot a CKD plant-based cooking class for patients aimed at making CKD education more actionable compared to the conventional lecture-based format.

Methods: A renal dietitian and chef created a menu of plant-based meals and modified recipes to minimize sodium and ensure low to moderate phosphorus, potassium, and protein content. We recruited adult (age ≥18 years) patients and their support persons from a university-affiliated nephrology clinic and a local dialysis unit. We administered a pre-class phone survey to determine baseline cooking skills, meal planning, and satisfaction surveys.

Results: Of 11 participants who completed two surveys and attended the pilot CKD plant-based cooking class, 9 were female, 6 were black, and 7 had CKD stage ≥3, which included 3 who are dialysis-dependent. At baseline, 73% of respondents reported intermediate to advanced cooking skills, but 45% were not confident in their ability to describe a diet good for kidney health. All 11 class attendees reported high satisfaction and 91% reported improved understanding of a CKD diet, a high likelihood of changing eating patterns and attending another class.

Conclusions: A hands-on plant-based cooking class is an accepted and effective method to improve understanding of a healthful CKD diet and provide actionable steps to adopt plant-based eating. A follow-up survey will assess if participants actually changed their diet, and future classes will provide opportunity to collect additional participant feedback.

Funding: Other NIH Support - Vascular Medicine Institute NIH T32 Translational Research Training, 2T32HL110849-11A1

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

FR-PO070
Patient Questions Related to Peritoneal Dialysis: An Analysis of Online Search Data
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Background: End-stage renal disease patients must often decide whether to receive peritoneal dialysis (PD) or hemodialysis (HD), and much of the academic literature has focused on comparing quality of life differences between PD and HD. However, the type of information that patients themselves seek when considering PD is relatively unknown.

As more patients utilize the Internet to access health information, understanding PD search trends can help identify areas for targeted improvement in patient education. Here, we address this knowledge gap by characterizing online search data related to PD.

Methods: In May 2023, Google search data based on the term “Peritoneal Dialysis” were analyzed using “Search Response” (https://searchresponse.io), a search engine optimization tool. Searches were performed for the most common People Also Ask (PAA) questions against a dataset of over 150 million queries, and the top 100 PAA questions relevant to the “Peritoneal Dialysis” keyword were ranked based on popularity.

Results: The Search Response tool generated 1,747 PAA questions for “Peritoneal Dialysis.” Coding of the top 100 questions revealed that the greatest number of questions related to Procedure (41) (e.g., “What are the steps in peritoneal dialysis?”), Complications (14) (e.g., “What are the side effects of peritoneal dialysis?”), Definition (10) (e.g., “What does peritoneal dialysis mean?”), Diagnosis (8) (e.g., “How long can you live on peritoneal dialysis?”), Quality of Life (8) (e.g., “Can you swim with a peritoneal dialysis catheter?”), and then Comparison to Other Forms of Dialysis (6) (e.g., “Which is better hemodialysis or peritoneal dialysis?”). Thirteen questions were uncategorized (e.g., “How long is training for peritoneal dialysis?”).

Conclusions: The most common theme for questions related to PD was Procedure, which reveals a knowledge gap in the procedural aspects of PD. While it is important to compare different treatment options from a quality of life standpoint, providers should take steps to thoroughly educate patients about the procedural details surrounding PD (e.g., the equipment used or the steps involved in PD) to address patients’ most common questions and informational needs.

Funding: NIDDK Support

FR-PO071
Investigating Online Search Trends to Improve Patient Education in Nephrolithiasis
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Background: Nephrolithiasis can cause severe pain and affects one in ten individuals globally. Successful treatment requires patient cooperation, and managing the condition during treatment is crucial. While a variety of treatment options are available, a majority of patients seek answers to hydrochlorothiazide to shock wave lithotripsy exist, patients’ informational needs for nephrolithiasis are not well understood within the literature. As an increasing number of patients turn to the Internet for health information, analyzing search trends offers an opportunity to identify knowledge gaps and improve health literacy. Here, we characterize online search data related to nephrolithiasis to inform efforts to improve targeted patient education.

Methods: In May 2023, Google search data based on the term “Kidney Stones” were analyzed using “Search Response” (https://searchresponse.io), a search engine optimization tool. Searches were performed for the most common People Also Ask (PAA) questions against a dataset of over 150 million queries, and the top 100 PAA questions related to the “Kidney Stones” keyword were ranked based on popularity.

Results: The Search Response tool generated 19,376 PAA questions for “Kidney Stones.” Coding of the top 100 questions revealed that the greatest number of questions related to Management and Nutrition (31) (e.g., “What is the best food to eat when you have kidney stones?”), Treatment and Medication (25) (e.g., “What is the best treatment for kidney stones?”), Definition, Diagnosis, and Symptoms (20) (e.g., “What are the 4 types of kidney stones?”), and then Causes, Risk Factors, and Prevention (15) (e.g., “What are the main causes of kidney stones?”). Nine questions were uncategorized (e.g., “How painful is a stent for kidney stones?”).

Conclusions: The most common themes for questions regarding nephrolithiasis were Management and Nutrition, followed by Treatment and Medication; Definition, Diagnosis, and Symptoms; and Causes, Risk Factors, and Prevention. Therefore, targeted provider information about nutrition and other lifestyle interventions should be prioritized to address patients’ most common concerns regarding nephrolithiasis, and may help improve health literacy for this widespread condition.
Enhancing Patient Education: ChatGPT’s Potential in Addressing Dialysis FAQs

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Background: Patient education empowers those with ESKD to understand and navigate their treatment options. FAQs websites are valuable resources for information on dialysis, but AI’s effectiveness in addressing patient queries about dialysis remains unexplored. ChatGPT, an AI model powered by natural language processing, has shown promise in providing accurate information across varied domains. This study evaluates ChatGPT’s performance in delivering accurate patient education on dialysis.

Methods: A total of 57 patient questions related to dialysis were collected from the official Mayo Clinic website for the purpose of patient education. These questions were categorized into five steps: original questions, paraphrased questions with different interrogative adverbs, paraphrased questions with incomplete sentences, paraphrased questions with misstated words, and 5 paraphrased questions with verbs and prepositions removed. ChatGPT (March 23 Version) generated responses to each question; the accuracy of its answers was evaluated by nephrologists and compared with the FAQs websites.

Results: ChatGPT consistently demonstrated high accuracy by providing correct responses to all 57 questions across various complexity levels and paraphrasing variations. ChatGPT’s answers to patient FAQs for 1) original questions, 2) paraphrased questions with different interrogative adverbs, 3) paraphrased questions with incomplete sentences, 4) paraphrased questions with misstated words, and 5) paraphrased questions with verbs and prepositions removed were all consistently accurate. However, there was one inconsistent response to “what are the requirements for a patient undergoing hemodialysis?”. ChatGPT initially provided the expected requirements related to patient behavior but later included technical requirements for patient dialysis candidacy.

Conclusions: These results highlight the ChatGPT’s accuracy in providing education on dialysis across different complexity levels and variations in question paraphrasing, indicating that it has the potential to serve as a valuable resource for patient information on dialysis, supplementing FAQs websites. However, one inconsistency calls for refinement to ensure accurate information. With improvements, AI models potentially can significantly contribute to patient education, further empowering those with ESKD.

FR-PO075
Utility of Urinary Microscopy Score to Identify Patients with Subclinical AKI and Subsequent Clinical AKI
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Background: ADQI group has proposed a new AKI classification to recognize early stage of AKI termed subclinical (1S) using functional and structural biomarkers. However, these novel structural biomarkers are not available in resource-limited settings. We propose that urinary sediment score (USS), which reflects kidney structural damage could detect subclinical AKI and subsequent development of clinical AKI.

Methods: We included 103 consecutive hospitalized patients who were at moderate to high-risk of AKI using AKI Risk Assessment algorithm (Rizo-Topete et al. Blood Purif. 2017;43(1-3):82-88). Fresh urine was obtained and examined and urine sediment was assigned a score (Perazella et al. score Clin J Am Soc Nephrol 2010 Mar;(5):402-8.) from 1 to 3 at admission, at 48 hours and at day 7. Renal function was followed up daily up to 7 days. We defined subclinical AKI (ADQI stage 1S) as a urinary sediment score (USS) ≥2 in the absence of rise in serum creatinine (sCr). Clinical AKI was defined by KDIGO ≤3 criteria and classified using the new proposed ADQI classification (1A, 1B, 2A, 2B, 3A or 3B) depending on the presence or absence of elevated damage (USS) or functional (sCr) biomarkers. We analyzed the predictive value of this scoring system for the subsequent development of clinical AKI, need of kidney replacement therapy (KRT) and mortality.

Results: Among 103 patients, 38% (39/103) have a USS ≥2 and were classified as AKI-1S. At 48 hours, 80% (31/39) patients of the AKI-1S group developed clinical AKI; 4/7 patients with a USS ≥2 developed clinical AKI vs. 75% of AKI-1S patients; p < 0.0001. A USS ≥2 at admission have a good performance in predicting clinical AKI with a ROC-AUC 0.84 (95% CI 0.75-0.92); p < 0.0001. Need of KRT (10.3% vs. 1.6%; p = 0.05) was higher in patients with AKI-1S vs. patients with normal kidney function who later developed clinical AKI. Mortality was also higher in patients who developed AKI-1S versus patients with normal kidney function at admission (43.6% vs. 14.6%; p = 0.008).

Conclusions: Urine sediment score can identify early phase of AKI and will be useful tool to refine the diagnostic and staging criteria for AKI especially in resource-limited settings.

FR-PO076
A Case of Semaglutide-Associated Severe AKI in an Immunocompromised Patient
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Introduction: Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have been FDA approved for weight loss and are increasingly prescribed for patients with diabetes or obesity. So far, only 3 cases of semaglutide associated acute kidney injury (AKI) were reported. Herein, we report a unique case of a patient with heart transplant who developed rapid worsening of renal function after an increased dose of semaglutide.

Case Description: A 61-year-old woman presented to the hospital with 4 weeks of decreased appetite, 2 weeks of nausea, vomiting and diarrhea. Five months prior to the index hospitalization, semaglutide 0.25 mg was prescribed and the dose was eventually up-titrated to 1 mg, 5 weeks prior to the presentation. Symptoms began 1 week after the dose
of semaglutide was increased to 1 mg. Medical history pertinent for heart transplantation, type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) 3b. Laboratory data at the time of admission revealed elevated serum creatinine (Scr) of 12.5 mg/dL (baseline 1.5 mg/dL), blood urea nitrogen of 83 mg/dL, tacrolimus level of 2.4 mg/mL, urine protein to creatinine ratio (UPCR) of 1.83 g/g. Urinalysis positive of 1+ protein, 2+ blood and 4 red blood cells per high-power field. Urine microscopy revealed hyaline, granular and a few muddy brown casts. Serological evaluation for acute glomerulonephritis, CMV, EBV, BK PCR resulted negative. Kidney ultrasound was normal. Semaglutide was held on admission and IV fluids were started without improvement in Scr. Kidney biopsy was performed and revealed acute tubular injury (ATI) with diffuse flattening of tubular epithelium and brush border attenuation, chronic striped fibrosis secondary to long term exposure to calcineurin inhibitors (CNI) and mild diabetic nephropathy. No immune complex or paraprotein deposits identified by IF or EM. Patient had gradual recovery of renal function with a Scr down to 1.6 mg/dL on last follow up.

Discussion: GLP-1RAs can be associated with severe volume depletion from suppressed appetite and intractable vomiting, predisposing to ischemic ATI. Patients

FR-PO077

GLP-1 Agonists-Associated Kidney Toxicities

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Background: Data on kidney related side effects of GLP-1 agonists have not been well defined. Sparse case reports of AKI have been reported.

Methods: We reviewed the FDA adverse event reporting system (FAERS) and queried for kidney adverse events associated with GLP-1 agonists (semaglutide, exenatide, tirzepatide, liraglutide, dulaglutide, Ozempic, Bydureon, Mounjaro, Victoza, Trogarzo, Semglee, Tirzepatide). The drug was queried for kidney adverse events associated with GLP-1 agonists causing acute interstitial nephritis (AIN) primarily in the setting of discontinuation of the drug as opposed to the underlying disease or concomitant medications or by prior drugs administered to these patients. In addition, we cannot get an accurate assessment of incidence rate.

Conclusions: As GLP-1 agonists are being used for DMII and weight loss, as nephrologists we need to be aware of AKI as a potential adverse event associated with this class of agents. The mechanism of injury needs to be determined.

FR-PO079

Nonsteroidal Anti-Inflammatory Drug (NSAID)-Induced Acute Tubular Injury with Eosinophiluria

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Introduction: Age, Diabetes and Hypertension are major risk factors of AKI resulting in hospitalizations. Age adjusted acute kidney injury hospitalizations increased by 230% between 2000-2014 and are mostly related to drugs. We share an interesting/ atypical presentation of drug induced Acute Tubular Injury causing Eosinophiluria.

Case Description: 74 year old male with history of hypertension presented with chest pain, lower extremities edema, shortness of breath and a diffuse rash which started one day ago following Ketorolac injection for back pain. Vital signs on presentation showed blood pressure of 95/65 and tachycardia. Physical exam revealed a diffuse erythematous rash, mild wheezes in bilateral lungs and anasarca. Laboratory studies were only remarkable of a baseline creatinine 1.8 (baseline 1.0), blood urea nitrogen 41, white blood cells 21.9, eosinophils 32.3%. Echocardiogram, electrocardiogram, renal parenchyma ultrasound, venous doppler ultrasound of lower extremities and chest X-Ray were unremarkable. Further evaluation showed random urine creatinine 274.8, urine protein 19, spot UPCR 100 mg/dL (1-2+) and protein-creatinine ratio of 9.04 mg/mg. Further work-up including ANA, anti-GBM Ab, HIV, ANCA, Ds-DNA Ab, C3/C4 was normal. A renal biopsy showed interstitial inflammatory infiltration, focal interstitial edema, and mild tubular injury. No evidence of acute glomerulonephritis, immune complex glomerulopathy, or paraprotein related nephropathy was identified. Patient was extensively counseled to discontinue use of both ARB and liraglutide, however he declined to stop liraglutide since he had been achieving excellent weight loss results.

Discussion: Drug-induced AIN is often considered when unexplained renal insufficiency is detected or when an abnormal urinalysis is noted in someone who has been exposed to medications known to cause AIN, with renal biopsy being the gold standard investigation to make a definitive diagnosis. Our case highlights a patient with no CKD and GI symptoms with rapid elevation of creatinine following initiation of liraglutide for weight loss. This effect seems to have been compounded by existing use of ARB, which highlights importance of closer and more frequent monitoring of patients on GLP-1 agonists to prevent unwarranted adverse effects.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Severe AKI due to Antibiotic Loaded Cement Spacer of Knee
Northwell Health, New York, NY.

Introduction: Periprosthetic joint infection after total knee arthroplasty is frequently treated with a two-stage revision involving an antibiotic-loaded acrylic bone cement spacer (ALCS) placed in the joint space for infection control weeks before placement of a new prosthesis. The antibiotics within the spacer are expected to remain localized, but spacer (ALCS) placed in the joint space for infection control weeks before placement of a new prosthesis. The antibiotics within the spacer are expected to remain localized, but

Case Description: Our patient had a history of hypertension and CKD 3, who had developed a joint infection with methicillin sensitive staph aureus. An ALCS containing vancomycin, tobramycin and gentamicin using standard doses was placed. Five days post operatively creatinine was 4.1 mg/dl, from 1.75 mg/dl the day of the surgery. Antibiotics levels were sent, tobramycin and gentamicin levels were elevated at 13 mcg/ml and

2.5 mcg/ml respectively (Figure). Despite daily hemodialysis (HD), tobramycin levels remained in toxic range, prompting spacer exchange with a spacer containing 3 grams of ceftazolin. He required 8 weeks of HD before recovering.

Discussion: Previous studies have shown a risk for developing new AKI after exposure to antibiotics in bone cement spacers of 14-27% with increased risk in those patients with underlying CKD. Tobramycin appears to be strongly linked but concomitant gentamicin in the ALCS may increase the risk. Clinicians should be cognizant of the potential of serious nephrotoxicity from the antibiotics in the ALCS, especially when they are at high doses in patients with underlying CKD. Combined aminoglycoside antibiotics may exacerbate the risk.

FR-PO080
Renal Tubular Injury Biomarkers in the Early Detection and Diagnosis of Drug-Induced AKI: IMI/SAFE-T/TransBioLine
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Background: Drug induced kidney injury (DIKI) is a common adverse outcome in clinical practice and clinical trials. Serum creatinine (Scr) and urine output are “gold” standard biomarkers used to diagnose and stage acute kidney injury (AKI), limited by their sensitivity and delayed detection of measurable change from time of injury. Novel AKI biomarkers with more proximal times to onset are increasingly recognized as clinically useful for earlier detection of AKI.

Methods: IMI/SAFE-T analyzed data from 2 different clinical trial cohorts — (i)105 oncology patients (normal baseline eGFR) receiving their 1° dose of IV cisplatin (65 mg/ m2 /cycle); (ii) 20 patients with similar cancers treated with non-nephrotoxic agents. Blinded samples were collected for all participants. 3 blinded expert nephrologists adjudicated presence or absence of AKI. Biomarkers (adjusted for Urealt for urine biomarkers) maximum change from baseline accuracy — area under the ROC (AUROC), sensitivity, specificity, and 95% confidence intervals — for Cisplatin treated and AKI cases versus non-treated patients were then estimated for 3 standard biomarkers or 8 novel biomarkers.

Results: Individual novel biomarkers exceeded performance in treated vs non-treated control patients and in AKI-adjudicated vs non-treated control patients. Well performing novel biomarker median time-to-peak value was 1-3 days vs. standard biomarkers (7 days). Combination of biomarkers has also the potential to increase sensitivity and specificity of detecting AKI (exploratory result not shown in abstract).

Conclusions: Multiple individual novel urine biomarkers (urGST, uKIM1, uOPN) exceeded performance and/or signalled AKI onset prior to individual standard biomarkers (Scralt, eGFR, uALB).

FR-PO082
Validation of Urine Clusterin and MCP1 in Predicting Drug-Induced AKI
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Background: We have published that elevated urine clusterin, MCP1, β2MG, KIM1 and cystatin-C predict drug-induced AKI in patients receiving nephrotoxic drugs(vancomycin, aminoglycosides and calcineurin inhibitors) with a 1–3 day lead-time. We aim to validate the best-performing biomarkers for drug-induced AKI prediction in suitable patients.

Methods: The reproducibility of the five proposed urine biomarkers to predict AKI in 13 drug-induced AKI patients and 13 controls was determined, to curate the best-performing three biomarkers using a multiplex assay. A prospective single-centre study of 137 patients receiving nephrotoxic drugs was subsequently conducted. Urine samples were collected 2–5 days before AKI onset by KDIGO criteria or before the end of nephrotoxic therapy in non-AKI patients. The primary analysis was the ability of the selected biomarkers to predict AKI with a 2-day lead time using individual ELISA.

Results: Urine clusterin, MCP1, β2MG yielded consistent AKI prediction with respective AUCs of 86%, 75%, 74%, and were superior to that of KIM1 and cystatin-C in the initial 26 patients. Of the validation cohort of 137 patients, 28% developed AKI. AKI and non-AKI patients had a similar mean age of 53 years, with AKI patients having a higher eGFR than non-AKI patients (104 vs 98 mL/min/1.73m2 respectively, p=0.01). Median levels of biomarkers were higher in eventual AKI cases vs non-AKI patients (p=0.0001 for clusterin and MCP1, p=0.03 for β2MG). Their AUC for AKI prediction was 73(64-82) with clusterin, 77(68-86)% with MCP1, and 62(51-72)% with β2MG. We determined threshold levels of clusterin and/or MCP1 for optimal AKI prediction.

Conclusions: Urinary clusterin >150 ng/mL or MCP1 >200 pg/mL predicts drug-induced AKI, with best precision achieved by further elevations of both biomarkers.

Funding: Government Support - Non-U.S.
Apixaban in CKD, a Life-Threatening Cause of Pericardial Bleed with Resultant Acute Tubular Necrosis (ATN) and Dialysis Dependency

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Introduction: Bleeding is a common complication associated with oral anticoagulants. It can be revealed or concealed, including upper and lower gastrointestinal hemorrhage, central nervous system macro and microbleeds, and bleeding in the genitourinary system. After a thorough literature search, we found no reported case of a large pericardial bleed causing cardiac tamponade. Therefore, we report a case of a large pericardial bleed that caused tamponade, which resulted in ATN in a patient with chronic kidney disease (CKD) who then required dialysis.

Case Description: A 77-year-old Chinese woman with a history of diabetes mellitus type-2, hypertension, atrial fibrillation, left middle cerebral artery stroke status post thrombectomy, and CKD with a baseline creatinine of 1.8 mg/dl (two months prior) was brought to the emergency department (ED) due to elevated blood urea nitrogen (BUN) and creatinine. On arrival at the ED, her creatinine was elevated at 8.3 mg/dl, BUN at 76 mg/dl, and hemoglobin at 7.0 g/dl, with normal platelet and white cell count. She was alert but not oriented and had jugular venous distension, with a blood pressure of 109/60 mmHg. EKG showed no acute changes, a chest x-ray revealed a globular heart, and the septic workup was negative. Echocardiogram demonstrated severe pericardial effusion with right ventricular collapse. She was taking Apixaban 5 mg twice daily. Renal failure workup was all negative or normal, including autoimmune and hepatitis profile, inflammatory markers, and myeloma screening. Pericardial bleed was suspected in light of an acute drop in hemoglobin, so a pericardial window was made, and a 2-liter bloody effusion was drained on day-1 with a total of 4 liters over a week. Pericardial fluid was negative for atypical cells, gram stain, AFB stain, QuantIFERON, and viral PCRs, and cultures were negative for bacteria and fungi.

Discussion: Oral anticoagulants can cause a potentially life-threatening pericardial bleed and resultant cardiac tamponade. Though apixaban and other non-vitamin K analogs require less monitoring than warfarin and may be associated with lesser chances of bleeding, however, it can cause a large pericardial bleed and can lead to shock and death. Care should be exercised in prescribing apixaban to patients who have an increased risk of bleeding, especially those with CKD.

Validation of a Six-Point Bedside Risk Score for Prediction of AKI After Transcatheter Aortic Valve Replacement


Background: Post-transcatheter aortic valve replacement (TAVR) acute kidney injury (AKI) is a significant complication linked to increased mortality, dialysis rates and myocardial infarction underscoring the need for a reliable prediction tool. Zirkovic et al. (2018) developed a bedside risk score with six pre-procedural variables (NYHIA class, non-femoral access, valve-in-valve procedure, hemoglobin level, creatinine clearance, weight) to predict post-TAVR AKI. Validation of this score improve evidence for wider adoption in patient care.

Methods: A retrospective analysis of 205 patients who had TAVR was done. Patient characteristics were compared between AKI and non-AKI groups. Diagnostic accuracy was assessed using the receiver operating characteristics curve.

Results: AKI incidence was 18%. Significant AKI predictors were NYHA class (OR: 2.1170; p=0.001), non-femoral access site (OR: 2.6672; p=0.021), elevated baseline creatinine (OR: 4.1459; p=0.001), decreased hemoglobin levels (OR: 0.6319; p=0.001), eGFR<30 (OR: 0.9634; p=0.001). Age, gender and contrast volume showed no differences. AKI group had higher 10-year follow-up mortality (54.05% vs 31.55%, p=0.010), with 40% of AKI group mortalities occurring in the first year post-TAVR compared to 20% in non-AKI. Post-TAVR dialysis was higher in the AKI group (immediately after: 18.9%, 1 year post-TAVR: 16.2% vs. 0.0% respectively, p<0.001). The bedside risk score demonstrated promising discrimination (AUROC 0.75; accuracy of 69.76%), with a 23.43% increased odds of AKI per score increase.

Conclusions: Zirkovic et al.’s risk score shows promise in predicting post-TAVR AKI and can improve patient care through targeted monitoring and intervention. Guideline development for timely nephrology referral based on the risk score will optimize outcomes for high-risk patients.

Methods: We performed a retrospective observational study within a tertiary hospital from 2011 to 2021. AKI was defined according to KDIGO serum creatinine criteria. GFR estimates were calculated by three GFR estimation equations: 2009 and 2021 CKD-EPI, and EFK2C. AKI risk discriminative performances were evaluated with area under receiver operator curves (AUROC) and net reclassification improvement (NRI).

Results: A total of 187,139 individuals, including 27,447 (14.7%) of AKI and 159,692 (85.3%) of controls, were included. In multivariable regression prediction model, 2009 CKD-EPI model (0.7583 [0.755 – 0.7617]) showed superior performance in AKI prediction compared to 2021 CKD-EPI model (0.7564 [0.7531 – 0.7597], <0.001) or EFK2C model in AUROC (0.7577 [0.7543 – 0.761], <0.001). In reclassification of AKI, 2021 CKD-EPI and EFK2C models showed a worse classification performance than 2009 CKD-EPI model. (-7.24 [8.21 – 6.21], -2.38 [2.72 – 1.97]).

Conclusions: Regarding AKI risk stratification, the 2009 CKD-EPI equation showed better discriminative performances compared to 2021 CKD-EPI equation.

Figure 1. Performance of GFR estimating equations in classifying AKI using Multivariable ROC-AUC

Figure 2. Net reclassification improvement for AKI (multivariable-model 2)

Influence of Acute Kidney Disease on the Incidence of AKI and Patient Outcomes in Critically Ill Patients Admitted to the Intensive Care Unit

Methods: This was a retrospective study based on the electronic medical record-extracted ICU cohorts in two 3rd affiliated hospitals in South Korea. We retrospectively categorized baseline kidney function status as no kidney disease (NKD), AKD, and chronic kidney disease (CKD) based on the eGFR levels. AKI was defined based on the KDIGO serum creatinine criteria. The outcome measurements were the incidence of AKI in the ICU and in-hospital mortality.

Results: A total of 7,153 patients were included. The median age was 67 (18-110) years, and 57.6% were male. In all, baseline NDK, AKD, and CKD were seen in 4,792 (66.6%), 926 (12.9%), and 1,465 (20.5%) patients, respectively. During the ICU stay, AKI was observed in 2,461 (34.4%) patients, which was more frequent in AKD [OR 2.354(1.996-2.776)] and CKD [OR 2.347(2.028-2.716)] compared to NDK (Fig 1A). During the median 16(9, 23) days of hospital stay, 819 (11.4%) were dead. The in-hospital mortality rate was 2.176(1.625-2.915) folds higher in AKD compared to NDK (Fig 1B).

Conclusions: AKI was observed in 12.9% of ICU-admitted patients, and it was associated with a higher risk of in-hospital mortality. This study implies the significance of recognizing AKD in the management of ICU patients.

Funding: Government Support - Non-U.S.
Impact of Fluid Balance After Sepsis-Associated AKI on Development of SA-pAKI

**Background:** Lower skeletal muscle mass at intensive care unit (ICU) admission has been associated with poor outcomes. In this study, we investigate the independent association between computed tomography (CT)-measured skeletal muscle mass and survival, as well as renal recovery from dialysis, in patients with sepsis-induced acute kidney injury (SIAKI) who are undergoing continuous renal replacement therapy (CRRT). Method: In this retrospective study, a total of 618 patients with SIAKI who CRRT at our ICU were included. Within three days prior to ICU admission, all patients underwent abdominal CT scans. The cross-sectional area of skeletal muscle at the 3rd lumbar vertebra was measured, and the skeletal muscle index (SMI), a normalized measure of skeletal muscle mass, was calculated. Patients were categorized into sarcopenia and non-sarcopenia groups using Korean-specific cutoffs of SMI.

**Results:** Out of the 618 patients included in the study, 301 expired within 28 days of ICU admission. Non-survivors exhibited a higher prevalence of sarcopenia and SMI compared to survivors. The results of multivariable Cox regression analysis revealed that sarcopenia independently predicted 28-day mortality (hazard ratio [HR] 2.66; 95% confidence interval [CI]: 1.42–3.28; P < 0.001). Among the survivors, sarcopenia was independently associated with a lower likelihood of renal recovery from dialysis within 28 days of ICU admission (HR 0.42; 95% CI 0.26–0.68; P < 0.001). Kaplan-Meier analysis demonstrated that sarcopenic patients had lower renal and survival recovery from dialysis within 28 days of ICU admission compared to non-sarcopenic patients.

**Conclusions:** This study demonstrated that sarcopenia assessed by CT-derived skeletal muscle mass was independently associated with both survival and renal recovery from dialysis within 28 days of ICU admission compared to non-sarcopenic patients.

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Impact of NFB-48 on Development of SA-pAKI

**Background:** Lower fluid balance within 48h after onset of AKI (NFB-48) is associated with development of SA-AKI. Fluid overload is common in patients with SA-AKI and is associated with worse outcomes. It is however unclear if net fluid balance within 48h after onset of SA-AKI is associated with development of SA-pAKI.

**Methods:** We conducted a retrospective study using MIMIC IV database. We identified adult patients (≥18y) with sepsis who developed AKI within 48 hours of ICU admission. We defined AKI using both creatinine and urine output based KIDIGO criteria. We then identified association between NFB-48 (used as tertiles) with development of SA-pAKI using logistic regression adjusted for demographics, comorbidities, SOFA, vital signs, laboratory measurements, vasopressors and mechanical ventilation use.

**Results:** Of 10,739 SA-AKI patients, 62.2% developed SA-pAKI. In comparison with patients whose SA-AKI resolved within 48h, those with SA-pAKI had higher max creatinine level (1.1 vs 1.7 mg/dL; P<0.001), higher SOFA score (4.3 vs 6.3; P<0.001), more use of vasopressors (28% vs 47%; P<0.001) and mechanical ventilation (38% vs 56%; P<0.001). They also had a higher NFB-48 (0.4 vs 1.7L; P<0.001). On adjusted analysis positive NFB-48 was significantly associated with increased odds of developing SA-pAKI in a step ladder pattern (Table 1).

**Conclusions:** We have shown that positive NFB within 48h after onset of SA-AKI is significantly associated with development of SA-pAKI. The study underscores the need for optimal fluid balance in patients with SA-AKI.

**Funding:** NIDDK Support, Other NIH Support - WO: T32DK077577 1L1C007278 01HIG006910 U01DK116100

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Impact of CAR on Mortality in Patients with AKI Requiring Continuous Kidney Replacement Therapy: A Multicenter Retrospective Study

**Background:** The C-reactive protein-to-albumin ratio (CAR) is a prognostic marker in various diseases that represents patients’ inflammation and nutritional status. Here, we aimed to investigate the prognostic value of CAR in critically ill patients with severe acute kidney injury (AKI) requiring continuous kidney replacement therapy (CRRT).

**Methods:** We retrospectively collected data from eight tertiary hospitals in Korea from 2006–2021. The patients were divided into quartiles according to CAR levels at the time of CRRT initiation. Cox regression analyses were performed to investigate the effect of CAR on inhospital mortality. The mortality prediction performance of CAR was evaluated using the area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

**Results:** In total, 3995 patients who underwent CRRT were included, and the in-hospital mortality rate was 67.3% during the follow-up period. The 7-day, 30-day, and in-hospital mortality rates increased toward higher CAR quartiles (all P<0.001). After adjusting for confounding variables, the higher quartile groups had an increased risk of in-hospital mortality (quartile 3: adjusted hazard ratio [aHR] 1.15, 95% confidence interval [CI], 1.02–1.30, P=0.023; quartile 4: aHR, 1.53; 95% CI, 1.18–1.50, P=0.001). CAR combined with APACHE II or SOFA scores significantly increased the predictive power compared to each severity score alone for the AUC, NRI, and IDI (all P<0.05).

**Conclusions:** A high CAR is associated with increased in-hospital mortality in critically ill patients requiring CRRT. The combined use of CAR and severity scores performs better in predicting mortality than each severity score alone.

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Impact of Fluid Balance After Sepsis-Associated AKI on Development of Persistent AKI

**Background:** Persistent AKI (pAKI), defined as AKI lasting ≥48h is seen in over half the patients with sepsis associated AKI (SA-AKI). Fluid overload is common in patients with SA-AKI and is associated with worse outcomes. It is however unclear if net fluid balance within 48h after onset of SA-AKI (NFB-48) is associated with development of SA-pAKI.

**Methods:** We conducted a retrospective study using MIMIC IV database. We identified adult patients (≥18y) with sepsis who developed AKI within 48 hours of ICU admission. We defined AKI using both creatinine and urine output based KIDIGO criteria. We then identified association between NFB-48 (used as tertiles) with development of SA-pAKI using logistic regression adjusted for demographics, comorbidities, SOFA, vital signs, laboratory measurements, vasopressors and mechanical ventilation use.

**Results:** Of 10,739 SA-AKI patients, 62.2% developed SA-pAKI. In comparison with patients whose SA-AKI resolved within 48h, those with SA-pAKI had higher max creatinine level (1.1 vs 1.7 mg/dL; P<0.001), higher SOFA score (4.3 vs 6.3; P<0.001), more use of vasopressors (28% vs 47%; P<0.001) and mechanical ventilation (38% vs 56%; P<0.001). They also had a higher NFB-48 (0.4 vs 1.7L; P<0.001). On adjusted analysis positive NFB-48 was significantly associated with increased odds of developing SA-pAKI in a step ladder pattern (Table 1).

**Conclusions:** We have shown that positive NFB within 48h after onset of SA-AKI is significantly associated with development of SA-pAKI. The study underscores the need for optimal fluid balance in patients with SA-AKI.

**Funding:** NIDDK Support, Other NIH Support - WO: T32DK077577 1L1C007278 01HIG006910 U01DK116100

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Impact of CAR on Mortality in Patients with AKI Requiring Continuous Kidney Replacement Therapy: A Multicenter Retrospective Study

**Background:** The C-reactive protein-to-albumin ratio (CAR) is a prognostic marker in various diseases that represents patients’ inflammation and nutritional status. Here, we aimed to investigate the prognostic value of CAR in critically ill patients with severe acute kidney injury (AKI) requiring continuous kidney replacement therapy (CRRT).

**Methods:** We retrospectively collected data from eight tertiary hospitals in Korea from 2006–2021. The patients were divided into quartiles according to CAR levels at the time of CRRT initiation. Cox regression analyses were performed to investigate the effect of CAR on inhospital mortality. The mortality prediction performance of CAR was evaluated using the area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

**Results:** In total, 3995 patients who underwent CRRT were included, and the in-hospital mortality rate was 67.3% during the follow-up period. The 7-day, 30-day, and in-hospital mortality rates increased toward higher CAR quartiles (all P<0.001). After adjusting for confounding variables, the higher quartile groups had an increased risk of in-hospital mortality (quartile 3: adjusted hazard ratio [aHR] 1.15, 95% confidence interval [CI], 1.02–1.30, P=0.023; quartile 4: aHR, 1.53; 95% CI, 1.18–1.50, P=0.001). CAR combined with APACHE II or SOFA scores significantly increased the predictive power compared to each severity score alone for the AUC, NRI, and IDI (all P<0.05).

**Conclusions:** A high CAR is associated with increased in-hospital mortality in critically ill patients requiring CRRT. The combined use of CAR and severity scores performs better in predicting mortality than each severity score alone.
FR-PO093
Clonal Hematopoiesis of Indeterminate Potential Is Associated with AKI
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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is a recently recognized risk factor for several chronic diseases of aging including cardiovascular disease and chronic kidney disease. In these contexts, clonal populations of mutated myeloid cells contribute to end-organ damage through inflammatory dysregulation. We recently identified CHIP as a novel risk factor for AKI: it was associated with an increased risk of incident AKI in ICD code-based prospective clinical data from three large cohorts totalling nearly half a million individuals (adjusted hazard ratio: 1.26, 95% CI: 1.19–1.34).

Methods: In the current work, we sought to investigate whether CHIP was associated with improved functional recovery from AKI. We first examined the association between CHIP and AKI recovery in the ASSESS-AKI cohort. We then assessed long-term post-AKI outcomes in a mouse model of CHIP (partial Tet2+ bone marrow transplant) subjected to ischemia reperfusion injury.

Results: We identified that certain subtypes of CHIP exhibited a non-resolving pattern of injury and had poorer long-term outcomes after AKI. At 28 days post-ischemic injury, we observed higher levels of kidney injury markers KIM-1 and NGAL as well as more kidney fibrosis in the CHIP mice compared to wild type mice. Kidney macrophage infiltration was markedly increased in CHIP mice at this timepoint, and concomitant upregulation of pro-inflammatory and fibrotic signaling pathways was noted.

Conclusions: This work identifies CHIP as a novel and potentially targetable risk factor for impaired recovery from AKI.

Funding: NIDDK Support, Other NIH Support - Canadian Institutes of Health Research Project Grant (application # 427810, R01DK132155, Government Support - Non-U.S.

FR-PO094
Genome-Wide Association Study (GWAS) in Critically Ill Sepsis Patients Identifies Single Nucleotide Polymorphisms (SNPs) Associated with AKI by Multiple Definitions

Background: Identifying replicable genetic variants associated with AKI has been challenging, potentially due to differences in AKI definition across studies. We conducted GWAS of AKI, defined multiple ways, in critically ill sepsis patients.

Methods: We included 1955 critically ill patients without ESKD enrolled in a sepsis cohort from 2011-2020. We extracted genomic DNA from whole blood and genotyped 100,000 SNPs and 100,000 copy number variations. We conducted GWAS of AKI, defined multiple ways, in critically ill sepsis patients.

Results: We identified 432 SNPs of interest (Table). SNPs of interest

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO095
Association of Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use with Kidney Diseases Among Long-COVID and Non-Long-COVID Adults: Retrospective Cohort Study of Real-World Data
Yue Zhang,1 Jibril Ba,2 Nasrollah Ghahramani,3 Vernon M. Chinchilli, Penn State College of Medicine, Hershey, PA.

Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are widely prescribed for hypertension. In vitro studies have suggested that ACEIs/ARBs upregulate ACE-2 expression, the receptor for SARS-CoV-2 entry, particularly in kidneys. It was hypothesized that the risk of kidney diseases may be elevated in individuals with Long COVID receiving ACEI/ARB therapy. The objective of this research was to examine the relationship between ACEI/ARB use and the occurrence of acute kidney injury (AKI) in both Long COVID and non-Long COVID populations.

Methods: A retrospective cohort study using TrinTex datasets was conducted, with diagnoses of long COVID and kidney outcomes identified via International Classification of Diseases, 10th Revision (ICD-10). Four cohorts were defined: Long COVID ACEI/ARB users (LCAU), Long COVID non-users (LCAN), non-long COVID ACEI/ARB users (NLCAU), and non-long COVID ACEI/ARB non-users (NLCAN). Multivariable stratified Cox proportional hazards regression models were used to analyze the association. The relationship between ACEI/ARB use and acute kidney injury, chronic kidney disease (CKD), and mortality was assessed.

Results: A total of 164,070 qualified participants were included from 10/01/2021 to 02/14/2023, with 10,627 long COVID patients and 12,574 ACEI/ARB users. After adjustment for demographics, drug histories, and comorbidities, ACEI/ARB did not significantly impact the risk of AKI, CKD, and make, when comparing LCAU to LCAN, and NLCAU to NLCAN. However, an increased AKI risk was associated with long COVID when comparing LCAU to NLCAU (HR, 1.61; 95% CI, 1.27 – 2.06). No difference in HR of each kidney outcome between ACEI/ARB and CCB was found in both long COVID and non-long COVID cohorts.

Conclusions: ACEI/ARB use does not appear to elevate the incidence of AKI in comparison to non-users and active comparators for both Long COVID and non-Long COVID participants. Instead, it is Long COVID that has been associated with an increased risk of AKI.

Funding: Government Support - Non-U.S.
FR-PO097

Effects of Sodium Bicarbonate on Clinical Outcomes in CKD Patients with Contrast-Associated AKI (CA-AKI): A Meta-Analysis on Randomized Controlled Trials (RCTs)
Yen Chung Lin, 1,2 Taipei Medical University Hospital, Taipei, Taiwan; 1Taipei Medical University, Taipei, Taiwan.

Background: Contrast Associated Acute kidney Injury (CA-AKI) has been linked to the causal effect in a small increase of creatinine without serious adverse outcomes. However, this transient decrement in kidney function may associate with serious adverse outcomes such as dialysis or mortality. Intravenous fluid volume expansion with sodium bicarbonate (NaBiC) were highly recommended for prevention of CA-AKI in KDIGO guidelines. However, the independent role of NaBiC in CA-AKI is not fully explored especially on patients with chronic kidney disease (CKD).

Methods: The randomized controlled trials with NaBiC supplementation were compared to that of hydration in CKD patient with CA-AKI were surveyed. Electronic databases: PubMed, Embase, Web of science, and Cochrane library were searched with predefined key words/MeSH terms to identified relevant studies. In addition, reference list of included studies were screened manually. We conducted meta-analysis by using random effects model. The results were expressed as risk ratio for categorical outcomes with 95% confidence interval and mean difference with 95% confidence interval for continuous outcomes.

Results: A total 25 studies were included in our final analysis after screened with predefined criteria, including 4396 patient with CKD. The risk ratio of CA-AKI when comparing NaBiC to hydration is 0.74 [95% CI: 0.56, 0.97] subgroup of early CKD (eGFR > 45-60mL/min). However, the risk ratio of dialysis and mortality are 0.97 [95% CI: 0.46, 2.03] and 0.90 [95% CI: 0.67, 1.20] in all population, respectively. Mean difference of creatinine between NaBiC group and hydration group within 24 hours, 48 hours and hours are -0.04 [95% CI: -0.10, 0.02] mg/dL, -0.02 [95% CI: -0.12, 0.08] and -0.04 [95% CI: -0.16, 0.08], respectively. Mean difference of eGFR within 24 hours, 48 hours and 72 hours between NaBiC and hydration group is 0.06 [95% CI: -0.23, 0.35], 0.12 [95% CI: -0.06, 0.30] and 0.67 [95% CI: 0.34, 1.01] mL/min/1.73m². Mean difference of hospital stay length is -0.55 [95% CI: -1.56, 0.47] days between NaBiC and hydration group. The funnel plot showed no bias.

Conclusions: In compared to intravenous fluid volume expansion, sodium bicarbonate may benefit in eGFR in early CKD patients, however, in regards to mortality, dialysis or hospital stay, NaBiC supplementation showed no additional advantages in patients with CKD.

FR-PO098

The Use of Anti-Adrenergic Agents as a Predictor of AKI and Delayed Recovery of Kidney Function: The NARA-AKI Cohort Study
Masatoshi Reooyama, 1,2 Taipei Medical University, Taipei, Taiwan; 1Taipei Medical University, Taipei, Taiwan.

Background: The Use of Anti-Adrenergic Agents as a Predictor of AKI and Delayed Recovery of Kidney Function was delayed among those with anti-adrenergic agents (p=0.048). Of 37 AKI patients, was noted in 34 cases. There was no correlation found between rising creatinine levels and anti-adrenergic agents (excluding patients requiring inotropic support or haemodialysis). Urine NGAL was measured on day of admission, at 48 hours and at 72 hours post admission. AKI was defined as a decrease of hospital stay length is -0.55 [95% CI: -1.56, 0.47] days between NaBiC and hydration group. The funnel plot showed no bias.

Conclusions: In compared to intravenous fluid volume expansion, sodium bicarbonate may benefit in eGFR in early CKD patients, however, in regards to mortality, dialysis or hospital stay, NaBiC supplementation showed no additional advantages in patients with CKD.

FR-PO099

FR-PO100

AKI in Patients with Acute Decompensated Heart Failure Undergoing Aggressive Diuresis and Its Effect on Short-Term Outcome
Anil J. Jha, 1 Manoj Singhal, Lovy Guat, Manisha Dass. Max Super Specialty Hospital Vaishali, Ghaziabad, India.

Background: Acute heart failure (AHF) patients treated with diuretics often develop worsening of renal functions with resultant acute kidney injury (AKI) during hospitalization. AKI could be a result of renal tubular injury or simply indicate a hemodynamic / functional change in glomerular filtration.

Methods: 100 AHF patients who underwent aggressive diuresis were included (excluding patients requiring inotropic support or haemodialysis). Urine NGAL was measured on the day of admission and after 72 hours. Serum creatinine was measured on day of admission, at 48 hours and at 72 hours post admission. AKI was defined as a decrease of creatinine by 0.3mg/dL or more in 48 hours or urine output < 0.5 mL/kg/h for 6 hours. All patients were contacted at 30 days and reviewed regarding requirement of readmission/mortality. Patients who developed AKI got their creatinine checked again at day 30 from the day of admission.

Results: Mean eGFR of patients was 48.1 ml/min/m². Mean NT-proBNP was 11000 pg/mL. Mean UFV was 43%, with 38% patients having HFpEF and 62% patients had HFpEF. Of total 100 patients, 37 developed AKI. Rise in NGAL from day 0 to day 3 was noted in 34 cases. There was no correlation found between rising creatinine levels and rising NGAL levels (including patients with AKI). Mean NT-proBNP was higher in patients with AKI as compared to those without AKI (p-value=0.048). Of 37 AKI patients,
FR-PO101

Analysis of Influencing Factors of Poor Prognosis in Patients with Acute Respiratory Distress Syndrome Complicated with AKI

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Background: To study the influencing factors of poor prognosis in patients with acute respiratory distress syndrome (ARDS) complicated with acute kidney injury (AKI) in ICU.

Methods: Retrospective analysis was performed on patients with ARDS complicated with AKI admitted to the ICU. The stage of AKI was determined according to the change of blood creatinine value within 7 days after the diagnosis of AKI. They were divided into 28-day survival group (28-S) and 28-day death group (28-D) according to their survival time in 28 days. Multivariate COX regression analysis was used to analysis of influencing factors of 28-day death in patients with ARDS complicated with AKI.

Results: 265 patients with ARDS complicated with AKI has a median age of 68 (54, 75) years old. 154 patients died within 28 days (8.1%). Compared to the 28-S group, age, proportion of renal failure early unrecovered, proportion of combined corona heart disease, proportion of combined malignant tumor, acute physiologic and chronic health evaluation scoring system II, proportion of pulmonary ARDS, proportion of positive fluid balance accumulated on day 2 of ICU admission, proportion of severe AKI, blood lactate acid of the 28-D group were higher (P<0.05). The arterial partial pressures of oxygen, arterial oxygen saturation, oxygenation index of the 28-D group were lower (P<0.05). Multivariate COX regression analysis showed that renal function early unrecovered (HR=1.936, 95%CI 1.238–3.027, P=0.004), combined malignant tumor (HR=1.938, 95%CI 1.301–3.023, P=0.001), positive fluid balance accumulated on day 2 of ICU admission (HR=1.429, 95%CI 1.013–2.015, P=0.042), oxygenation index (HR=0.647, 95%CI 0.447–0.937, P=0.021) were independent influencing factors for the 28-day death in patients with ARDS complicated with AKI.

Conclusions: Renal function early unrecovered, combined malignant tumor, positive fluid balance accumulated on day 2 of ICU admission, oxygenation index decreased are associated with poor prognosis in patients with ARDS complicated with AKI.

Funding: Government Support - Non-U.S.

Influencing factors of 28-day death in ARDS patients complicated with AKI

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<tr>
<th>Factors</th>
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<td>P-value</td>
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<td>Renal Failure Early Unrecovered(Y/N)</td>
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<td>Combined Malignant Tumor(Y/N)</td>
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<td>Positive Fluid Balance Accumulated on Day 2 of ICU Admission(Y/N)</td>
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<td>Oxygenation Index(28-D group)</td>
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FR-PO102

Building a Prediction Model for Postoperative AKI Using Machine Learning: The CMC-AKIL Model

Jeeyoung Yoon,1 Ji Won Min,2 Suyeon Hong,1 Tae Hyun Ban,3 Eun Sil Koh,4 Byung ha Chung,5 Yong Kyun Kim,5 Seok Joon Shin,5 Hye Eun Yoon.1 The Catholic University of Korea. 1Catholic University of Korea Incheon Saint Mary’s Hospital, Incheon, Republic of Korea; 2Catholic University of Korea Bucheon Saint Mary’s Hospital, Bucheon, Gyeonggi-do, Republic of Korea; 3Ulsan University Medical Hospital, Ulsan, Republic of Korea; 4University of Ulsan, College of Medicine, Ulsan, Republic of Korea; 5Catholic University of Korea Eunpyeong St Mary’s Hospital, Seoul, Republic of Korea; 6Catholic University of Korea Yeouido Saint Mary’s Hospital, Seoul, Republic of Korea; 7Seoul Saint Mary’s Hospital, Seoul, Republic of Korea; 8Catholic University of Korea Saint Vincent Hospital, Suwon, Republic of Korea.

Background: Postoperative acute kidney injury (AKI) is associated with increased mortality and morbidity in patients undergoing surgeries performed under general anesthesia. There are several models that predict postoperative AKI risk, but most are single-center studies that need external validation.

Methods: In this retrospective cohort analysis, we included noncardiac surgeries performed between 2009 and 2019 at 7 university hospitals in South Korea. Postoperative AKI was defined as an increase of serum creatinine at least 1.5 times the baseline value or initiation of renal replacement therapy within 30 days of the postoperative period. We tested 6 machine learning prediction models: deep neural networks (DNN), logistic regression, decision tree, random forest, light gradient boosting machine (GBM), and naive Bayes, and compared model performance using the area under the curve (AUC) of the receiver-operating characteristic.

FR-PO104

Novel Data-Driven Phenotyping to Support Genome-Wide Association Study (GWAS) Exploration in AKI

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Background: Traditional phenotyping may have limited sensitivity for detecting meaningful phenotypes. Machine learning may detect patterns of variables for novel phenotypes identification. We applied this approach to identify phenotypes of acute kidney injury (AKI).

Methods: A cohort of VA patients hospitalized from 2002-2019 was aggregated. AKI was defined as KDIGO Stage 1 or greater during hospitalization. 5,513 data features including individual demographics, laboratory tests, medications, and billing codes were used to calculate longitudinal curves anchored on each patient hospitalization, and endophenotypes inferred with Independent Component Analysis (ICA). Ten iterations from
200,000 randomly selected hospitals with AKI were analyzed, resulting in 11,985,029 MVP patient hospitalizations with <120, 120-129, and 130-139, relative to >140 mm Hg. The primary outcome was time to death. Cox Proportional Hazards regression was adjusted for demographics, chronic lung disease, unexplained weight loss, dementia, congestive heart failure (CHF), hematocrit, blood urate, instance, bilirubin, and albumin. [Y1] To evaluate the impact of BP control over time, we calculated hazard ratios (HR) at 7 different timepoints (30, 60, 90, 120, 180, 270, and 365 days after discharge).

Results: A total of 97,376 Veterans were included and 14,819 (15%) died within 1 year of discharge. The prevalence and high rates of AKI associated with fractures such as age, gender, history of chronic kidney disease, hypertension, diabetes, cardiac history, cancer, and osteoporosis. Sensitivity analysis using other chemotherapy regimens confirmed the association was also undertaken.

Conclusions: In a large cohort of patients representing an Australian local health district, AKI was found to be associated with an increased risk of fractures. This association should be further examined and verified in other patient cohorts.

FR-P0105

Assessment of Individualized Mean Pressure Target for Cardiac Surgery-Associated AKI: PrevHemAKI Trial

Background: Acute kidney injury (AKI) complicates 20-25% of hospital admissions, and is associated with increased long-term mortality. Effective blood pressure (BP) control following AKI may improve outcomes, but appropriate BP targets and optimal timing of BP medication initiation are unclear.

Methods: This retrospective cohort analysis included adult Veterans admitted from 2013 to 2018 with in-hospital AKI and a blood pressure measurement within 30 days of discharge. AKI was defined by the KDIGO criteria. Patients were randomized to follow target of MPP >75% baseline vs standard treatment following the first 24h. Results: 98 patients were recruited, 82.7% male with mean age 72.96 ±7.25 years and eGFR of 55.3 ±16.6 ml/min. 49 were randomized to the intervention arm and 49 to the standard treatment arm. Mean MAP during the intervention was higher in the intervention group (73.6/75.9 vs. 68.0/74.8, p=0.008), with no differences in mean MAP and MPP of the first 24h (75.5 vs 76.7, p=0.32 and 66.5 vs 67.5, p=0.375 respectively) although a higher use of noradrenaline was found in the intervention arm (38.78 vs 63.27, p=0.026). The percentage of time with MPP<75% baseline was similar in both groups (31.3% – 38.1%), Mean 24h fluid balance was similar (331 ±38-1206 vs 2698–999, p=0.154). The incidence of AKI was similar in both groups but with a tendency to a higher incidence of AKI in the presence of PFM deficit of >20% (p=0.064).

Conclusions: There was a tendency to a higher incidence of AKI if MPP deficit >20% but individualized hemodynamic management based on MPP compared to standard treatment did not reduce the incidence of AKI associated to cardiac surgery in our study. Larger cohorts are needed in order to confirm these findings.

FR-P0107

Real-World Evidence on the Impact of Incident AKI on Mortality, Healthcare Resource Utilization, and Costs Among Patients Undergoing Cardiac Surgery with Extracorporeal Bypass (CABP) from US Hospitals

Background: AKI is among the most common complications in hospitalized patients, including 100,000 US cases per year in patients undergoing CPB. AKI is underdiagnosed and its severity is not routinely captured by ICD-10 codes. Therefore, we used serum creatinine measurements consistent with Kidney Disease Improving Global Outcomes (KDIGO) criteria to evaluate the true impact of AKI on mortality, healthcare resource utilization (HCRU), and costs among inpatients undergoing CPB.

Methods: Using an all-payer US hospital-based database, this retrospective cohort study included adult patients undergoing CPB with an index visit between January 2018 and December 2020. Patients undergoing surgery were excluded. AKI was defined by KDIGO criteria and/or an ICD-10 (or dialysis procedure) code at index. Propensity score matching was used to create matched cohorts to address differences in demographic and clinical characteristics between patients with and without AKI (HR 3.199, p=0.001) and no AKI (stage 1). A comparison by presence vs absence of AKI by ICD-10 code was done as a reference.

Results: More severe AKI was associated with higher risk of death and greater HCRU (Table). Adjusted analysis indicated independent associations of severe AKI with 34.1x and 2.5x higher odds of death and 30-day readmission, mean LOS increase of 9.8 days, and mean increased costs of $58.4k compared to confirmed non-AKI or AKI stage 1. The impact of severe AKI was underestimated for ICD-10 AKI diagnosis vs. absence: 9.3x and 1.9x higher odds of death and 30-day readmission, mean LOS increase of 5.4 days, and mean increased costs of $25.5k.

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

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FR-PO109
Renal Functional Reserve After AKI Predicts Adverse Outcomes at 180 Days
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Background: There is a lack of evidence to guide optimal post-acute kidney injury (AKI) care. Renal functional reserve (RFR) measures the capacity of the kidney to increase glomerular filtration rate (GFR) under various physiologic stresses and is potentially a marker to predict the susceptibility to injury and refine the recovery of kidney function. We aim to examine the association between post-AKI RFR and major adverse kidney events at 180 days after hospital discharge (MAKE180) including death, new kidney replacement therapy, and persistent renal dysfunction.

Methods: We enrolled patients with baseline eGFR of >60 mL/min/1.73 m² who survived from moderate to severe AKI with eGFR of >30 mL/min/1.73 m² at hospital discharge between November 2021 to March 2023. RFR was measured by using intravenous amino acid infusion at 3 months after discharge. Primary end point is the predictive performance of post-AKI RFR for MAKE180. Secondary end points include the performance of RFR to predict recurrent AKI and incident chronic kidney disease (CKD) within 6 months.

Results: Among 56 AKI survivors enrolled, median RFR at 1 and 3 months after AKI are significantly lower in those who developed MAKE180 compared with those who did not (0.86 (4.6-10.6) vs 13.48 (8.6-21.8) mL/min/1.73 m², p=0.002 and 0.69 (4.67-3.5) vs 17.57 (10.83-38.1) mL/min/1.73 m², p=0.001, respectively). Patients with MAKE180 had RFR declination (negative difference RFR), in contrast, those without MAKE180 had RFR improvement over 3 months (-4.39 (-7.42-0.64) vs 14.34 (9.7-22.14) mL/min/1.73 m², p<0.001). The RFR at 1 and 3 months could predict MAKE180 with an AUC of 0.77 (95% CI 0.62-0.93) with the cut-off value of 8.3 mL/min/1.73 m² (sensitivity 74%, specificity 81%) and AUC of 0.91 (95% CI 0.81-1) with the cut-off value of 8.6 mL/min/1.73 m² (sensitivity 93%, specificity 85%), respectively. Those who developed incident CKD and recurrent AKI had a significantly lower post-AKI RFR at 1 and 3 months and predicted incident CKD and recurrent AKI with good AUC.

Conclusions: Post-AKI RFR is highly predictive of poor kidney outcomes at 6 months. Larger prospective studies are warranted to explore the association between a reduced RFR and poor outcomes in post-AKI survivors.

FR-PO110
The Incidence, Aetiology, and Short-Term Outcomes of AKI in Adults
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Background: Acute Kidney Injury (AKI) is a common clinical syndrome in hospitalized patients associated with an increased risk of poor prognosis and mortality. We aimed to identify the incidence, aetiology, and short-term outcomes of adults with AKI on presentation to the hospital.

Methods: Data were prospectively collected over a two-month period. The patients were followed till the time of discharge from the hospital. Patients admitted over two months were investigated, and those with AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria were identified at the time of admission. Patients with known End Stage Renal Disease (ESRD) on dialysis, renal transplant, Paediatric, and Gynaecology admissions were excluded. Data was collected from the admission records in the emergency department, medical notes, laboratory system and discharge summaries.

Results: There were a total of 2847 patients admitted over the study period, and 2357 were reviewed. The incidence of AKI was 5.92% (n=142). In the AKI population, 54.22% were males and 45.77% were females. The mean±standard deviation(SD) age was 74.6±14.7 years. Chronic kidney disease was present in 53.52%. The mean±standard deviation(SD) age was 74.6±14.7 years. Chronic kidney disease was present in 53.52%. The mean±standard deviation(SD) age was 74.6±14.7 years. Chronic kidney disease was present in 53.52%. The mean±standard deviation(SD) age was 74.6±14.7 years.

Conclusions: Severe AKI in patients undergoing CPB is associated with significantly high mortality, HCRU, and cost compared to no or mild AKI. ICD-code based definitions can underestimate the impact of AKI.

Funding: Commercial Support - Janssen Research & Development

FR-PO111
Clinical Characteristics and Outcomes in AKI in Non-Critically Ill Patients
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Background: Although many studies have been focused on critically ill patients in ICUs, AKI occurs even in non-critical care settings. Epidemiological data of AKI outside the ICU are not well investigated. We aim to describe main features and outcomes of AKI in non-critically ill patients in our teaching hospital.

Methods: We performed a retrospective analysis including AKI patients referred to nephrology consultation in a 6-month period at AO Policlinico, Bari, Italy. We analyzed the main features of AKI episodes, including AKI stages, the need for dialysis, mortality rate and factors associated to kidney function recovery (KFR).

Results: Among 899 patients referred for nephrology, 415 (46%) were evaluated for AKI. 52.5% of AKI episodes were classified as KDIGO Stage 3, and 54 patients (13%) required RRT. In-hospital mortality was 36.9%, higher in patients with pre-existing CKD, in patients with stage 3 AKI and among those who did not present KRF. Cox analysis showed a higher mortality risk for older age (HR 1.032, 95%CI 1.012-1.053, p=0.002) and pre-renal AKI (HR 2.823, 95%CI 1.219-6.536, p=0.015), while KRF was associated to lower mortality (HR 0.246, 95%CI 0.098-0.615, p=0.003). KFR was observed in 197 patients (47.5%) mainly in patients with mild AKI (stage 1 62.6% vs stage 2 57.6% vs stage 3 36.8%, p=0.001). Higher baseline eGFR (OR 1.025, 95%CI 1.014-1.036, p=0.001) was associated with KFR. Severe AKI was independently associated with lower probability of KFR (OR 0.420, 95%CI 0.249-0.711, p=0.001).

Conclusions: AKI episodes outside the ICU are severe and associated with a high mortality rate even outside the ICU. A timely nephrologist consultation is important to limit AKI severity.

FR-PO112
In-hospital survival curve stratified according to baseline eGFR (a), severity of AKI (b) and kidney function recovery (c)
FR-PO112

Development and Feasibility of a Remote Patient Monitoring Program for AKI Survivors

Background: One-third of acute kidney injury (AKI) survivors lack appropriate follow-up after hospital discharge. Remote patient monitoring (RPM) may improve post-discharge care quality. We report an AKI RPM program’s development and preliminary feasibility.

Methods: Mayo Clinic launched an AKI RPM program in October 2021 for individuals who experienced AKI with a nephrology consultation during a hospitalization. Once enrolled, patients were discharged with RPM technology (e.g., blood pressure cuff, scale), and vital signs and symptoms were monitored daily. In-center laboratory assessments were scheduled weekly. RPM nurses evaluated the data daily and adhered to prespecified protocols for alerts and care escalation management. Patients were followed for up to three months. Individuals graduated from the AKI RPM program if they remained dialysis independent, with a stable creatinine for 2 consecutive weeks, and no urgent or emergent results in the prior week. Feasibility was defined as the proportion of enrolled patients who submitted at least one set of vitals or symptom data after program initiation.

Results: Of the 50 people approached, 41 (82.0%) were enrolled in RPM. The median (IQR) baseline eGFR was 37 (28, 60) mL/min/1.73 m² and 83% experienced stage 3 AKI. The length of time in the program was 31 (28, 38) days. Eight (20%) patients were lost to follow-up or withdrew. Thirty (73%) individuals had at least 1 RPM alert, most for weight gain or edema. Six emergency department referrals were made for AKI RPM patients. Among the 33 patients who graduated from the AKI RPM program, 25 (76%) were referred to nephrology for evidence of chronic kidney disease. 17 (68%) of those individuals completed a nephrology visit within 90 days of program graduation.

Conclusions: The AKI RPM workflow was feasible and addressed a vital gap for AKI care after discharge. Digital health solutions such as RPM offer a unique opportunity to bridge the care transition from hospital to home, increase access to quality care for the most vulnerable AKI survivors, and direct the attention of nephrologists to patients most likely to benefit from specialty consultation.

FR-PO113

A Self-Funded, Value-Based, Post-AKI Care Program: Predicted vs. Observed Outcomes

Background: Readmissions occur in 20% patients with Acute Kidney Injury (AKI), adding $25,000 in healthcare costs. While post-AKI care improves outcomes, studies are limited to non-dialysis referred patients. As one of the earliest post-AKI clinics, we set up a self-sustaining multi-disciplinary post-AKI care program.

Methods: Target population/interventions were finalized by interviewing nephrologists, patients and AKINow Workgroup. Since May 2022, hospitalized adults with high-risk stage 2/3 AKI at Geisinger Medical Center were identified in real-time. Those eligible were provided inpatient AKI education, nurse coordinator services, flexible scheduling, non-face-to-face care and expedited nephrology visits. Follow-up was up to 90 days post-discharge. Observed vs Predicted (Grampian-Abbeens model) 90-day rehospitalization/mortality risk were compared.

Results: On screening 1198 patients, 303 were eligible; 195 (64.4%, 5% on dialysis) lost to follow-up or withdrew. Thirty (22%) individuals had at least 1 RPM alert, most for weight gain or edema. Six emergency department referrals were made for AKI RPM patients. Among the 33 patients who graduated from the AKI RPM program, 25 (76%) were referred to nephrology for evidence of chronic kidney disease. 17 (68%) of those individuals completed a nephrology visit within 90 days of program graduation.

Conclusions: We developed a value-based comprehensive post-AKI care model showing improvement over predicted outcomes. Our approach allows quasi-experimental analysis and could be widely applicable.

FR-PO114

An Exploratory Needs Assessment for AKI Patient Education: Results from a Focus Group
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Background: Literature on the type, content, and effectiveness of patient education regarding acute kidney injury (AKI) is scarce. The American Society of Nephrology AKINow Education Workgroup conducted a focus group of relevant stakeholders with
AKI: Outcomes, RRT

Clinic Minnesota, Rochester, MN

Evaluating ChatGPT’s Accuracy on Core Questions

Kattah, Rozalina
Heather Survivor Program in Primary Care

through all phases of the AKI experience and to co-produce these resources with patients.

Major themes from session 4 included: the need for multimodal patient education (e.g.,
written and multimedia resources) in addition to education from trusted providers.

Conclusion: This is an urgent need to improve education for patients with AKI
through all phases of the AKI experience and to co-produce these resources with patients.

FR-PO115 Feasibility of a Randomized Pilot Trial of a Multidisciplinary AKI Survivor Program in Primary Care


Background: AKI survivor care delivery in nephrology specialty clinics has been
limited by poor recruitment. The AKI in Care Transitions (ACT) Program was designed to
address this barrier by facilitating kidney follow-up within primary care. This study
tried to describe the recruitment and retention of patients in a clinical trial on the
feasibility of ACT compared to usual care.

Methods: The study included adults with stage 3 AKI during hospitalization from
2022-2023 at Mayo Clinic in Rochester, MN, who were expected to discharge to
home in the local area, not on dialysis.Consenting individuals were randomized 1:1 to
ACT or usual care. Patients in the ACT group received education before discharge and
coordination of post-discharge laboratory and clinician (primary care physician [PCP],
pharmacist) follow-up in primary care within 14 days. The Usual Care group received no
study-specific intervention. The percentage of AKI survivors screened, approached, and
who provided consent was reported. Reasons for declining participation were recorded.

Conclusion: We described the proportion of patients in the ACT group in which pre-
discharge education was completed and post-hospital laboratory and clinician follow-up
orders were placed.

Results: An electronic health record alert identified 549 potential candidates. There
were 429 exclusions based on pre-specified study criteria and 106 individuals were
approached for participation. Forty-five (42%) consented to participate and were enrolled.
Among those consented, 1:1 randomization with a reason, concerns about time commitment,
and feeling overwhelmed predominated. Of 23 ACT patients, 22 completed education, and
21 had orders placed for post-discharge follow-up. One patient withdrew from the ACT
group due to feeling overwhelmed.

Conclusion: These data demonstrate the ability to recruit AKI survivors into a
care transitions program within primary care. While ACT recruitment appeared more
successful than in other controlled trials of nephrologist follow-up, feeling overwhelmed
remained an important barrier to participation. AKI survivor interventions should be
simplified where possible to limit treatment burden.

Funding: Other NIH Support - Agency for Healthcare Research and Quality
HS028060-01

FR-PO116 Evaluating ChatGPT’s Accuracy on Core Questions

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Background: ChatGPT is a state-of-the-art language model with exceptional
precision in various natural language processing tasks, including generating responses
that closely mimic human-generated ones. While there is growing speculation about
ChatGPT’s potential to serve as a substitute for physicians in clinical settings, its
precision in nephrology, including acute kidney injury and critical care nephrology,
remains uncertain. This study aims to evaluate the performance of ChatGPT in answering
core questions related to acute kidney injury and critical care nephrology.

Methods: The accuracy of ChatGPT was evaluated in answering questions related to
acute kidney injury and critical care nephrology using the Nephrology Self-Assessment
Program (NephSAP) and Kidney Self-Assessment Program of the American Society of
Nephrology (KASAP). Questions containing images were excluded from the assessment
due to ChatGPT’s limited image processing capabilities. One hundred ten
questions were included in the evaluation, 45 from NephSAP and 55 from KASAP. Each
question bank was executed twice using ChatGPT. The level of concordance between the
initial and subsequent runs, with a 2-week gap between the two weeks apart, was also examined.

Results: In the case of NephSAP questions, ChatGPT achieved accuracies of 55%
and 69% on the initial and subsequent runs, respectively. For KASAP questions, it achieved
accuracies of 46% and 40%, respectively. ChatGPT’s accuracy on all 110 questions
combined was 52% and 51% for the initial and subsequent runs. The overall concordance
between the initial and subsequent runs was 78%, with 86 questions (78%) receiving
the same response and 24 (22%) receiving different responses. Correct concordance
was 57%, and incorrect concordance was 43%. Among the 24 questions with divergent
responses, ChatGPT responded to 70% of these questions correctly.

Conclusion: Our study shows that ChatGPT only responded correctly to half of the
questions related to acute kidney injury and critical care nephrology with low reliability.
Therefore, ChatGPT as an educational tool may not be precise or reliable, and further
development may be necessary to improve its performance.

FR-PO117 Epidemiology and Outcome of Community- and Hospital-Acquired AKI in a Developing Country

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Background: Acute Kidney Injury (AKI) is associated with adverse short-term
and long-term outcomes in hospitalized patients. In developing countries, including
India, Community acquired AKI (C-AKI) is more common than hospital acquired AKI
(H-AKI) and the pattern varies with different geographical areas. This single-centre
study aimed to assess the clinical spectrum, risk factors for in-patient mortality and
care transitions program within primary care. While ACT recruitment appeared more
successful than in other controlled trials of nephrologist follow-up, feeling overwhelmed
remained an important barrier to participation. AKI survivor interventions should be
simplified where possible to limit treatment burden.

Results: A total of 476 AKI patients were enrolled in this study; 395 (83%) were
C-AKI. The mean age was 44.8±18.7 years. Sepsis (176/476; 36.9%) was the most
common cause of AKI. The in-hospital mortality was 38%. The peak serum urea and
creatinine levels were higher in patients with C-AKI than H-AKI. The need for ventilator
(34.9% v 67.9%), inotropic support (38% v 73%) and in-hospital mortality were
73% v 73%) was more in H-AKI. Patients with H-AKI had significantly higher mortality (72%
v 31%). Age >60 yrs (HR=1.51; 95% CI,1.11–2.07), oliguria (HR=1.48; 1.05–2.10),
need for ventilator (HR=2.31; 1.36–4.41) and/or inotropes (HR = 14.4; 6.28–33.05) were
predictors of in-hospital mortality. Of the 295 patients discharged, 146 (50.7%)
completed renal recovery, while 149 (31.3%) had partial renal recovery. Of the 295
patients on follow-up, 211 (71.5%) patients had normal renal function, 4 (1.4%) died
and 41(14%) developed CKD while 6(2%) were dialysis dependent. All patients having
CKD on follow-up were patients of C-AKI group.

Conclusion: Present cohort study with long follow-up showed that there is a definite
risk of CKD in recovered patients and they should be monitored periodically. AKI in
hospitalized patients still has high mortality especially in patients with H-AKI.

FR-PO118 AKI in the Surgical Ward: A Single-Center Study

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Background: Acute Kidney Injury (AKI) is a non- uncommon condition with
unknown incidence, mostly it take place in hospitalized patients and it is often under
recognized. AKI significantly affects short and long-term morbidity and mortality.

Methods: A retrospective single center cohort study was performed, using
the electronic medical records (EMR) of the hospital. AKI was defined as an increase of
serum creatinine level of at least 0.5 mg/dl from the previous test. We identified patients
with AKI in the period January 1st – December 31, 2019 who were hospitalized in the
non-cardiac surgical clinics during this period. Chronic dialysis patients were
excluded from the analysis.

Results: The final analysis included 203 patients hospitalized in Surgical wards.
Of these, 118 patients was 75 (39-97), while 62% were men, almost 50% were diabetics,
showing a mean Charlson score of 6. Almost 50% had CKD before the hospitalization
with a median eGFR 61 ml/min. Seventy seven percent of patients were operated during
the hospitalization. Most (66%) of operations were non elective. In 9% cases
renal replacement therapy (RRT) was performed. All of them underwent non-elective
operations. Patients needing RRT were younger, with lower hemoglobin, more frequent
use of nephrotoxic antibiotics, received intravascular contrast, were mechanically
ventilated and hypotensive, with sepsis. All-cause 90-day mortality was 33%. All-
cause 90-day mortality was higher in cases of non-elective operations, in patients with
hemoglobin level less than 8 mg/dl, higher American Society of Anaesthesiologists score,
and hypotension during the hospitalization. Mortality rate was lower in diabetic patients
(p=0.009). Management of AKI: only 47% of patients had urinalysis, renal imaging
was done in 15%, monitoring of urine output was performed in 76%. Only in one third of
cases there was any addressing to AKI in the EMR, and only in 43% of AKI was a main
diagnosis at discharge.

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

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Greater individualization of dialysis orders may improve patient care. Temperature were also similar. In the AKI-D group (5.3 versus 5.9 mg/dL, 0.9 versus 1.1 kg, and 135 versus 144 mmHg, creatinine, interdialytic weight gain and pre-dialysis systolic blood pressure, were lower in the one year before and one year after the in-house LDD program launch.

Methods: We evaluated ICU stays requiring LDD in the one year before and after the month of the dialysis quality improvement program launch. EHR data were reviewed. compiled and analyzed by ICU staff, using MS Excel. Data include, demographics, select clinical diagnoses including kidney disease, heart failure, sepsis, and COVID. The results are presented as descriptively only. No cohort adjustments or statistical significance tests were performed.

Results: There were 145 ICU stays with 3,641 hours of CRRT among 145 pts before, and 116 ICU stays with 5,098 hours of LDD among 116 pts in the year after program launch. Mean dialysis treatment hours per patient were reduced from 93.7 to 43.1, increasing ICU nurse productivity by 50.6 hours per patient. Similar dialysis treatment time savings occurred in both COVID and no-COVID subsets. Concurrently, mean ICU length of stay for these patients declined by 4.8 days between the pre and post periods, from 13.2 to 8.4 days, respectively. Mortality declined between the periods, from 60.7% to 50.9% overall, and declining in both COVID and no-COVID subsets. Total mean ICU length of stay for these patients declined by 4.8 days between the pre and post periods, respectively.

Conclusions: Converting from an outsourced CRRT-only program to an in-house adaptive long-duration dialysis program, a medium-size hospital ICU in Michigan improved dialysis care quality and patient outcomes, while reducing costs and increasing nurse productivity.

Initial outpatient dialysis prescriptions in AKI-D and ESKD

FR-PO119
Intensive Care Unit Improves Dialysis Care Quality While Reducing Costs
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Background: In November 2021, a medium-size hospital ICU in Michigan initiated a quality improvement dialysis program, converting their outsourced continuous renal replacement therapy (CRRT-only) to an in-house adaptive long-duration dialysis (LDD) model, using the Table9 Hemodialysis System (Table9) to provide treatments ~6 hours, as medically necessary. This conversion was done with the goals of (1) improving quality of care for ICU patients requiring LDD, and (2) reducing both dialysis-related nursing staff burden and dialysis treatment costs. We compared patient characteristics and treatments performed in the one year before and one year after the in-house LDD program launch.

Methods: We evaluated ICU stays requiring LDD in the one year before and after the month of the dialysis quality improvement program launch. EHR data were reviewed, compiled and analyzed by ICU staff, using MS Excel. Data include, demographics, select clinical diagnoses including kidney disease, heart failure, sepsis, and COVID. The results are presented as descriptively only. No cohort adjustments or statistical significance tests were performed.

Results: There were 145 ICU stays with 3,641 hours of CRRT among 145 pts before, and 116 ICU stays with 5,098 hours of LDD among 116 pts in the year after program launch. Mean dialysis treatment hours per patient were reduced from 93.7 to 43.1, increasing ICU nurse productivity by 50.6 hours per patient. Similar dialysis treatment time savings occurred in both COVID and no-COVID subsets. Concurrently, mean ICU length of stay for these patients declined by 4.8 days between the pre and post periods, from 13.2 to 8.4 days, respectively. Mortality declined between the periods, from 60.7% to 50.9% overall, and declining in both COVID and no-COVID subsets. Total mean ICU length of stay for these patients declined by 4.8 days between the pre and post periods, respectively.

Conclusions: Converting from an outsourced CRRT-only program to an in-house adaptive long-duration dialysis program, a medium-size hospital ICU in Michigan improved dialysis care quality and patient outcomes, while reducing costs and increasing nurse productivity.

FR-PO120
Initial Outpatient Dialysis Orders in AKI-D vs. ESKD
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Background: Many hospitalized patients with dialysis-requiring acute kidney disease (AKI-D) do not fully recover renal function and are discharged to continue hemodialysis (ESKD). Little is known about dialysis practice patterns in this population.

Methods: We examined initial outpatient dialysis orders for 1,754 AKI-D patients initiating in-center hemodialysis between 7/1/2017 and 6/30/2022 across 67 dialysis centers operated by a medium-sized, not-for-profit dialysis provider. For comparison, 6,197 contemporary patients initiating in-center hemodialysis for ESKD were identified.

Results: Patients initiating outpatient dialysis for AKI-D and ESKD had similar demographics (mean age, 63 in AKI-D vs 64 in ESKD; 60% male in both groups) and body mass indices (mean, 29 kg/m2 in both groups). However, mean pre-dialysis serum creatinine, interdialytic weight gain and pre-dialysis systolic blood pressure, were lower in the AKI-D group (5.3 versus 5.9 mg/dL, 0.9 versus 1.1 kg, and 135 versus 144 mmHg, respectively). Despite these differences, initial dialysis orders were similar. The initially prescribed hemodialysis frequency was 3x/week dialysis for 94% of AKI-D patients and 95% of ESKD patients. Hemodialysis session duration, dialysate sodium, and dialysate temperature were also similar.

Conclusions: Despite dissimilar medical profiles at hemodialysis initiation in the outpatient setting, initial hemodialysis orders for AKI-D and ESKD are largely the same. Greater individualization of dialysis orders may improve patient care.

Funding: NIDDK Support, Commercial Support - Satellite Healthcare, Inc, not-for-profit dialysis provider

Impact of Using Blood Warmer During Continuous Kidney Replacement Therapy on Hemodynamic Instability
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Background: Continuous kidney replacement therapy (CKRT) can lead to heat loss in the extracorporeal circulation. Hypothermia may have detrimental effects; however, re-warming of blood may alter vascular reactivity and induce hypotension.

Methods: We screened patients with acute kidney injury (AKI) who required CKRT between 1/1/2012 and 1/1/2021 and were admitted at a tertiary academic hospital. Intra-dialytic hypotension (IDH) was defined as mean arterial pressure (MAP) ≤ 60 millimeter-mercury (mmHg) or a decrease in MAP by > 10 mmHg, systolic blood pressure (SBP) less than or equal to 90 mmHg or a decrease in SBP by ≥ 20 mmHg, or increased vasopressor requirement. These were measured in 15-minute increments and the number of episodes in each hour was recorded. The number of events was analyzed by Poisson regression with repeated-measures analysis of variance with use of the generalized estimation equation.

Results: There were 669 patients with AKI who required CKRT during the study period. Use of blood warmer on first day of CKRT was in 324 (48%) patients. Patients where a blood warmer was used were more likely to have required vasopressor or inotropes (56% vs 45%, p < 0.003), be diagnosed with sepsis/septic shock (81% vs 74%, p = 0.04), and were in a less positive fluid balance at the time of CKRT initiation (1.0 vs 1.3 L, p < 0.03) compared to patients where a blood warmer was not used. The incident rate ratio for IDH during the first 24 hours of CKRT in patients where a blood warmer was used was 1.06 (95%CI 0.98, 1.13) compared to those where blood warmer was not used. After adjusting for variables that were different between the two groups and clinically relevant ones (norepinephrine equivalents, mechanical ventilation and MAP at time of CKRT initiation and ultrafiltration on CKRT day1), using a blood warmer did not increase risk for IDH episodes. Overall, the within-subject effect of temperature on IDH on first day of CKRT was negative, meaning that higher temperature was associated with fewer IDH (relative risk of 0.94, 95% CI 0.90, 0.98 for each 10 degrees increase, p = 0.007).

Conclusions: Blood warming techniques during CKRT were not associated with worsening hemodynamic instability during first day of CKRT.

Funding: Other NIH Support - National Institute of General Medical Sciences of the NIH under Award Number 2U54GM104942-07. Dr. Ankit Sakhuja disclosed funding from NIH/NIDDK 1K08DK131286.

Impact of Ultrafiltration Rate Among Adults with AKI Treated with Continuous Renal Replacement Therapy (CRRT)
Samantha Gunning, Joy L. Koyner. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: Observational data supports the view that fluid removal with dialysis in critical illness confers survival benefit. The optimal fluid removal rate is unknown with some suggesting that ultrafiltration (UFR) greater than 1.75 mL/kg/hr may be harmful.

Methods: We conducted a single-center retrospective cohort study among adult AKI patients admitted to the intensive care unit (ICU) at University of Chicago treated with CRRT from April 1, 2016 to March 31, 2020. We collected information regarding patient demographics, severity of illness, daily fluid balance (all intakes minus outputs, inclusive of RRT), RRT ultrafiltration, and outcomes (length of stay, dialysis dependence, and mortality). We calculated UFR restricted to the first 72 hours of dialysis treatment as net ultrafiltrate (mL/h) per hour treatment duration adjusted for patient’s baseline body weight.

Results: 742 patients had low UFR (≤1.01 mL/kg/hr), 269 had moderate UFR (between 1.01 and 1.75 mL/kg/hr), and 167 had high UFR (≥1.75 mL/kg/hr). Those with low UFR were older, had higher baseline body weight, and had less positive fluid balance in the 72 hours prior to starting dialysis. Severity of illness (SOFA) and burden of co-morbidities were not significantly different across UFR groups. Those with low UFR had a median cumulative fluid balance of 2.38 L over 72 hours, lower likelihood to remain dependent on dialysis at 90-days, and highest 90-day mortality (Table 1).

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In an adjusted Cox proportional hazards model, low UFR was associated with an increased risk of 90-day mortality (HR 1.88, 95% CI 1.10–3.21; p=0.02) whereas high UFR was not significantly associated with 90-day mortality (HR 0.66, 95% CI 0.31–1.42, p=0.29).

**Conclusions:** Low UFR is associated with increased 90-day mortality while high UFR was not associated with 90-day mortality. Future studies should investigate the ideal UFR to improve patient outcomes.

**Funding:** Commercial Support - Fresenius Medical Care

**Outcomes By 72 Hour Net Ultrafiltration Rate**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low UFR</th>
<th>Moderate UFR</th>
<th>High UFR</th>
<th>Non-significant</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>742</td>
<td>269</td>
<td>167</td>
<td></td>
</tr>
<tr>
<td>72H Fluid Balance (L)</td>
<td>2.38 (1.62-3.97)</td>
<td>4.62 (3.53-5.77)</td>
<td>5.25 (4.58-6.93)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>72H UFR (mL/kg/h)</td>
<td>0.39 (0.07-0.71)</td>
<td>1.29 (0.46-1.78)</td>
<td>2.27 (1.36-3.28)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hospital Days (med)</td>
<td>14 (2.27)</td>
<td>19 (3.35)</td>
<td>19 (3.35)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>RRT at Day 90 (%)</td>
<td>11 (14.5)</td>
<td>15 (21.1)</td>
<td>16 (23.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>90-Day Mortality (%)</td>
<td>52 (70.8)</td>
<td>62 (90.2)</td>
<td>66 (85.7)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

**FR-PO123**

**Impact of Positive Fluid Balance and Timing of Renal Replacement Therapy in AKI in a Real-Life Scenario**

**Background:** Objective: To determine if a fluid overload of less than 10% of body weight and early initiation (<12 hours) of RRT behave as an independent prognostic factor for mortality in patients with AKI KDIGO 3 in the ICU.

**Methods:** Retrospective cohort study that included patients hospitalized in the ICU of a hospital in Medellin-Colombia with a diagnosis of AKI KDIGO 3 and need for RRT.

**Results:** 278 patients with a median age of 63 years, 58.6% (163) men and 60.4% (168) diagnosed with sepsis were included. 166 (59.7%) were classified as early RRT and 112 (40.3%) as late RRT. The cumulative fluid balance was 9565 ml and 7496 ml, respectively. Mortality was 69% (192), with no significant differences according to the time of RRT (67 vs. 71%). There were no statistically significant differences between the early and late therapy group (OR adjusted 1.34, 0.65-2.75); nor in those with a percentage of accumulated fluid balance greater than 10% of body weight (OR adjusted 1.27; CI 0.73-2.23).

**Conclusions:** Early initiation of RRT, less than 12 hours from diagnosis, and with an accumulated fluid balance of less than 10% of body weight, did not have a lower risk of in-hospital mortality in patients with AKI KDIGO 3 in the ICU.
Methods: Patients with acute kidney injury (AKI) who required CRRT between 1/1/2011 and 12/31/2021 and were admitted to a tertiary academic hospital were included. We assessed the impact of hypotensive episodes on in-hospital mortality and major adverse kidney events (MAKE) at 90 days. MAKE is a composite outcome of need of kidney replacement therapy, doubling of the serum creatinine from baseline or death. Hemodynamic instability episodes were defined as mean arterial pressure (MAP) < 60 mmHg or a decrease in MAP by ≥10 mmHg, systolic blood pressure <90 mmHg or a decrease in SBP by ≥20 mmHg, or increased vasopressor requirement. These were measured in 15-minute increments and the number of episodes in each hour was recorded.

Results: There were 669 patients with AKI that required CRRT during the study period. The median number of hypotensive episodes during the first 24 hours of CRRT was 51 (Interquartile range: 46-55). There were 320 (48%) who suffered in-hospital mortality and 463 (69%) who had hospital mortality. Patients who had in-hospital mortality were older (62 vs 58), and had higher SOFA score (11 vs 9), higher norepinephrine equivalent (NEE) requirement (0.16 vs 0.07 mcg/kg/min), more frequent hypotensive episodes (medians: 52 vs 49), higher lactate (6.2 ± 3.2 mmOL/L), lower mean arterial pressure (MAP) (74 vs 79 mmHg) and were more likely to be requiring mechanical ventilation (81% vs 61%) at CRRT initiation compared to patients who did not suffer in-hospital mortality, p<0.001. After adjusting for age, baseline serum creatinine and SOFA score, lactate, MAP, mechanical ventilation and NEE at CRRT initiation, the number of hypotensive episodes during the first 24 hours was independently associated with in-hospital mortality (OR: 1.2, 95% CI: 1.11-1.35, p<0.001) and MAKE-90 (OR: 1.1, 95% CI 1.01-1.2, p-value=0.04) per 10 increase in hypotensive episodes.

Conclusions: Hypotension is a significant independent risk factor for in-hospital mortality and occurs frequently in patients receiving CRRT.

FR-PO126

Association of Dynamic Hemoglobin Change and Renal Recovery in Patients with Severe AKI Requiring Continuous Renal Replacement Therapy

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Background: Anemia in patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is associated with increased mortality and morbidity. However, the relevance of dynamic hemoglobin level variability (HbV) to renal recovery after AKI is still largely unknown. This study investigated the correlations between HbV and renal recovery at the time of discharge in patients with severe AKI who requiring CRRT.

Methods: We collected 1,897 AKI patients who underwent CRRT from two university hospitals between 2006 and 2021. The HbV was defined as the standard deviation (SD) and coefficient of variation (CV) during CRRT. To investigate the effects of HbV on RRT-dependence at discharge, we estimated the sub-distribution hazard ratio (HR) considering the mortality, adjusted by sex, age, charlson-comorbidity index, hypertension, SOFA, APACHE, and serum chemistry data.

Results: Of 1,897 AKI patients, 38 % were male and the mean (standardized deviation) age was 66.1 (±16.1) years. The proportion of outcome at discharge was 8% for RRT dependence, 29% for RRT independence, and 63% for mortality. The Cox regression analysis showed that HbV was positively correlated with RRT-dependence (SD, HR 0.77, 95% confidence interval [CI], 0.66 to 0.89; CV, HR 0.67, 95% CI 0.56 to 0.81). Finally, we classified patients into four groups based on hemoglobin variability during dialysis: (1) low HbV < 0.2 g/dL, (2) intermediate HbV 0.2 - 0.4 g/dL, (3) high HbV > 0.4 g/dL. The mortality was lower in patients with low and intermediate HbV compared to high HbV during dialysis.

Conclusions: This study showed that HbV during dialysis was associated with short-term renal recovery after severe AKI requiring CRRT.

FR-PO127

Association of Changes in Platelet and White Blood Cell Counts with Hospital Mortality in Patients with AKI requiring CRRT: A Multicenter Cohort Study

Chloé G. Braun,1 Lan N. Bui,2 Augusto Cama-Olivares,2 Lucas J. Liu,3 Tomornori Takeuchi,1 Victor M. Ortiz-Soriano,1 Joshua Lambert,2 Ashita J. Tolwani,1 Kianoush Kashani,1 Javier A. Neira,1 The University of Alabama at Birmingham, Birmingham, AL; 2University of Alabama at Birmingham, Birmingham, AL; 3University Peruana Cayetano Heredia, Lima, Peru; 4University of Kentucky, Lexington, KY; 5Brookwood Baptist Health, Birmingham, AL; 6University of Cincinnati, Cincinnati, OH;7 Mayo Foundation for Medical Education and Research, Rochester, MN.

Background: The relationship of platelet and white blood cell counts and adverse outcomes has been extensively studied in diverse critically ill populations. These parameters have seldom been studied in patients with AKI requiring CRRT. Given that the delivery of CRRT may directly impact these parameters, we aim to examine the association of changes in platelet and white blood cell (WBC) counts from pre-CRRT to during CRRT with hospital mortality.

Methods: Multicenter retrospective cohort study of 1,413 critically ill adult patients with AKI requiring CRRT at two academic medical centers between 2011 and 2021. Platelet and WBC count change from pre- to during CRRT was assessed as a percentage change from baseline at the start of CRRT. Platelet and WBC counts and categorized by SD groups (<1 SD, >1 SD, and >1 SD of the mean). Multivariable regression and interaction analyses were utilized to investigate associations with hospital mortality.

Results: Hospital mortality occurred in 53.2% of patients. In models adjusting for demographics, comorbidity, baseline kidney function, and SOFA scores, >1 SD platelet elevation during CRRT (>62% from pre-CRRT) was independently associated with hospital mortality (aOR: 1.82, 95% CI: 1.06, 3.13), while >1 SD WBC count increase during CRRT (>136% from pre-CRRT) exhibited non-significant increased mortality (aOR 1.41, 95% CI: 0.88, 2.29). Four high-risk patient phenotypes were identified from interaction analyses: 1. Pre-CRRT low platelet count that remained low, 2. Pre-CRRT normal platelet count with a drop of >1 SD, 3. Pre-CRRT elevated WBC count that remained high and 4. Normal or elevated pre-CRRT WBC count that increased to >1 SD. Conclusions: In critically ill adult patients with AKI requiring CRRT, a drop in platelets and an increase in WBC from pre-CRRT to during CRRT can assist in patient phenotyping and mortality risk-classification. Further discovery and validation of relevant CRRT patient phenotypes is needed to better guide CRRT delivery.

FR-POI128

Hypomagnesemia in Critically Ill Patients Undergoing Continuous and Prolonged Intermittent Kidney Replacement Therapies: Still a Matter of Debate?

Francesca Di Mario,1 Umberto Maggiore,2 Giuseppe Regolisti,3 Benedra Menegazza,4 Maria C. Pacchiarii,5 Paolo Greco,6 Caterina Maccari,7 Enrico Fiaccheriodi. Parma University Hospital, Parma, Italy.

Background: Hypomagnesemia may represent a fearsome complication in critically ill patients undergoing Continuous and Prolonged Intermittent Kidney Replacement Therapy (CRRT, PIKRT). Given its negative impact on morbidity and mortality, strategies aimed at reducing its incidence should be timely implemented. We carried out a prospective observational study aimed at assessing the incidence and outcome of hypomagnesemia in ICU patients undergoing CRRT and PIKRT with Regional Citrate Anticoagulation.

Methods: KRT was performed by the Prismax system and AN69 filters (Baxter), combining a trisodium citrate solution (Regiocit 18/0, Baxter) with a Mg-containing solution used as dialysis and/or post-dilution replacement fluid (Mg2+ 0.75 mmol/L; Biphozy1, Baxter). Each patient underwent KRT or PIKRT with Regional Citrate Anticoagulation.

Conclusions: Hypomagnesemia may represent a fearsome complication in critically ill patients undergoing Continuous and Prolonged Intermittent Kidney Replacement Therapy (CRRT, PIKRT). Given its negative impact on morbidity and mortality, strategies aimed at reducing its incidence should be timely implemented. We carried out a prospective observational study aimed at assessing the incidence and outcome of hypomagnesemia in ICU patients undergoing CRRT and PIKRT with Regional Citrate Anticoagulation.

Results: We enrolled 47 patients on CVVH, CVVHDF and SLED (mean APACHE II 25±7.0); s-Mg was 2.07±0.48 mg/dL at baseline and decreased by -0.25 mg/dL during KRT (P<0.0003, Figure 1), with the nadir being reached since the first KRT session. Hypomagnesemia (s-Mg<1.6 mg/dL) was observed, at least once, in 46.8% of patients, despite an average supplementation of 1.18 g/day. There was a trend, albeit not statistically significant, of lowest s-Mg values to be associated with increased mortality, and adjusting for potential confounders.

Conclusions: Hypomagnesemia is an incident complication of CRRT and PIKRT, mainly depending on baseline s-Mg. It seems associated with ICU mortality. Among preventive strategies, the evaluation of ionized s-Mg levels may represent a useful tool to better clarify Mg mass transfer during KRT.
FR-PO129
Magnesium Supplementation Is Associated with Reduced Mortality in AKI Requiring Continuous Kidney Replacement Therapy (CRRT)
Ryo Matsuura, Yoshifumi Hamasaki, Masasumi Nangaku, Kent Doi. The University of Tokyo Hospital, Tokyo, Japan.
Background: Hypomagnesemia is a common electrolytic disorder and associated with mortality and delayed renal recovery in AKI patients. Although prevention and treatment of hypomagnesemia are suggested, evidence that magnesium (Mg) supplementation could improve survival is still lacking.
Methods: We retrospectively collected the data on AKI patients requiring CRRT with the support of vasopressors and/or ventilators. After excluding patients without measurement of serum magnesium at the day of CRRT start and those who died within 48 hours from CRRT start, patients were divided in two groups according to presence or absence of Mg supplementation within 48 hours of CRRT. Propensity score matching was performed using a 2:1 nearest neighbor matching algorithm. The primary and secondary outcomes were mortality and KRT free at 90 days. The association with Mg supplementation and outcomes was evaluated using a multivariable Cox regression model and a Fine and Gray model.
Results: After excluding 290 patients who died within 48 hours or did not have measurement of serum mg, 296 patients without and 37 with Mg supplementation were analyzed. After propensity score matching, 68 patients without and 34 patients with Mg supplementation were analyzed. There is no difference in age, sex, presence of sepsis, baseline kidney function, illness severity and serum magnesium. Patients with Mg supplementation received 24.4±10.6mg/kg of Mg during 48 hours. The mortality rate was lower in patients with Mg supplementation than in those without (Figure). Mg supplementation is inversely associated with 90-day mortality with adjusted hazard ratio of 0.38 (95%CI, 0.18 – 0.83). Mg supplementation was associated with KRT free at 90 days with hazard ratio of 2.07 (95%CI, 1.23-3.49).
Conclusions: The study using propensity score matching revealed the association of Mg supplementation with improving survival rate and renal recovery.

FR-PO130
Calcium Balance in Slow Extended Dialysis: Effect of Regional Citrate
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1Heart Institute, São Paulo, São Paulo, Brazil; 2University of California San Diego Department of Medicine, La Jolla, CA; 3University of São Paulo Medical School, São Paulo, Brazil.
Background: Regional citrate anticoagulation (RCA) has been used as an alternative to heparin during slow extended dialysis (SLED) in patients with acute kidney injury (AKI). However, there is scanty data on the impact of different anticoagulation strategies on calcium balance during these procedures. This study aimed to determine calcium balance in SLED using RCA compared to saline or heparin in a crossover randomized clinical trial (RCT).
Methods: We included 20 critically ill adults with AKI who were eligible to be SLED (6 to 8 hours) in a tertiary center in Brazil. They were randomized to either RCA or standard of care (heparin as the first choice or continuous saline flush, in case of heparin contraindication) in a crossover manner. Dialysis was carried out using single-pass batch equipment, until the maximum of six therapies per subject. RCA used ACD 2.2% at 3 mmol/L, 1.3 mmol/L, post filter calcium target 0.6 - 0.7mmol/L, and pre-filter calcium target 1.10 - 1.32mmol/L. Dialysate calcium was 1.25 mmol/L in all therapies. The primary outcome was calcium balance.
Results: In 48 procedures, 24 used citrate, and 24 used heparin or continuous saline. Each participant performed 2 (±3) sessions in the protocol. Patients age was 66 (40 - 71) years, 55% men, 15% on mechanical ventilation, and 20% using vasoactive agents. All groups had a negative calcium balance, markedly in dialysis using RCA.

FR-PO131
Association Between Body Mass Index and Clinical Outcomes in Patients with AKI Requiring Continuous Renal Replacement Therapy
Hyeong Duk Kim,1 Yaei Kim.2 Catholic University of Korea Eunpyeong St Mary’s Hospital, Eunpyeong-gu, Seoul, Republic of Korea; 2Seoul Saint Mary’s Hospital, Seocho-gu, Seoul, Republic of Korea.
Background: Obesity is associated with higher mortality in general population. However, there has been controversy over the effect of obesity in critically ill patients. Therefore, we retrospectively reviewed medical records to investigate the association between body mass index (BMI) and mortality in critically ill patients who admitted to intensive care unit (ICU) and receiving continuous renal replacement therapy (CRRT).
Methods: A total of 991 adult patients were admitted to the ICU and received CRRT at three institutions of the Catholic Medical Center from July 2012 to December 2020. Of these patients, 845 subjects were eligible for the study, excluding patients without BMI data or patients with extracorporeal membrane oxygenation (ECMO) treatment. Patients were categorized into 4 groups according to the BMI criteria of the Korean Society for The Study of Obesity (BMI less than 18.5, 18.5-22.9, 23.0-24.9, 25.0kg/m² or greater). The association between BMI and 1-year overall mortality and 1-year ESRD incidence were investigated.
Results: The 1-year mortality was 43.3%, 47.9%, 36.2% and 39.0% in the underweight, normal, overweight, and obese groups respectively. The mortality rate of obese patients was significantly lower than that of normal patients in Kaplan-Meier analysis (p=0.002). Multivariable logistic regression analysis showed that obese patients had a decreased risk of mortality (normal group [hazard ratio (HR) 0.59-0.99] vs. obese group, p=0.005). The 1-year ESRD incidence was 43.6%, 37.9%, 32.4% and 25.0% in the underweight, normal, overweight, and obese groups respectively. In a multivariable logistic regression analysis adjusted for confounding factors, obesity was associated with a decreased risk of ESRD (HR, 0.56; 95% CI, 0.34-0.92; P=0.023). In subgroup analysis according to age, 1-year mortality consistently showed an inverse correlation between BMI and mortality, but ESRD incidence was inversely related with obesity only in patients with age ≥ 65. In critically ill patients admitted to ICU with AKI requiring CRRT, obesity (BMI=25.0kg/m²) was associated with lower 1-year mortality and 1-year ESRD incidence, suggesting obesity paradox in patient survival and renal survival.

FR-PO132
Effect of Urinary Output on Withdrawal from Continuous Renal Replacement Therapy in a Tertiary Referral Center in Western Mexico
Background: The withdrawal of Continuous Renal Replacement Therapy (CRRT) in patients where AKI has not been signaled by deterioration. New evidence suggests that releasing CRRT too soon, as well as unneeded and extended CRRT, might negatively affect the clinical course and economic cost of AKI.
Methods: A retrospective cohort of critically ill adult patients hospitalized in four intensive care units of a tertiary care center in western Mexico, who presented with acute kidney injury requiring CRRT, in which renal replacement therapy (RRT) was interrupted without the intention of migrating to another form of RRT, from January 2016 to March 2021. We defined CRRT withdrawal success as ≥72 h without the need for a TTR reset after CRRT discontinuation.
Results: Fifty-two patients who met the inclusion criteria were evaluated. Due to the abnormal distribution of the uresis values in both groups, it was decided to carry out the analysis by quartiles, finding the distribution regarding the success or failure of CRRT withdrawal. We found that uresis below the first quartile (<1,200 ml) was a risk factor for failure to withdraw CRRT (OR 2.85, 95% CI 1.84-4.41, p=0.001). Other variables that showed a risk of CRRT withdrawal failure in the multivariate analysis were lower systolic and diastolic blood pressure, the presence of comorbidities, more total hours of CRRT, and absence of diuretic use at the time of CRRT withdrawal.
Conclusions: A urine output of less than 1 liter was associated with almost three times the risk of failure to withdraw CRRT in our population. In turn, diuretics use

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facilitated withdrawal. Urinary volumes were greater in our CRRT-withdrawing study compared to those reported in other places.

FR-PO133

Proenkephalin May Improve Strategies for Successful Weaning from RRT

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Background: Acute kidney injury (AKI) is associated with fatal outcomes, particularly in patients requiring renal replacement therapy (RRT). Conventional kidney biomarkers such as serum creatinine (SCr) are incapable of indicating kidney recovery in patients receiving RRT. Proenkephalin A (penKid) is a novel kidney biomarker with unprecedented characteristics. We hypothesized that penKid could provide a more accurate prediction of successful weaning from RRT than established standards of care.

Methods: Measurement of penKid plasma levels were implemented in the daily blood routine at our center. In this preliminary analysis, data of 1473 patients were gathered. The start of a weaning trial was defined as 48h without RRT, and weaning was considered successful if a patient did not require RRT for five consecutive days.

Results: RRT procedures were performed in 234 patients of whom 54 patients were chronically dependent on hemodialysis prior ICU admission. Baseline and maximum penKid levels showed a stepwise increase with rising AKI stage (KIDGO criteria). Median penKid levels at RRT start were 128.2 pmol/L and increased further under RRT. In contrast, SCr levels decreased in association with RRT procedures. In patients with pre-existing chronic RRT-dependency, penKid levels were significantly higher than in patients with acute RRT requirements at any time after RRT initiation (Day 3 after RRT Start: 134.7 vs. 70.9 pmol/L), while SCr was already indifferent on day 3 (1.60 vs. 1.49 mg/dL). Differing RRT modalities had no effect on penKid levels, whereas continuous RRT forms were more effective than intermittent RRT in clearing SCr. On the day of last RRT, ROC analysis yielded an Area Under the Curve (AUC) for predicting successful weaning higher for penKid compared to UO with 0.76 (95% CI 0.58-0.94, p=0.014) and 0.74 (95% CI 0.55-0.94, p=0.039), respectively. One day earlier, predictive performance was even more favorable for penKid compared to UO (AUC 0.72 [95% CI 0.54-0.91, p=0.036] vs. 0.58 [95% CI 0.36-0.80, p=0.879]).

Conclusions: Our data suggest that penKid may provide additional information to standard of care regarding kidney integrity under RRT, making it a valuable biomarker to predict liberation from RRT. This has large clinical implications given the importance of avoiding unnecessary RRT-procedures.

FR-PO134

Predictors of Early Peritoneal Dialysis Start in Newborns and Young Infants Following Cardiac Surgery

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Background: This single center, retrospective cohort study was conducted to investigate the predictors of early peritoneal dialysis (PD) start initiation in newborns and young infants undergoing cardiac surgery.

Methods: There were fifty-seven newborns and young infants. All subjects received PD catheter after completion of the cardiopulmonary bypass (CPB). Worsening postoperative (post-op) positive fluid balance and oliguria (<1 ml/kg/hour) despite furosemide were the clinical indications to start early PD (PD+). Demographic clinical and laboratory data were collected from the pre-operative, intra-operative and immediately post-operative periods.

Results: Demographic and laboratory data were different except that PD+ group had more newborns. Preoperative serum creatinine was higher for PD+ group (p=0.025). PD+ group had longer CPB time (p=0.044), longer aorta cross-clamp time (p=0.044) and less urine output during early post-op 24 hours (p=0.008). In the univariate logistic regression model, pre-op serum creatinine was significantly associated with higher odds of being in PD+ (p=0.021) and post-op systolic BP (p=0.018) and post-op MAP (p=0.001) were significantly associated with reduced odds of being in PD+ (p=0.018 and p=0.001, respectively). Post-op MAP showed a statistically significant association (OR=0.89, 95% CI [0.81, 0.96], p=0.004) with PD+ in multivariate analysis after adjusting for age at surgery.

Conclusions: In our single center cohort, pre-op serum creatinine, post-op systolic BP and MAP were demonstrated statistically significant association with PD+. This finding may help to lower risk straitly newborns and young infants for early PD start following cardiac surgery.

FR-PO135

Role of Immunomodulation Therapy with Selective Cytopheretic Device (SCD) in Reversing Acute on Chronic Liver Failure (ACLF) with Hepatorenal Syndrome (HRS) and Multi-Organ Failure

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Introduction: ACLF is a clinical disorder characterized by acute clinical deterioration in patients with pre-existing chronic liver disease. ACLF develops from systemic inflammation, often due to bacterial infections or alcoholic hepatitis, and progresses to multi-organ failure. Severe ACLF with ≥4 organ failure has a grave prognosis with a mortality rate at 28 days of 100%. Early liver transplant is the treatment of choice for those who are refractory to medical intervention. To mediate objectives and lessen this systemic inflammatory state may alter the progression of multi-organ dysfunction and allow time for liver transplantation.

Case Description: Case 1. A male patient in his 30s presented with acute alcohol associated hepatitis, ACLF, HRS, and a4 organ failure. He required vasopressors, mechanical ventilation, and CRRT. MELD score was 38. Case 2. A male patient in his 60s with non-alcoholic steatohepatitis (NASH) was admitted for hypotension and decompensated cirrhosis. He required vasopressors and developed HRS. MELD score was 37. Both patients were enrolled into a clinical trial (NCT 04898010) to evaluate an extracorporeal immunomodulating device, SCD. Both patients showed rapid clinical improvement associated with a decline in elevated blood cytokine concentrations and diminution of activation levels of circulating leukocytes. On follow up Case 1 was alive at day 90 after treatment and undergoing liver transplantation evaluation and Case 2 had a successful liver transplant 6 days after SCD therapy ended.

Discussion: The final common pathway of systemic hyper-inflammation resulting in multi-organ failure is the effector cells of the innate immunologic system. The activation of neutrophils and monocytes is the key driver of the developing hypoxic and toxic tissue damage of solid organs. The immunomodulation of these cellular elements rather than removal or inhibition of soluble cytokines or chemokines of inflammation is the critical target for effective therapy, as demonstrated with SCD treatment. These cases represent the first in human treatment of ACLF with SCD. These results suggest a role for SCD treatment in the management of HRS-AKI and SCD as a bridge to liver transplantation.

FR-PO136

Safety Summary of the Selective Cytopheretic Device (SCD): A Review of Safety Data Across Multiple Clinical Trials in ICU Patients with AKI and Multi-Organ Failure

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Background: AKI is a frequent and serious complication in critically ill patients, occurring at a rate of 1 in 5 adults and 1 in 3 children hospitalized with acute illness. AKI requiring CRRT is a significant complication in ICU patients with mortality rates exceeding 50%. A disregulated immune response can lead to systemic inflammation caused by a hyperactivity of pro-inflammatory neutrophils & monocytes leading to tissue damage. Resulting from hyperinflammation associated with AKI frequently progresses to other organs, such as the heart, lung, or liver. The SCD is an investigational medical device in a new class of cell-directed extracorporeal therapies distinct from cytokine adsorbers or filters, as it targets activated leukocytes, the key cellular sources driving the hyperinflammatory process. This report summarizes safety data from the major clinical studies of the SCD across a variety of patient types with AKI and multi-organ failure.

Methods: Safety was assessed in each study through the collection of AEs & SAEs. All-cause mortality was also assessed. As all-cause mortality can help in interpreting safety, this report will also summarize survival rates in each study.

Results: Results from each of the 5 studies will be described herein, including that 5 of 6 studies had no device-related SAEs and AEs from each study were consistent with those expected in a critically-ill ICU population. Although studies were not powered to detect differences in mortality, there were trends toward higher survival rates in SCD patients vs. controls.

Conclusions: These studies support that the SCD can be added as a therapeutic intervention in critically ill AKI patient populations with additional multi-organ failure without adding additional safety risks. Any intervention with the potential to improve survival in such a critically patient population would be welcome.

Funding: Commercial Support - SeaStar Medical

Summary of Adverse Events from Studies

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FR-PO137
Sepsis-Associated AKI (SA-AKI) Requiring Kidney Replacement Therapy (KRT): Role of Hemofiltrate Reinfusion (HFR)-Supra on Inflammation and Outcome
Giuseppe Geronem, Michele Russo. ASL Bari, Bari, Italy.

Background: Sepsis is life-threatening organ dysfunction caused by dysregulated body response to an infection. Mortality rate ranging over 60% for septic shock. AKI is a final common pathway of this immune dysregulation leading to systemic inflammation (SI) due to uncontrolled circulating levels of pro-inflammatory mediators and cytokines induced direct organ damage. KRT is often required in SA-AKI and could improve SI removing pathogens and inflammatory factors. Various blood purification techniques have been used: HCO/MCO membranes, hemoperfusion, plasma filtration/adsorption and, anecdotally, Hemo Filtrate Reinfusion Supra (HFR): endogenous renin HDF based on adsorbing resin cartridge that remove pro-inflammatory cytokines but whose full spectrum is not yet known. Aim of this study is to test HFR on outcome of SA-AKI in critically ill pts.

Methods: Retrospective observational study evaluated 8 SA-AKI pts requiring KRT. All were treated with daily HFR(Bello-Medronic), today, mean of 8.3 ± 5.4 treatments. We daily assessed (as mean ±SD): urea, sCr, CRP, procalcitonin (PCTC), WBC, myoglobin(Myo), albumin; in addition need for vasopressor and outcome. AKI was defined according to KDIGO.

Results: The mean age was 74 ± 19.4 years, 6 pts were male (75%). Over 30% obese with nephropathies, some hypertensive, with diabetes or COPD. HFR: Qb= 250 ± 18.8 mL/min, TT 238.7 ± 27.7 min. HFR confirm valid URR, highly significant abatement of CRP. The difference was 10.5 ± 20.2 p< 0.03 and Myoglobin (363.5 ± 1709.2 511.7 ± 435.9 ± < 0.01), stable Albumin. Lower need of vaspressors (13.5 ± 3.7 ± 3.1 p < 0.002) highlighted improved hemodynamic instability with no poor intradialytic complience. 3 pts not survived (2 for surgical, 1 for pulmonary complications) everyone else had renal recovery.

Conclusions: HFR decrease SI and support renal recovery in SA-AKI pts, even in the not survived. The sorbent cartridge remove many proinflammatory cytokines, that lead to improved MAPs and lower critical illness scores, and allow to eliminate myoglobin too. Finally, hemofiltrate technique for SA-AKI in comparison to the other (eg CRRT, HCO, Cytorosorb). There is no study on HFR in SA-AKI and very few experience on his use to hypermyoglobinemia. Larger studies need to confirm our evidence but, in the meantime, we could help to build a new scientific evidence.

FR-PO138
Plasma Cystatin C Predicts Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy (CRRT) for AKI
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Background: AKI requiring KRT is a common complication in hospitalized patients that confers increased mortality. Tools to predict timing of kidney function recovery and mortality are needed. Cystatin C (CysC) is a marker of kidney function that may reflect residual kidney function while on KRT. Herein, we tested the hypothesis that lower plasma cysC concentrations would predict early kidney function recovery in patients with AKI requiring CRRT.

Methods: 51 patients without chronic kidney disease requiring CRRT for AKI were studied. Plasma was collected prior to CRRT initiation, and plasma and effluent were collected on days 1, 2, and 3 of CRRT. Two groups were studied: early kidney function recovery (ERKF) (liberated from dialysis within 7 days of CRRT initiation, N = 15) and delayed kidney function recovery or death (DKFR/D, on dialysis 21 days after CRRT initiation or death prior to renal recovery, N = 36). CysC, creatinine, and blood urea nitrogen (BUN) were measured in plasma and effluent, and CRRT dose and urine output were recorded.

Results: Mean plasma cysC (mg/L) was significantly lower on days 1 (1.79 ± 2.41, p = 0.03) and 2 (1.91 vs 2.41, p = 0.03) of CRRT in patients with EKF versus DKFR/D. There was no difference in serum creatinine or BUN between the two groups. CysC on days 1 and 2 of CRRT predicted early kidney function recovery (day 1 ROC AUC 0.765 ± 0.03; day 2 ROC AUC 0.751, p = 0.01). CRRT clearance of cysC and cysC sieving coefficient were similar between the two groups. The average cysC sieving coefficient in all patients was 0.59, 0.61, and 0.61 on days 1, 2, and 3 of CRRT respectively.

Conclusions: CysC on days 1 and 2 of CRRT predicts early kidney function recovery. The lower concentration of plasma cysC in patients with EKF was not due to differences in CRRT cysC clearance. Since cysC is moderately cleared by CRRT, it may be only predictive at early timepoints after CRRT initiation. CysC is available in clinical practice, thus measuring cysC in patients on CRRT for AKI is feasible and would fill a void in data that is needed to support discussions between clinical providers and patients regarding outcomes and prognosis.

Funding: Commercial Support - Baxter Investigator Initiative Grant, Private Foundation Support

FR-PO139
Impact of Early Renal Replacement Therapy in Leptospirosis on Mortality and Long-Term Renal Function: A Retrospective Analysis over 11 Years in Reunion Island
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Background: Leptospirosis is a widespread zoonosis that can cause severe acute kidney injury (AKI-L) and remote chronic renal disease (CKD-L). Anciend evidence suggests that early renal replacement therapy (RRT) may improve mortality associated with AKI-L. Conversely, intensive care unit (ICU)-based trials, including the landmark AKI trial have carried have disproved a positive impact of early RRT on patient mortality. We aim to determine (i) whether the temporal pattern (ii) whether the timing of RRT impacts mortality (iii) provide an estimation of the incidence of post-leptospirosis CKD.

Methods: We conducted a retrospective study over 11 years in Reunion Island including adult patients with confirmed leptospirosis complicates by KDIGO 2 or 3 AKI. The endpoint was a composite endpoint including death and CKD-L up to 3 years after hospital discharge. Factors associated with CKD-L and death were determined using logistic regression models with different adjustment variables.

Results: Three hundred eighty eight patients were included, 39% of whom required RRT with a median time to initiation of 1 day (0-2 days). According to the composite criterion, the mortality rate was 4% in the study population and the incidence of CKD-L was 8%. On univariate analysis, factors associated with the composite criterion included ICU severity scores, age, baseline kidney function, oligo-anuria and the need for RRT. Using bivariate models adjusting on age or SAPSD or prior renal function, we showed that when compared to patients who did not require dialysis, no significant difference was found between early or late dialysis initiation on the composite endpoint. Odds ratio (OR) for RRT before 24h was 5.7 (1.9-17.9) and OR for RRT after 24h was 5.7 (2.1-16.3).

Conclusions: In conclusion, leptospirosis accounts for significant CKD. Early RRT does not seem to improve the composite mortality-CKD endpoint. Further investigations are needed to substantiate the potentially protective effects of early RRT on CKD-L.

Bivariate analysis of factors associated with death or CKD at last follow-up, according to time to initiation of RRT and patients’ SAPSD score

FR-PO140
A Roadmap to Recovery: Managing AKI in a Case of Hemophilia B
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Introduction: Hemophilia, a rare inherited bleeding disorder, poses challenges in the management of patients requiring renal replacement therapy. Acute Kidney Injury is a serious complication that can occur in hemophiliac patients following prolonged hospitalization secondary to trauma. There is limited data on the appropriate dialysis modality selection, and prescription of dialysis treatments in these patients.

Case Description: We present a case report highlighting the innovative approach adopted for the management of acute kidney injury (AKI) in a 31-year-old male hemophiliac patient with a history of traumatic bilateral knee injury as the incident.

The diagnostic workup revealed intra-abdominal bleeding and sepsis, leading to the development of AKI. Given the patient’s complex clinical profile, a tailored approach was necessary to balance the need for renal replacement therapy while minimizing the bleeding risks associated with hemophilia. Sustained low-efficiency daily dialysis (SLEDD) was utilized for renal support, with modifications made to minimize bleeding risks. The modifications included the use of normal saline and cryoprecipitate to maintain adequate clotting factor levels, to minimize bleeding during catheter insertion and removal and to prevent coagulation of the circuit, and close monitoring of coagulation parameters throughout the dialysis sessions. 6 such dialysis sessions were done following which the acute kidney injury was resolved.

Discussion: In this case, the key challenge to overcome was the use of heparin to prevent coagulation in the extracorporeal circuit, but at the same time it carried the risk of prolonging the already prolonged Activated Partial Thromboplastin Time (APTT). The solution was to use saline and cryoprecipitate in the process to maintain the dialysis circuit and the hemodynamic stability of the patient. The modality of choice was SLEDD, because of its capacity to offer continuous renal support while retaining a low risk of bleeding. SLEDD with modifications proved to be a safe and effective method for managing AKI in our patient. Further research is needed to establish optimal management strategies for AKI in patients with Hemophilia B.

FR-PO141
Suspected Scleroderma Renal Crisis in Patient with Severe Hypertension and AKI
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Introduction: Although rare, scleroderma renal crisis is a potentially fatal complication that affects up to 10% of patients with systemic sclerosis. The etiology of scleroderma renal crisis is poorly understood, however it is thought that vascular
endothelial injury, vascular thrombosis and arterial narrowing leads to decreased perfusion of the kidneys. This in turn activates the renin-angiotensin-aldosterone system causing severe hypertension.

**Case Description:** A 67 year old male with history of scleroderma, pulmonary hypertension, pulmonary fibrosis and hyperlipidemia presented with worsening shortness of breath. Initial systolic blood pressure noted to be in the 180s on occasion reaching 220s with diastolic blood pressures in the 100s. Labs significant for BUN 47, creatinine 1.6 (baseline 0.7), GFR 47 (baseline 100s), CRP 1.17, troponin 0.248, platelets 80, LDH 405, lactoglobulin < 20 and urinalysis showing protein > 500 mg. Renal ultrasound showed echogenic kidneys consistent with chronic parenchymal disease. Scleroderma renal crisis was suspected and plan was to initiate captopril 6.25 mg q 4 hrs, however medication was non-formulary. Therefore, Enalapril 2.5 mg IV q 4 hrs was ordered and after 1 dose, systolic blood pressures noted to be in the 130s-150s and diastolic blood pressures in the 70s-90s. He was then started on lisinopril 5 mg po qHS and amlodipine 5 mg po daily to control his blood pressure.

**Discussion:** The diagnosis of scleroderma renal crisis must be considered in all patients with systemic sclerosis presenting with AKI and accelerated hypertension. Several risk factors for development of scleroderma renal crisis include renal impairment within first 5 years of disease course, scleroderma skin involvement, glucocorticoid therapy within 6 months and autoantibodies to RNA polymerase III. Scleroderma renal crisis is a diagnosis of exclusion and treatment is more likely to be effective when initiated early, therefore prompt recognition significantly improves outcomes and mortality.

The patient initially presented with typical features of scleroderma renal crisis, his hemodynamic stability and rapid response to ACEi makes it unlikely. Once the patient’s blood pressure was controlled, renal function significantly improved. The patients symptoms more representative of hypertensive emergency in setting of poorly managed hypertension.

**FR-PO142**

**Ichthyosiform Sarcoïdosis with Renal Involvement**

Tareq Hanouneh, Carmen E. Cervantes, 1 Lois J. Arend, 1 Mohamad A. Hanouneh. 2 Mayo Clinic in Florida, Jacksonville, FL; 1 Johns Hopkins University School of Medicine, Baltimore, MD; 3 Johns Hopkins University, Baltimore, MD; 4 Nephrology Center of Maryland, Baltimore, MD

**Introduction:** Ichthyosiform, also called disorders of keratinization, are a heterogeneous group of disorders characterized by generalized skin scaling. The great majority of ichthyoses are inherited, but acquired forms can develop in the setting of malignancy, autoimmune or infectious diseases.

**Case Description:** A 51-year-old man presented to the hospital for evaluation of acute kidney injury. The skin exam showed xerosis with hyperpigmented scales seen on his arms, legs, abdomen, and back (Figure 1-A). Initial workup revealed the following: creatinine 6.27 mg/dL (baseline 0.8 mg/dL), calcium 15.1 mg/dL, PTH 9.1 pg/mL (10-55 pg/mL), vitamin D1 125, 25-hydroxyvitamin D3 97.3 pg/mL (20-76 pg/mL), and angiotensin-converting enzyme 120 u/L (14-82 u/L). Uremia was positive for proteinuria with a urine protein/creatinine ratio of 900 mg/g Cr. Renal biopsy demonstrated diffuse granulomatous interstitial nephritis (Figure 2-A). Immunofluorescence showed granular capillary wall IgG. Electron microscopy showed podocyte foot process effacement and subepithelial electron-dense deposits (Figure 2-B). Skin biopsy revealed hyperkeratosis with non-necrotizing granulomas. The patient was diagnosed with ichthyosiform sarcoidosis, granulomatous interstitial nephritis, and secondary membranous nephropathy. He was started on prednisone 60 mg daily. His serum creatinine and serum calcium returned to normal with significant improvement in his ichthyosis (Figure 1-B).

**Discussion:** Ichthyosiform lesions are one of the extremely rare cutaneous manifestations of sarcoidosis that may precede or coincide with the diagnosis of systemic sarcoidosis. Renal manifestations include abnormal calcium metabolism, nephrocalcinosis, acute interstitial nephritis, and membranous glomerulonephritis.

**FR-PO143**

**Successful Management of TAFRO Syndrome-Related Renal Thrombotic Microangiopathy with Interleukin-6 Inhibitor**

Ahmed I. Abdelkader, Salem Vilayet, Evelyn Bruner, Anand Achanti, Milos N. Budasavljevic. Medical University of South Carolina, Charleston, SC.

**Introduction:** TAFRO [Thrombocytopenia, Anasarca, edema, pleural effusions, ascites, Fever, Reticulin myelofibrosis (or Renal insufficiency), and Organomegaly (lymphadenopathy and hepatosplenomegaly)] that represents a severe subtype of idiopathic multicentric Castlemain’s disease (iMCD). Kidney involvement in TAFRO syndrome can be severe and may require hemodialysis (HD). However, detailed descriptions of this syndrome’s aspect remain limited.

**Case Description:** A 28-year-old male presented as transfer from another hospital with anasarca, malaise, diffuse lymphadenopathy, and non-oliguric acute kidney injury. He has no past medical history. Initial concern for lymphoma; however, bone marrow biopsy, ascites, pleural fluid examination and flow cytometry were negative for malignancy. The lymph node biopsy showed diagnostic findings of Castlemain disease-TAFRO variant. HIV-8, HIV-6, CMV, EBV and HIV were negative. Kidney functions continued to deteriorate driving hyperkalemia necessitated HD. Kidney biopsy was done showing thrombotic microangiopathy (TMA) with mesangiolysis. Serum Interleukin-6 (IL-6) and VEGF were high. Prednisolone was started and Siltuximab, an IL-6 monoclonal antibody, was initiated and continued at 3 weeks intervals. Patient started to improve within days after the first dose of IL-6 inhibitor and HD was discontinued along with full improvement of clinical symptoms and kidney functions.

**Discussion:** Rates of renal failure are much higher in TAFRO syndrome variant than typical iMCD. Histopathology of renal involvement in TAFRO syndrome has been reported in few publications. The majority have demonstrated a pattern consistent with membranoproliferative glomerulonephritis and few showed TMA. iMCD is known as hyper-IL-6 syndrome with polyclonal lymphadenopathy. Early recognition of disease and early initiation of IL-6 inhibition and glucocorticoids are of paramount importance in attaining complete.

**FR-PO144**

**Investigating Vasopressin-Dependent Renal Medullary Osmolarity as a New Target for Renoprotection**


**Background:** The renal medulla is characterized by a hyperosmolality that depends on Avp2 signaling. High osmolality in the kidney medulla is required for urine concentrating mechanisms. However, the role of the hyperosmotic medulla beyond electrolyte-free water reabsorption is not well understood. Here, we investigate the role of high osmolality in regulating kidney injury responses at molecular and cellular levels.

**Methods:** We analyzed kidneys from C57Bl/6N mice treated with tolvaptan (Avp2 antagonist) and compared them to kidneys from control mice. Our analysis included single-nuclei and bulk RNA sequencing, in situ hybridizations, Avp2 antagonist treatment protected the renal medulla from fibrosis following unilateral renal ischemia-reperfusion injury.

**Results:** Tolvaptan treatment reduced renal medullary osmolality and caused significant changes in the gene expression of tubular cells in the renal medulla. These changes included decreased expression of stress response and immune activation-related genes (such as Atf4, Ddit3, Hmgb1) and genes influenced by high tissue osmolality (such as Cryab, and Nup1). The results were confirmed through bulk RNA sequencing and in situ hybridizations. Avp2 antagonist treatment protected the renal medulla from fibrosis following unilateral renal ischemia-reperfusion injury.

**Conclusions:** Applying unbiased single-cell transcriptomics and orthogonal validation, we discovered that inhibiting Avp2 in mice reduced the expression of osmolality-regulated genes in tubular cells of the renal medulla, including those associated with stress and immune responses. Avp2 inhibition protected the renal medulla from fibrosis development following ischemia-reperfusion injury. These findings suggest that targeting Avp2-dependent medullary osmolality could be a potential strategy for renoprotection.

**Funding:** Government Support - Non-U.S.
FR-PO145

Caspase-3 Activation Increases with Age and Aggravates Kidney Injury After Ischemia-Reperfusion

Imane Kaci,1,2 Shanshan Lan,1,2 Hyunyun Kim,1,2 Annie Karakeussian Rimbaud,2 Francis Migneault,2 Julie Turgeon,2 Natalie Patey,1,2 Mélanie Dieude,1,2 Marie-Josée Hebert.1,2,3 Université de Montréal, Montreal, QC, Canada; 2Centre de Recherche du Centre Hospitalier Universitaire Sainte-Justine, Montreal, QC, Canada.

Background: Rarefaction of peritubular capillaries (PTC) after ischemia-reperfusion injury (IRI) predicts progressive renal failure, especially in older kidneys. We previously demonstrated the importance of caspase-3-dependent microvascular damage in progressive kidney dysfunction after IRI. We also showed that renal IRI increases circulating levels of ApoExo; an immunogenic type of exosome-like vesicles produced by apoptotic endothelial cells downstream of caspase-3 activation, and characterized by the presence of LG3/perlecan autoantigen and active 20S proteasome. Here, we hypothesize that age modulates caspase-3 activation after renal IRI leading to increased release of ApoExo, enhanced PTC rarefaction, and fibrosis.

Methods: Unilateral renal pedicle clamping (30 minutes) and contralateral nephrectomy were performed in young (8 weeks-old) and old (27 and 53 weeks-old) mice. ApoExo were purified from serum-free medium conditioned by apoptotic murine endothelial cells in vitro and injected to mice via tail vein every other day. Endpoints were assessed 21 days post-IRI. ApoExo circulating levels were measured by protease activity and anti-LG3 titers by ELISA. Complement deposition, caspase-3 activation, PTC rarefaction and fibrosis were assessed by immunohistochemistry. Renal function was monitored by BUN level.

Results: At baseline, old mice showed higher levels of caspase-3 activation within PTC, lower PTC density and higher anti-LG3 titers. Renal IRI led to significant increase in PTC caspase-3 activation, ApoExo and anti-LG3 circulating levels with age. PTC Cd4 deposition, interstitial fibrosis and renal function were worsened by age. To test the role of ApoExo in fueling maladaptive responses to IRI, young mice were injected with ApoExo to reach circulating levels observed in old mice. ApoExo injection increased anti-LG3 formation, PTC Cd4 deposition, caspase-3 activation, PTC rarefaction and interstitial fibrosis, and aggravated renal dysfunction.

Conclusions: Our results suggest that caspase-3 activation within PTC increases with older age leading to more ApoExo production post-IRI. The latter enhances microvascular damage and fibrosis, favoring progressive kidney dysfunction.

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

FR-PO146

Hypoxia-Inducible Factor-1Alpha Induces Apoptosis of Tubular Cells in Renal Ischemia-Reperfusion Injury via Regulating Glutathione-Specific Gamma-Glutamylcyclotransferase 1

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Background: Renal ischemia-reperfusion (IR) is the major cause of acute renal failure in the native and transplanted kidneys. Hypoxia-inducible factor (HIF)-1α is a transcription factor for cellular adaption to hypoxia. It is shown that HIF-1α expressed in renal tubules is up-regulated during renal ischemia and contributes to recovery of the IR induced kidney injury (IRI). However, precise mechanisms for the renal protective effect of HIF-1α in the IRI remain unclear. In the present study, we aimed to clarify the role of HIF-1α on renal IRI by employing a heterozygous HIF-1α knockout (hKO) mouse model.

Methods: Male hKO and wild type (WT) littermate mice were used for IRI model. Mice were anesthetized and the right kidney was resected. Then the left kidney was occluded with a vascular clamp at the hilus for 45 min. The clamp was removed to allow blood reperfusion. For hypoxia-reoxygenation (H/R) treatment, human renal epithelial cells were used for IR model. Mice were anesthetized and the right kidney was resected. Then the left kidney was occluded with a vascular clamp at the hilus for 45 min. The clamp was removed to allow blood reperfusion. For hypoxia-reoxygenation (H/R) treatment, human renal epithelial cells were used for IR model. Mice were anesthetized and the right kidney was resected. Then the left kidney was occluded with a vascular clamp at the hilus for 45 min. The clamp was removed to allow blood reperfusion.

Results: Serum creatinine and blood urea nitrogen in hKO mice with IRI were higher than those in WT mice, confirming that HIF-1α contributes to repair of IRI. Apoptosis is induced in early phase of IRI in WT, while it is induced in late phase in the hKO. In hKO mice, Bcl-2/Bax ratio was increased compared with that of WT mice, indicating that Bcl-2 is a cause for the temporal difference of the apoptosis induction. We found that the pro-apoptotic factor glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1) was upregulated in tubules of WT after IR but not in those of hKO. CHAC1 knockdown in HK2 cells induced Bcl-2 upregulation after H/R treatment. These results indicate that CHAC1 regulates apoptosis induction in tubules during IRI via Bcl-2 regulation. HIF-1α knockdown with RNA interference in HK2 cells reduced CHAC1 expression after H/R treatment, indicating direct regulation of CHAC1 by HIF-1α.

Conclusions: Induction of apoptosis in the early phase of IRI is regulated by HIF-1α-CHAC1 axis, contributing to the repair of IRI.
AKI model to investigate the Nrf2/Keap1 pathway, we used the Nrf2 activator CDDO-Imidazolide (CDDO-IM) to benchmark its effects in cisplatin (Sic) nephrotoxicity, cecal ligation and puncture (CLP) sepsis, and ischemia reperfusion (IRI) induced AKI models in mice. Methods: The Cis-AKI model was induced by 20 mg/kg cis in C57 mice. The CS sepsis-AKI was caused by a single dose of 450 ul of CS. The IRI-AKI was induced by bi-clamping of mouse renal pedicles for 26 min. The mice were treated with CDDO-IM (10 mg/kg, PO) prior to AKI induction. Renal function was evaluated by plasma creatinine (pCr) and expression of Nrf2 target genes (NQO1/TXNRD1), tubular injury markers (KIM1/NGAL), Acute tubular necrosis was evaluated and scored. Results: In the cisplatin model pCr levels increased from d1 through d4 indicating acute kidney injury. Pre-treatment of mice with CDDO-IM significantly reduced the pCr levels through d4 (pCr 0.32±0.047 in CDDO-IM vs. Vehicle 0.98±0.23 mg/dl; p<0.001). Txnrd1 was upregulated while kidney injury markers KIM1 and NGAL were downregulated. Furthermore, tubular necrosis was reduced indicating CDDO-IM prevented tubular injury and improved recovery from AKI. Unexpectedly, pre-treatment with CDDO-IM did not attenuate kidney injury in the CS or IRI model despite clear enhancement of Nrf2 target expression. In contrast, Dexamethasone significantly improved renal function in sepsis and IRI mouse models of AKI. Conclusions: The protective effect of Nrf2 activator CDDO-IM was evaluated in commonly used AKI models. CDDO-IM pretreatment significantly attenuated plasma urea nitrogen (BUN). Transdermic glomerular filtration rate (tGFR) (WT=5 vs. KO=7) was evaluated prior to euthanasia. Whole kidney homogenates were used to measure mitochondrial electron transport chain (ETC) and tricarboxylic acid cycle (TCA) activities by spectrophotometric analysis and western blots (WT=11 vs. KO=5). Results: No significant difference in serum electrolytes, iGFR, and BUN were noted between MnsOD-KO and WT littersmates. MnsOD-KO and WT had no significant difference in citrate synthase activity, a surrogate marker of mitochondrial content. MnsOD-KO kidneys demonstrated a decrease in ETC-Complex I and ETC-Complex II protein expression and activities. In contrast, ETC-Complex III and Aconitase activities were increased in the KO kidneys. Conclusions: Tubular MnsOD deletion results in disruption of mitochondrial oxidative phosphorylation as well as TCA cycle enzymes 7 months post induction with preserved renal function. Future studies will provide insight into the implications of an adaptive response of mitochondrial oxidative metabolism in response to kidney injury.

FR-PO149
Recombinant Sestrin2 Ameliorates Oxidative Stress, Mitochondrial Damage, and Renal Dysfunction in Contrast-Induced AKI
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Background: Although the use of iodinated contrast agents is at times essential for accurate disease diagnosis, contrast-induced acute kidney injury (CI-AKI) is a possible complication. The pathogenesis of CI-AKI has not yet been fully elucidated, but increased oxidative stress is thought to be one important cause and mitochondrial damage is thought to accompany the consequences of oxidative stress. Sestrin2 is activated by many stress factors that have been associated with oxidative stress and mitochondrial damage. Methods: In vivo experiments, C37BL/6 mice were divided into control, recombinant sestrin2 (RS), CI-AKI and CI-AKI with RS groups. We examined the blood analysis, oxidative stress, mitochondrial damage and CT scans. Results: Our results showed that RS decreases oxidative stress in the CI-AKI model. Mitochondrial damage presenting as morphological changes were alleviated and ATP synthesis was restored after administration of RS. Also, the decreases in relative blood volume significantly increased compared to the CI-AKI group after RS administration in the CT scan. Finally, renal injury markers also decreased and kidney function was preserved with RS. These results suggested that RS can mitigate the deterioration of renal functions in CI-AKI model.

Conclusions: Sestrin2 could mitigate mitochondrial damage and apoptosis by regulating oxidative stress in a contrast-induced acute kidney injury model.

Funding: Government Support - Non-U.S.

FR-PO150
Dissecting the Role of Tubular Manganese Superoxide Dismutase (MnSOD): Mitochondrial Oxidative Metabolism Disruption as an Adaptive Mechanism
Gabriela Vasquez Martinez,1 Gabriel Mayoral Andrade,2 Birong Li,1 Ashley R. Jackson,1 Kranti A. Mapuskar,2 Douglas R. Spitz,1 Bryan Allen,2 Diana Zepeda-Orozco,2,3 Abigail Werner Research Institute at Nationwide Children’s Hospital, Columbus, OH; 3The Ohio State University, Columbus, OH; 4University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme that catalyzes the conversion of superoxide (O2-) to hydrogen peroxide (H2O2) in the mitochondrial matrix. Tubular MnSOD deletion results on renal histological abnormalities including tubular dilation, epithelial cell enlargement, and casts formation within the tubular lumen. However, there is no significant difference in serum creatinine or survival compared to WT mice suggesting that tubular MnSOD KO leading to an adaptive response in mitochondrial metabolism that prevents renal dysfunction. Methods: We developed a doxycycline-inducible pan-tubular MnSOD knock-out (Pax6rTA-TetOcre-MnSODfl/fl, tMnSOD-KO). Mice were induced with doxycycline at 6 weeks of age, and seven months later we measured serum electrolytes and blood urea nitrogen (BUN). Transdermic glomerular filtration rate (tGFR) (WT=5 vs. KO=7) was evaluated prior to euthanasia. Whole kidney homogenates were used to measure mitochondrial electron transport chain (ETC) and tricarboxylic acid cycle (TCA) activities by spectrophotometric analysis and western blots (WT=11 vs. KO=5).

Results: No significant difference in serum electrolytes, iGFR, and BUN were noted between tMnSOD-KO and WT littersmates. iMnSOD-KO and WT had no significant difference in citrate synthase activity, a surrogate marker of mitochondrial content. iMnSOD-KO kidneys demonstrated a decrease in ETC-Complex I and ETC-Complex II protein expression and activities. In contrast, ETC-Complex III and Aconitase activities were increased in the KO kidneys.

Conclusions: Tubular MnSOD deletion results in disruption of mitochondrial oxidative metabolism as well as TCA cycle enzymes 7 months post induction with preserved renal function. Future studies will provide insight into the implications of an adaptive response of mitochondrial oxidative metabolism in response to kidney injury.
in vivo and in vitro. Futhermore, TRPA1 agonists promoted mitochondrial dysfunction via mitochondrial-associated endoplasmic reticulum membrane. ERS inhibitors and GRP75 inhibitors increased cell proliferation activity, reduced cell apoptosis, and modulated ERS-mitochondrial damage and calcium overload to improve cell injury.

Conclusions: TRPA1 promotes DDP-induced AKI by regulating the ERS-mitochondrial damage.

FR-PO152
Long Noncoding RNA GSTM3P1 Induces mir-668 Degradation to Protect Ischemic AKI
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Background: Long non-coding RNAs (lncRNAs) play pivotal roles in ischemic acute renal failure. A previous study has shown that GSTM3P1 is induced by hypoxia and to significantly enhance renal proximal tubular cell apoptosis post ATP depletion. Its mouse homologue, gstm2-ps1, exhibited a similar injurious role and induced in C57BL/6 mouse proximal tubules after 30-minute ischemia and 3-hour reperfusion. Proximal tubular specific depletion of gstm2-ps1 significantly protected mice from ischemic AKI. Our research also suggests a potential mechanism of GSTM3P1 to target a renal protective microRNA-668 by co-precipitation in the RNA-induced silencing complex.

Methods: A binding site of mir-668 in GSTM3P1 was confirmed through luciferase assay. However, unlike the routine lncRNA/microRNA sponge and neutralization, GSTM3P1 overexpression resulted in the degradation of mature mir-668 without affecting its primary transcript or precursor. Mutation of the mir-668 binding site in GSTM3P1 attenuated the mir-668 degradation. Thus, we hypothesized that GSTM3P1 induces mir-668 degradation through target-directed microRNA degradation (TDMD), a new regulation pathway for lncRNAs to suppress microRNAs.

Results: Accordingly, an HEK cell line with ZSWIM8 (a key TMD complex component) knockdown was established. In comparison to the wild type HEK cells, ZSWIM8 knockout hindered the mature form mir-668 degradation by GSTM3P1. Furthermore, to protect kidneys from ischemic AKI, we tested the effect of gstm2-ps1 knockdown. In vitro in cultured mouse proximal tubular cells (BUMPT), gstm2-ps1 sIRnas significantly suppressed cellular ATP depletion and apoptosis. In vivo, male mice treated with negative control or gstm2-ps1 sIRnas and subjected to 25-minute bilateral kidney ischemia and 48-hour reperfusion injury. Compared to the negative control group, gstm2-ps1 knockdown exhibited significantly protection by reducing BUN and serum creatine levels. The histological examination indicated profound suppression of renal tubular necrosis and apoptosis, and a substantial decrease in renal tubular NGLAL induction post injury.

Conclusions: In conclusion, lncRNA GSTM3P1/gstm2-ps1 contributes to renal proximal tubular cell death and ischemic AKI by binding to and inducing mir-668 degradation via TDMD. GSTM3P1/gstm2-ps1 can be a potential therapeutic target for mitigating ischemic AKI.

Funding: NIDDK Support

FR-PO153
Activation of Branched Chain Amino Acid (BCAA) Catabolism Protect Against AKI
Samaneh Gholami, Sandeep K. Mallipattu, Sian Piret. Stony Brook University, Stony Brook, NY.

Background: BCAA (Valine, Leucine and Isoleucine) catabolic defects are implicated to be determinates of multiple diseases, however it is poorly studied in kidney injury. Activation of AMPK (AMP activated protein kinase) is a major factor for development of renal fibrosis and chronic kidney disease (CKD) but there are currently no therapies targeting a renal protective microRNA mir-668

Methods: A binding site of mir-668 in GSTM3P1 was confirmed through luciferase assay. However, unlike the routine lncRNA/microRNA sponge and neutralization, GSTM3P1 overexpression resulted in the degradation of mature mir-668 without affecting its primary transcript or precursor. Mutation of the mir-668 binding site in GSTM3P1 attenuated the mir-668 degradation. Thus, we hypothesized that GSTM3P1 induces mir-668 degradation through target-directed microRNA degradation (TDMD), a new regulation pathway for lncRNAs to suppress microRNAs.

Results: Accordingly, an HEK cell line with ZSWIM8 (a key TMD complex component) knockdown was established. In comparison to the wild type HEK cells, ZSWIM8 knockout hindered the mature form mir-668 degradation by GSTM3P1. Furthermore, to protect kidneys from ischemic AKI, we tested the effect of gstm2-ps1 knockdown. In vitro in cultured mouse proximal tubular cells (BUMPT), gstm2-ps1 sIRnas significantly suppressed cellular ATP depletion and apoptosis. In vivo, male mice treated with negative control or gstm2-ps1 sIRnas and subjected to 25-minute bilateral kidney ischemia and 48-hour reperfusion injury. Compared to the negative control group, gstm2-ps1 knockdown exhibited significantly protection by reducing BUN and serum creatine levels. The histological examination indicated profound suppression of renal tubular necrosis and apoptosis, and a substantial decrease in renal tubular NGLAL induction post injury.

Conclusions: In conclusion, lncRNA GSTM3P1/gstm2-ps1 contributes to renal proximal tubular cell death and ischemic AKI by binding to and inducing mir-668 degradation via TDMD. GSTM3P1/gstm2-ps1 can be a potential therapeutic target for mitigating ischemic AKI.

Funding: NIDDK Support

FR-PO154
TEAD1 Promotes Cisplatin-Induced AKI
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Background: Cisplatin is an inorganic platinum-based chemotherapeutic agent that is widely used for the treatment of solid tumors. However, a known complication of cisplatin administration is acute kidney injury (AKI). Despite recent advances in examining the molecular mechanisms, no potential strategy exists to prevent kidney injury. In this study, we examined the role of TEA domain family member 1 (TEAD1) in the pathogenesis of cisplatin-induced AKI.

Methods: We generated proximal tubule-specific TEAD1 knockout (TEAD1Δ/Δ) mice by crossing TEAD1Δ/Δ mice with PEPCk-Cre mice. Ten-week-old male TEAD1Δ/Δ mice and TEAD1+/+ (TEAD1Δ/+ mice) were administered a single intraperitoneal dose of cisplatin (20mg/kg body weight), or vehicle (saline) to induce AKI. Blood and kidneys were collected at 72h for assessment of kidney function, tubular cell injury, cell death and inflammation. Lentivirus transfection was utilized to knock down the expression of TEAD1 in mouse tubular epithelial cells in vitro. Cells were treated with cisplatin (20µM, 24h) for determination of intracellular ROS and mitochondrial function.

Results: TEAD1 expression was upregulated in tubular epithelial cells of kidneys with cisplatin-induced AKI. TEAD1+/- mice treated with cisplatin had increased tubular cell damage and enhanced kidney dysfunction compared with TEAD1Δ/Δ mice. Additionally, TEAD1Δ/Δ mice had augmented necroptotic cell death and inflammatory response compared with TEAD1Δ/Δ mice treated with cisplatin. Knockdown of TEAD1 in mouse tubular epithelial cells promoted intracellular ROS levels, which was associated with reduced ATP production and impaired oxygen consumption rate.

Conclusions: Taken together, our results indicate that TEAD1 plays an important role in the pathogenesis of cisplatin-induced AKI through regulation of necroptosis and inflammation which may be associated with impaired mitochondrial function. TEAD1 may represent a novel therapeutic target for cisplatin-induced AKI.

Funding: NIDDK Support

FR-PO155
AMPK Activation Protects Kidney Function After Renal Ischemia
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Background: The kidney has a high energy demand to carry out its function, and with Acute Kidney Injury (AKI) such as ischemia reperfusion, there is profound mitochondrial damage. Adenosine Monophosphate Kinase (AMPK) is a key regulator of mitochondrial function and bioenergetics. Here, we used a rat model of ischemia-reperfusion inducing AKI to explore the effect of pharmacological activation of AMPK.

Methods: Male Sprague Dawley rats were treated with a direct AMPK activator (n=12) or vehicle (n=12) one hour prior to ischemia reperfusion induced by bilateral clamping the renal pedicles for 35 minutes. Kidney functions was assessed by transcutaneous glomerular filtration rate (GFR) measured at 5-7 hours post ischemia reperfusion and inflammation. Lentivirus transfection was utilized to knock down the expression of TEAD1 with cisplatin-induced AKI. TEAD1 PKO mice treated with cisplatin had increased in vivo, and inflammation. Lentivirus transfection was utilized to knock down the expression of TEAD1 in mouse tubular epithelial cells in vitro. Cells were treated with cisplatin (20µM, 24h) for determination of intracellular ROS and mitochondrial function.

Results: Plasma creatinine and tGFR were significantly improved in the animals treated with AMPK activator compared to vehicle control with a 28% reduction of creatinine (1.53±0.257 versus 1.10±0.184 mg/dl, p=0.001) and 69% improvement in GFR (0.079±0.0452 versus 0.135±0.0378 ml/min/100g body weight, p<0.05). AMPK activation improved urinary NephroCheck score (0.076±0.050 versus 0.0089±0.0035 mg/ml/1000 of iGBFP7 and T IMM P2, p<0.001) and acute tubular necrosis in the cortex.

Conclusions: Pharmacological activation of AMPK alleviated kidney function and preserved tubular structure. These data support AMPK activation as a novel therapeutic approach for AKI.

Funding: Commercial Support - Janssen R&D

FR-PO156
Notch Signaling Pathway Mediates Anti-Inflammatory Effects of Vagus Nerve Stimulation
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Background: A novel strategy for the prevention and treatment of AKI is activating the cholinergic anti-inflammatory pathway (CAP), a neuroimmune circuit. The CAP can be initiated by vagus nerve stimulation (VNS) and subsequent activation of splenic and peritoneal macrophages (MΦ), leading to suppression of pro-inflammatory cytokine production. We previously showed that an increase in literacy and enhancer of split 1 (Hes1) in peritoneal MΦ contributes to renoprotective effects of CAP. Hes1 is a transcriptional factor, and its expression is regulated by the Notch signaling pathway. However, a direct

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
relationship between the CAP and Notch signaling has been unclear. In the current study, we performed an in vivo analysis of glutatione peroxidase 4. Knockdown of Clock in primary renal tubal cells decreased the expression of Nrf2 and its downstream antioxidant target genes, while over-expression of Clock restored the expression of Nrf2. Finally, 4-octyl ractanone was intraperitoneal injected to upregulate the expression of NRF2 at ZT12, with all the above results were confirmed by Western blotting.

Conclusions: The study shows the circadian clock regulates Nrf2 mediated antioxidant response, which in turn leads to diurnal differences in contrast-reduced renal injury.

Funding: Government Support - Non-U.S.

FR-P0157

Transient Nucleus-to-Cilium Microtubule Assays Initiate Senescence in Stressed Renal Tubular Cells

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Background: Cellular senescence plays a critical role in diminishing reparative capacity and exacerbating kidney injury. In previous research, we demonstrated that the translocation of a ciliary protein, FBF1, to promyelocytic leukaemia nuclear bodies (PML-NBs) is crucial for inducing senescence in stressed human cells. However, how FBF1 translocates into the nucleus upon exposure to stressors remains elusive.

Methods: Human renal cortical tubal epithelial cells (RCTE) were exposed with irradiation, inflammatory cytokines, or oxidative stress to induce cellular senescence. Nucleus senescence level was determined using Senescenct Associated (SA)-b-Gal staining, and protein and DNA levels of senescence and SASP markers. Immunofluorescence was employed to detect sinc-MTs. Microtubule assembly was disrupted in RCTE cells using Colchicine or knockdown CDK5RAP2. Knockdown of the tubulin glutamylated were performed to investigate the role of polyglutamylation in sinc-MT-mediated senescence induction. Western blotting, confocal imaging, and super-resolution Structure Illumination Microscopy (SIM) were used to determine the expression and subcellular localization of key components. Protein-protein interactions were analyzed through APEX2 based BioID analysis and confirmed by exogenous and endogenous immunoprecipitation assays.

Results: Here, we discovered a novel phenomenon that, in renal epithelial cells, irreparable stressors induce a transient assembly of nucleus-to-cilium microtubule assays (sic-MTs), which are highly polyglutamylated, unconventional polarized with minus-ends nucleating near the nuclear envelope and plus-ends anchored below the ciliary base. KIFC3 or CENEXIN1, a centrosomal protein CENEXIN1 as an adaptor to translocate FBF1 towards the nucleus along sinc-MTs. Deficiency of KIFC3 or CENEXIN1 abolishes both FBF1 translocation and senescence initiation in stressed cells.

Conclusions: Here, we elucidate the mechanistic insights into the essential role of a stress-induced sinc-MTs in transducing stress-induced ciliary signals into the nucleus to initiate senescence program in damaged renal epithelial cells. Our findings highlight the potential of targeting cilia as a therapeutic strategy for senescence-related kidney diseases.

FR-P0158

The Effects and Mechanism of Circadian Rhythm on Contrast-Induced Renal Injury

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Background: The circadian clock of mammals regulates various life activities. As an important metabolic organ, the kidney is a key to the circadian rhythm in glomerular filtration function and ion transport of renal tubules. In view of the huge basic population of using contrast agents for diagnosis and treatment, as well as the potential long-term risks of renal diseases, contrast-induced acute kidney injury (CI-AKI) is a clinical problem that cannot be ignored, although the pathogenesis of CI-AKI has been partially understood, the role and mechanism of circadian rhythm in contrast agent renal injury is still unknown.

Methods: The study retrospectively analyzed 33 patients undergoing percutaneous coronary interventions. Clinical data of patients with or without CI-AKI were compared. The expression of Nrf2 was assessed by qPCR. For CI-AKI mouse, specific Notch2 KO mice (C57/Black/Et/Notch2fl/fl) and controls (Notch2+/+) were subjected to VNS to evaluate whether Notch2 mediates anti-inflammatory responses in MΦ. Flow cytometry analysis was performed to examine the influence of MΦ-specific Notch2 expression on immune cell subpopulations.

Results: VNS suppressed an LPS-induced upregulation of pro-inflammatory cytokines (Tafna, il1b, and Ccl2) in MΦ in Knockdown-1 and Kim-1 mice. This effect was accompanied by an increase in Notch components including Hes1 in MΦ. After VNS and LPS treatments, BUN levels were increased in Notch2 KO mice, compared to Wt controls. Consistently, these Notch2 KO mice showed higher levels of Ccl2 (but not Tafna and il1b) and Kim-1 expression in the MΦ and kidneys, respectively. Flow cytometry analysis revealed that under physiological conditions, Notch2 deficiency in MΦ controls. Consistently, these immune cell subpopulations. Φ-specific Notch2 expression on evaluate whether Notch2 mediates anti-inflammatory responses in MΦ. Notch2 in MΦ and monocytes, which analysis revealed that under physiological conditions, Notch2 deficiency in MΦ controls. Consistently, these immune cell subpopulations.

Funding: Private Foundation Support

FR-P0159

Autophagy-Associated FIP200 Protects Renal Tubules Against Apoptosis Following Renal Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI) easily progresses to chronic kidney diseases. Renal ischemia-reperfusion injury (IRI) is an important cause of AKI. The pathogenesis of renal IRI is complex, and its pathological characteristics mainly include renal tubular epithelial cell injury. Apoptosis is one of the main mechanisms of hypoxia-induced renal tubular epithelial cell death. Autophagy regulates apoptosis and plays a key role in the development of renal IRI. FAK family-interacting protein of 200 kDa (FIP200) is a crucial component of the ULK-1-Agt13-FIP200 complex formed in mammalian cells upon autophagy induction. However, the precise mechanisms of FIP200 in renal IRI-mediated AKI remains elusive.

Methods: The Bilups hypoxic modular systems was used to establish the hypoxia-/ reoxygenation (I/R) cell model in HK2 cells. Cells were maintained under hypoxia for 5 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, and 24 h, and then reoxygenated for 24 h. Cells in the control group were not subjected to hypoxia then reoxyg enation. All animal studies were approved by the Ethics Committee of Sichuan Provincial People's Hospital (approval No. L201735). Twenty-four wild-type mice were divided into 8 groups, and the renal pedicles of their left kidney were clamped with microvascular forces. Then, 12 FIP200 conditional knockout (FIP200lox/lox--Ggt cre/mice) mice in the renal tubular epithelial cell, in parallel to 12 wild-type mice, were randomly divided into renal IRI group and sham operation group.

Results: The expression of the autophagy-related protein FIP200 was up-regulated in vivo and in vitro after renal IRI. Expression of FIP200 was down-regulated in renal tubules showed severe renal tissue damage after IRI. Overexpression and knockdown of FIP200 in HK2 cells revealed its protective effects on I/R injury of renal tubal epithelial cells. FIP200 could interact with HMGB1 by immunoprecipitation assays and co-localization on renal tissue of mice. While the injection of Iohexol at ZT12 increased the expression of kidney injury molecule 1 (KIM1), NGAL and lipid peroxidation products and reduced the renal tubular cell proliferation and suppressed expression of cyclin E, phosphorylation of CDK2, but increased p21 expression in the injured kidney. Furthermore, inactivation of Jmd3 enhanced I/R- or FA-induced expression of TGF-β1, vimentin and Snail, phosphorylation of Smad3, Stat3 and NF-kB and increased renal inflammation by F4/80+ macrophages. Finally, GSK34 treatment caused a further downregulation of Klotho, BMP-7, Smad7 and E-cadherin, all of which are associated with renal protection and anti-fibrotic effects.

Conclusions: Our data indicate that FIP200 has an important role in preventing renal tubular cell damage and death following renal IRI, and might be a novel potential target for prevention and treatment of AKI caused by IRI.

FR-P0160

JMD3 Activation Contributes to Renal Protection and Regeneration Following AKI in Mice

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Background: We have recently demonstrated that Junonji domain-containing protein D3 (JMD3), a histone demethylase of histone H3 on lysine 27 (H3K27me3), is protective against renal fibrosis, but its role in acute kidney injury (AKI) remains unexplored.

Methods: Murine renal tubular epithelial cells (mRTECs) were treated with GSK or siRNA specific for JMD3. A folic acid (FA)-induced AKI murine model was created by peritoneal injection of FA at 250 mg/kg and a bilateral I/R murine models were established by occluding with a non-traumatic vascular clamp for 35 minutes in mice. Apoptosis injury to the kidney was assessed in mRTECs. The expression of H3K27me3, which was coincident with renal dysfunction, renal tubular cell injury/ apoptosis and proliferation. Blocking JMD3 activity by GSK4J led to worsening renal dysfunction and pathological changes by aggravating tubular epithelial cell injury and apoptosis in both murine models of AKI. JMD3 inhibition by GSK4J also reduced renal tubal cell proliferation and suppressed expression of cytok E, phosphorylation of CDK2, but increased p21 expression in the injured kidney. Furthermore, inactivation of JMD3 enhanced I/R- or FA-induced expression of TGF-β1, vimentin and Snail, phosphorylation of Smad3, Stat3 and NF-kB and increased renal inflammation by F4/80+ macrophages. Finally, JMD3 treatment caused a further downregulation of Klotho, BMP-7, Smad7 and E-cadherin, all of which are associated with renal protection and anti-fibrotic effects.

Conclusions: These data provide strong evidence that JMD3 activation contributes to renal tubular cell survival and regeneration after AKI.

Funding: Government Support - Non-U.S.
FR-PO161

MLL1 Activation Contributes to Renal Protection and Regeneration Following AKI Induced by Folic Acid and Ischemia/Reperfusion

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Background: Mixed lineage leukemia 1 (MLL1) is a methyltransferase that induces histone lysine 4 trimethylation (H3K4me3) and exerts its functional roles by interacting with multiple subunits including WD repeat-containing protein 5 (WDR5) and Menin. In this study, we investigated the role and mechanisms of MLL1 in murine models of acute kidney injury (AKI) induced by folic acid (FA) and ischemia/reperfusion (IR).

Results: An FA-induced AKI model was created by peritoneal injection of FA at 250 mg/kg and a bilateral I/R murine models were established by occluding with a non-traumatic vascular clamp for 35 minutes in mice. By using Mll1 floxed mice, we observed that deletion of Mll1 prevented renal tubular cell injury and apoptosis and inhibited the dedifferentiation and proliferation in mice following FA injury. Further, Mll1−/− mice exhibited stronger renal fibrosis than wild-type mice. Moreover, Mll1−/− mice displayed lower BUN, serum creatinine (Scr), and creatinine (Cr) and reduced glomerular and tubular epithelial cell apoptosis. To determine the mechanism underlying these effects, we investigated the expression of renal fibrosis-related genes. We found that Mll1−/− mice exhibited lower expression of fibrosis markers, such as connective tissue growth factor (CTGF), transforming growth factor (TGF)-β1, and collagen I (Col1a1) compared to wild-type mice. Furthermore, we observed that Mll1−/− mice exhibited lower expression of pro-fibrotic genes, such as leptin (LEP), leptin receptor (LEPR), and connective tissue growth factor (CTGF) compared to wild-type mice. Finally, we confirmed the role of Mll1 in the suppression of renal fibrosis by using a conditional knockout of Mll1 in renal tubular cells.

Conclusions: These results suggest that repressing Mll1-induced renal fibrosis contributes to AKI prevention and regeneration following FA-induced AKI.

Funding: Government Support - Non-U.S.

FR-PO162

Histone Methyltransferase SMYD2 Promotes AKI and Renal Regeneration by Activating Epidermal Growth Factor Receptors

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Background: Protein methyltransferase SET and MYND domain containing protein 2 (SMYD2) is one of the most widely studied lysine methyltransferases. It is involved in the development of numerous tumors and renal fibrosis by inducing methylation of H3K16 and H3K4 as well as multiple non-histone proteins, but its role in acute kidney injury (AKI) remains unclear.

Methods: In this study, we investigated the role and mechanism of SMYD2 in murine models of AKI induced by folic acid (FA) and ischemia/reperfusion (IR). We used SMYD2 knockout mice and wild-type littermates for comparison. We observed that SMYD2-knockout mice had reduced renal tubular cell injury and apoptosis and inhibited the dedifferentiation and proliferation in mice following AKI. Further, SMYD2-knockout mice exhibited lower BUN, serum creatinine (Scr), and creatinine (Cr) and reduced glomerular and tubular epithelial cell apoptosis. To determine the mechanism underlying these effects, we investigated the expression of renal fibrosis-related genes. We found that SMYD2-knockout mice exhibited lower expression of fibrosis markers, such as connective tissue growth factor (CTGF), transforming growth factor (TGF)-β1, and collagen I (Col1a1) compared to wild-type mice. Furthermore, we observed that SMYD2-knockout mice exhibited lower expression of pro-fibrotic genes, such as leptin (LEP), leptin receptor (LEPR), and connective tissue growth factor (CTGF) compared to wild-type mice. Finally, we confirmed the role of SMYD2 in the suppression of renal fibrosis by using a conditional knockout of SMYD2 in renal tubular cells.

Conclusions: These results suggest that repressing SMYD2-induced renal fibrosis contributes to AKI prevention and regeneration following FA-induced AKI.

Funding: Government Support - Non-U.S.

FR-PO163

Uregulating NRF2 is a Critical Regulatory Mechanism for the Protective Effect of Ultrasound to Mitigate Sepsis-Associated AKI

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Background: Sepsis-induced oxidative stress and dysfunction of innate immune response have emerged as key players in the pathogenesis of sepsis-associated acute kidney injury (S-AKI). Nuclear factor-erythroid-derived 2-related factor 2 (NRF2), a key oxidative stress regulator, has been implicated to play an important role in T cell-specific augmentation of NF22 to mitigate oxidative stress. Our previous studies indicated that pulsed ultrasound (pUS) can reduce inflammation and acute kidney injury in mice. We hypothesize that pUS mediated protection is associated with enhanced the expression of NRF2 and reduced immune system dysfunction. In this study, we utilized LPS-induced S-AKI in normal and NF22−/− mice, and we used RAW264.7 cells to investigate the effects of pUS on LPS-induced kidney injury, macrophage infiltration and NRF2. In addition, we also evaluated whether pUS mediated the enhanced NRF2 expression and disturbed CD4+ T cells immune function in human Jurkat T cells.

Methods: C57BL/6 mice received pUS 24 hours before LPS (5 mg/kg, ip) treatment. The parameters of pUS therapy followed the protocol we previously published. In vitro studies were performed using RAW cells and Jurkat T-cell lines, which were cultured and stimulated with LPS (100ng/ml) for 6h. NRF2 protein and mRNA expression was measured by immunofluorescence and RT-PCR respectively. Kidney injury was assessed by Ki67, cleaved-caspase-3 and plasma creatinine assay. Iba1, F4/80 and CD4+ T cells were counted to evaluate immune cells/macrophage infiltration.

Results: LPS produced AKI and macrophage/lymphocyte infiltration in WT mice with a dramatic decline of NRF2. Furthermore, pUS-treated mice with high NRF2 expression had fewer Iba1+ and F4/80+ macrophage infiltration in the kidney and CD4+ T cells in Jurkat T cells and attenuated sepsis-induced AKI. In contrast, LPS stimulus induced higher infiltration of microphages, as well as more early time and more severe renal injury in NF22−/− mice compared with litter mate control mice. pUS attenuated S-AKI.

Conclusions: These results suggest that upregulating NRF2 antioxidant defenses in kidney and in T cells are essential for ultrasound to attenuate oxidative stress-induced AKI. Our results reveal a novel mechanism for pUS protection from kidney injury during S-AKI.

Funding: NIDDK Support

FR-PO164

AKI-Induced Senescence as a Key Player in CKD Progression: Insights from an Aristolochic Acid Model

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Background: Senescence is a persistent cell cycle arrest accompanied by a senescence-associated secretory phenotype (SASP). The role of tubular senescence in driving chronic kidney disease (CKD) following acute kidney injury (AKI) remains controversial due to the multiple animal models used and different timepoints of senescent cell depletion. To accurately represent a direct injury induction of tubular senescence, we utilized a new model of Aristolochic Acid (AA)-induced, pro-fibrotic, and inflammatory injury that more accurately setting to promote DNA damage specifically in tubulal epithelial cells (TECs). Our model of persistent injury following AA-induction of AKI leads to tubulointerstitial fibrosis and allows for study of different timepoints of CKD progression.

Methods: An AKI to CKD model was created by a single intraperitoneal injection of 5 mg/kg of AA into male C57BL/6 mice. In vitro studies utilized 1×10^6mg/ml AA, and HK-2 (human proximal tubule cell line), mTECs (primary mouse TECs), and NRK-49F (kidney fibroblast cell line). Senolytics (ABT-263) were used to eradicate senescent cells, while senomorphics (Metformin) inhibited SASP.

Results: In vivo: Compared to the control, AA-induced tubular senescence as early as 7 days post-injury, as shown by increased p53, p21, p16, p15 expression, and β-gal activity in tubules. AA-treated mice displayed CKD signs of tubular damage and renal fibrosis. In vitro: Studies showed strong AA-induced fibrosis. Tubulin senescent cells were added to human umbilical vein endothelial cells or NIH3T3 fibroblasts, which caused a marked increase in fibrosis as measured by Collagen I and Col3 content. Similarly, in primary TECs, senescent cell addition led to increased fibrosis. In vivo: AA-induced senescence in HK-2 and mTECs. Senescent cells added to NIH3T3 fibroblasts in vitro induced greater infiltration of microphages, as well as more early time and more severe renal injury in NF22−/− mice compared with litter mate control mice. pUS attenuated S-AKI.

Conclusions: These results suggest that AA induction of tubular senescence leads to an altered phenotype that is more pro-fibrotic compared to AA-induced AKI.

Funding: Government Support - Non-U.S.

FR-PO165

Spns2 Deficiency Protects the Mouse Kidneys During Ischemia-Reperfusion Injury

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Background: Senescent cells (Spns2−/− mice) are transmembrane protein that transports aminoglycoside 1-phosphate, a bioactive lipid that acts as an extracellular lipid and intracellular second messenger in a variety of biological functions. In the present study, we investigated the effect of inducible global Spns2 deletion or pharmacological inhibition of Spns2 in mouse kidneys after bilateral ischemia-reperfusion injury (IR).

Methods: Ubiquitin-CytEB2, Spns2+/+ mice (Spns2−/−/− and Spns2+/−/+ littermates were injected with tamoxifen (1 mg, i.p.) daily for 5 days and rested for 2 weeks before 28 min ischemia followed by 24 h reperfusion. C57BL/6 mice were pre-treated 24 h before IR with Spns2 inhibitor (SLF181851, 10 mg/kg, i.p.) or vehicle. Relative kidney weight, histology, proteinuria, renal mRNA expression analysis were performed. p800 g hemoglobin, and renal fibrosis were performed using Masson’s trichrome staining.

Conclusions: These results suggest that deletion or pharmacological inhibition of Spns2 reduces renal fibrosis and senescence, offering a potential alternative to senolytics.

Funding: Government Support - Non-U.S.
Kidney injury was evaluated by measuring plasma creatinine (PCr) and BUN and by scoring tubule damage in H&E stained sections. MK-2206 was administered 30 min prior to the insult and 24 h after the insult. Meprin β activity was measured in mice treated with MK-2206 and wild-type (WT) animals using a fluorogenic peptide substrate. Results: Meprin β activity was significantly reduced in MK-2206 treated mice compared to WT animals (P<0.01). Histological analysis of kidney cortex of wild type (WT) and NHERF1 knockout littermates (KO) in wild type (WT) and NHERF1 knockout littermates (KO) revealed significant increases in IL-6, PCNA, p-AKT and p-ERK in select tubules in both genotypes at 96 h post-IR compared to controls. Kidneys from mice that underwent ischemia-reperfusion injury showed significant increases in IL-6, PCNA, p-AKT and p-ERK in select tubules in both genotypes at 96 h post-IR, indicating that the IRAK4 scaffold function is sufficient for canonical activation of NF-κB.

Methods: We used a unilateral IR as a model of renal inflammation in wild-type (WT) and meprin β knockout (KO) male mice, with the contralateral kidneys serving as controls. The mice were sacrificed at 96 h post-IR, and kidney tissue processed for evaluation by RT-PCR and immunohistochemistry. Statistical analysis of data utilized two-way ANOVA.

Results: Our PCR data showed significant increase in mRNA levels for IL-6 and PCNA in WT and jko mice at 96 h post-IR when compared to WT control kidneys. Immunohistochemical data revealed significant increases in IL-6, PCNA, p-AKT and p-ERK in select tubules in both genotypes at 96 h post-IR compared to controls. Data from immunofluorescence of kidney tissues showed that the levels of IL-6, PCNA, p-AKT and p-ERK were higher in meprin β-expressing proximal tubules (PTs), at 96 h post-IR when compared to the distal kidney tubules (DTs), which lack meprins. High levels of IL-6 were also present in the lumens of PTs and DTs from WT and jko kidneys at 96 h post-IR, suggesting increased release into filtrate and subsequently into urine. However, high levels of PCNA, p-AKT and p-ERK were present in the lumen of PTs only for both genotypes at 96 h post-IR.

Conclusions: In conclusion, our data shows that meprin β activity modulates cellular proliferation via trans-signaling IL-6-mediated AKT/ERK pathway in IR-induced kidney injury.

Funding: Other NIH Support - NIH/NIGMS Grant # R35GM141537

FR-PO168

Meprin β Activity Modulates Cellular Proliferation via Trans-Signaling IL-6-Mediated AKT/ERK Pathway in Ischemia/Reperfusion (IR)-Induced Kidney Injury

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Background: Inflammation plays a central role in the progression of kidney injury induced by ischemia/reperfusion (IR). Meprin metalloproteinases have been implicated in the pathophysiology of IR-induced kidney injury. We previously showed that meprin β modulates cellular survival (BCL-2) through IL-6/JAK/STAT signaling in AKI-induced kidney injury. However, it’s not known how meprin β modulation of the IL-6 signaling pathway impacts the cellular proliferation in IR-induced AKI. IL-6 trans-signaling induces proliferation through either MAPK/ERK or PI3K/akt pathway or in crosstalk with AKT/ERK. PCNA is a cellular proliferation marker that is induced through activation of the IL-6 signaling pathway. The goal of the current study was to determine how meprin β modulation of the IL-6 signaling pathway impacts downstream cellular proliferation in IR-induced kidney injury.

Methods: We used the unilateral IR as a model of renal inflammation in wild-type (WT) and meprin β knockout (Jko) male mice, with the contralateral kidneys serving as controls. The mice were sacrificed at 96 h post-IR, and kidney tissue processed for evaluation by RT-PCR and immunohistochemistry. Statistical analysis of data utilized two-way ANOVA.

Results: Our PCR data showed significant increase in mRNA levels for IL-6 and PCNA in WT and Jko mice at 96 h post-IR when compared to WT control kidneys. Immunohistochemical data revealed significant increases in IL-6, PCNA, p-AKT and p-ERK in select tubules in both genotypes at 96 h post-IR compared to controls. Data from immunofluorescence of kidney tissues showed that the levels of IL-6, PCNA, p-AKT and p-ERK were higher in meprin β-expressing proximal tubules (PTs), at 96 h post-IR when compared to the distal kidney tubules (DTs), which lack meprins. High levels of IL-6 were also present in the lumens of PTs and DTs from WT and Jko kidneys at 96 h post-IR, suggesting increased release into filtrate and subsequently into urine. However, high levels of PCNA, p-AKT and p-ERK were present in the lumen of PTs only for both genotypes at 96 h post-IR.

Conclusions: In conclusion, our data shows that meprin β activity modulates cellular proliferation via trans-signaling IL-6-mediated AKT/ERK pathway in IR-induced kidney injury.

Funding: Other NIH Support - NIH/NIGMS Grant # R35GM141537

FR-PO169

Kidney Metabolomics of NHERF1 Deficiency

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Background: Mice lacking NHERF1 (Na+-hydrogen exchanger regulatory factor isoform 1) show increased susceptibility to toxin-induced acute kidney injury (AKI) associated with increased activity of enzymes of the pentose phosphate pathway. We hypothesize that NHERF1 deficiency results in altered kidney cell metabolism associated with enhanced injury response. To test this hypothesis, we performed targeted metabolomic analysis of kidney cortex of wild type (WT) and NHERF1 knockout littermates (KO) in response to saline (vehicle; V) or cisplatin (C).

Methods: WT and KO littermate mice underwent IP injection with either saline or 20 mg/kg body weight of cisplatin (n=20). Kidneys were harvested after 72 h for metabolite extraction with HPLC-grade methanol. Ultra-high-performance liquid chromatography-tandem mass spectrometry performed by the UTSW Metabolomics Core was performed. The data were visualized using MetaboAnalyst and a subset of the data was analyzed using the METLIN database. The results were summarized using principal component analysis (PCA) and confirmatory analysis using targeted metabolic analysis of kidney cortex of wild type (WT) and NHERF1 knockout littermates (KO) in response to saline (vehicle; V) or cisplatin (C).

Results: Principal component analysis demonstrated significant variance between the four experimental groups implicating both NHERF1 absence and cisplatin-induced AKI in metabolic shift. A clear separation was seen between WTV and KOV. Enrichment and Pathway Analysis comparing WTV/KOV demonstrated enrichment of metabolites associated with methylhistidine and glycerophospholipid metabolism, phospholipid biosynthesis, nucleotide sugar metabolism, and mitochondrial electron transport chain.

Conclusions: NHERF1 deficiency alters carbohydrate and lipid metabolism similar to what is seen in response to kidney disease such as diabetes and uninephrectomy and alters metabolic response to injury. Whether these metabolic changes are due to deficient nutrient uptake or altered intracellular pathway integrity and how these changes predispose to acute injury are unknown.

Funding: Veterans Affairs Support
FR-PO170

Altered Lipid Metabolism Exacerbates Endotoxin-Associated Kidney Injury in Diabetes

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Background: Diabetes is a risk factor for endotoxin-associated acute kidney injury (sAKI). In a non-comorbid murine model of sAKI, we previously identified that renal tissue plays a role in the mediation of innate immune responses and cell-specific temporal changes in the lipid metabolism transcriptome, culminating in organ failure (16 hr) followed by recovery (24 hr). Bioactive lipids (bL) are spatially and functionally dysregulated in both diabetes and sepsis and play diverse roles in immunity, inflammation, mitochondrial injury, with ceramide at the nexus of sphingolipid metabolism. We hypothesized that metabolic dysregulation of BL mediates sAKI in the diabetic milieu.

Methods: Lipopolysaccharide (LPS) was given intravenously (iv) to diabetic (BKS.Cg-Dock7m+/+ Leprdb/J) mice (db) and littermates (db+) sacrificed at 0 (baseline), 16 (injury), 24 hr (recovery) after LPS iv, serum, kidneys collected. Serum creatinine (Scr) quantified (MS). ScRNAseq: dissociated kidneys sequenced (10x Chromium) and clustered (Seurat). Cryogel mounted tissue (15 uM) imaged and untargeted DESI-MSI (Scr) quantified (MS). SCRNAseq: dissociated kidneys sequenced (10x Chromium) and clustered (Seurat). Cryogel mounted tissue (15 uM) imaged and untargeted DESI-MSI (Scr) quantified (MS). ScRNAseq: dissociated kidneys sequenced (10x Chromium) and clustered (Seurat). Cryogel mounted tissue (15 uM) imaged and untargeted DESI-MSI (Scr) quantified (MS). ScRNAseq: dissociated kidneys sequenced (10x Chromium) and clustered (Seurat). Cryogel mounted tissue (15 uM) imaged and untargeted DESI-MSI (Scr) quantified (MS). ScRNAseq: dissociated kidneys sequenced (10x Chromium) and clustered (Seurat). Cryogel mounted tissue (15 uM) imaged and untargeted DESI-MSI (Scr) quantified (MS).

Results: Db at 24 hr (vs. 0 hr) had persistent renal injury (Kim1 Log.FC 8.3±1.01, Scr 0.38±0.34) vs. Db+ (Kim1 Log.FC 3.5±0.58, Scr 0.10±0.01). In db (vs db+), putative C16:1 ceramide remained elevated in the renal medulla (16, 24 hr), reduced levels of protective C24 ceramide in the cortex (0 hr). In db (0-24 hrs) there were significantly altered metabolism of glycerophospholipid (i.e., phosphoinositols), fatty acyls, sterols, compared to db+. Db ScrNASeq at 16,24 hrs had decreased expression in glycerophospholipid-metabolic enzymes (Glb1) in proximal tubule and similar changes in ceramide synthases (e.g., Cers 1-6), sphingosine 1-phosphate receptors involved in sAKI inflammatory and immune responses.

Conclusions: We identified several classes of deregulated lipids and altered transcriptomic expression of associated enzymes in db mice which exhibited persistent renal injury. This may lead to the deregulation of cellular function and thus, maladaptive recovery from sAKI in db. Additional work to identify ions/genes of interest and their similarities with the human metabolome will be necessary to determine causality.

Funding: Private Foundation Support

FR-PO171

Proteomics and Metabolomics Conjoint Analysis Revealed Mitochondrial Function and Metabolic Disorders in Sepsis-Induced AKI

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Background: Sepsis-induced acute kidney injury (S-AKI) is a severe and life-threatening condition with high morbidity and mortality and poses a significant risk of chronic kidney disease. However, the early diagnosis and prevention of S-AKI remain challenging due to lacking effective diagnostic biomarkers and treatment targets.

Methods: We established an S-AKI mouse model using intraperitoneal injection of lipopolysaccharide (LPS) and control mice with 0.9% saline (both n=5). After 24 hours, the mice were euthanized to collect blood and kidney samples. The kidney proteins and dissolved metabolites were analyzed using liquid chromatography-tandem mass spectrometry. We integrated proteomics and metabolomics analysis approaches through various bioinformatic analyses, including Gene Set Enrichment Analysis (GSEA), protein and protein interactions (PPI), and MetaboAnalyst analysis.

Results: A total of 5185 proteins were identified in the kidney, including 353 upregulated and 166 downregulated proteins in S-AKI mice compared with the control group. The GO and KEGG analysis of the differentially expressed proteins (DEPs) indicated that downregulated proteins in S-AKI kidneys were primarily involved in mitochondrial functions such as mitochondrial translation and mitochondrial respiratory chain complex assembly. The hub proteins in PPI networks were mainly involved in the mitochondrial electron transport chain. The GSEA also indicated that mitochondrial dysfunction was an incredibly crucial facilitator for S-AKI development. S-AKI kidneys had 111 increased and 66 decreased metabolites compared to the control group. MetaboAnalyst enrichment analysis suggested that S-AKI caused dysregulation of central carbon metabolism (such as transfer of acetyl groups into mitochondria, Warburg effect, and citric acid cycle), amino acid metabolism, and nicotinate and nicotinamide metabolism.

Conclusions: Proteomics and Metabolomics conjoint analysis provides new insights and a more comprehensive understanding of the pathophysiology of S-AKI with mitochondrial function and metabolic disorders, contributing to new diagnostic biomarkers and therapeutic targets.

FR-PO172

USP13 Targets MCL-1 to Protect Mitochondria-Attenuating AKI

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Background: Acute kidney injury (AKI) is a severe clinical syndrome with high mortality. Thus, investigation on its mechanism and drug targets is of great importance. Here we investigated the novel role and mechanism of ubiquitin specific proteases 13 (USP13) in AKI.

Methods: Eight weeks old WT and USP13-/- mice were subjected to cisplatin and folic acid (FA) to induce AKI. Rapid injection of USP13 plasmids via tail vein was applied to overexpress USP13 in kidney. The serum and kidney tissues were collected for analysis. In vitro cells were used for the mechanistic study.

Results: Immunofluorescence showed that USP13 was expressed in the kidney tubular epithelial cell of human and mouse. In WT mice, cisplatin or FA strikingly enhanced serum BUN, Cys C and Cr, which were further enhanced in USP13-/- mice by around 15% to 30%, respectively. Meanwhile, USP13-/- mice with AKI showed aggravated mitochondrial injury in kidney. In contrast, overexpression of USP13 in kidney significantly protected against AKI and mitochondrial damage. Furthermore, the mechanistic study suggested that USP13 deubiquitinated and stabilized myeloid cell leukemia-1 (MCL-1) to protect mitochondria under AKI, thus resulting in a protection against AKI. Finally, pharmacological inhibition of USP13 by spautin-1 (10mg/kg, IP, daily) also worsened AKI.

Conclusions: USP13 could deubiquitinate and stabilize MCL-1 to protect against mitochondrial injury and AKI. Targeting USP13 could be a potential strategy in treating AKI.

FR-PO173

Ultrastructural Analysis of AKI due to Rhabdomyolysis

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Background: Rhabdomyolysis (RM) is a severe and life-threatening muscle damage. The breakdown products are released into the bloodstream and filtered by glomeruli, causing tubular obstruction and inflammation due to protein precipitation. These injured the renal tubular and endothelial cells of the kidney and lead to acute kidney injury (AKI). However, the mechanism is still unclear. In this study, we analyzed the ultrastructure of the renal tubular and the endothelial glycocalyx in RM with scanning electron microscopy (SEM).

Methods: Ten-week-old male C57BL/6 mice were injected intramuscularly into the left thigh of the mice at a dose of 5 mL/kg of 50% glycerol after 24 hours of fasting to create an RM model mouse. The mice that survived were euthanized 96 hours after injection, and then kidney specimens and blood samples were obtained. To investigate the ultrastructure of the kidney, the glycocalyx fixation method, and the conventional fixation method were performed. Mice were perfused with a solution composed of glutaraldehyde without lanthanum nitrate at a 1:5 flow rate.

Results: Serum blood urea nitrogen and creatinine were significantly elevated in the RM group. SEM analysis revealed that renal tubules are nourished by capillaries flowing through their interstices, and in normal kidneys, tubules and capillaries exist in close contact. However, in RM kidneys, a capillary fibrosis is created between the capillaries, creating a distance between the capillaries and the tubules. The surface of the proximal tubular cells in normal kidneys is densely packed with microvilli of unequal length and thickness, forming a brush border. In RM, microvilli on the surface of the proximal tubules had disappeared and their density was sparse. Under the RM condition, the endothelial glycocalyx was disrupted compared to the control group.

Conclusions: In conclusion, our data have shown the renal tubular and the vascular endothelial glycocalyx were injured and the newly formed gap creates a distance between them.
Following AKI, Transcriptional Expression of Repair Genes Are Differentially Regulated By 5-HT1F Receptor Agonism

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Background: Acute kidney injury (AKI) is often accompanied by a persistent reduction in mitochondrial function, fatty acid oxidation and vascular injury. We have shown that the FDA-approved 5-HT<sub>1</sub>F<sub> receptor antagonist lasmiditan stimulates mitochondrial biogenesis (MB), decreases vascular injury, and accelerates renal recovery in a mouse model of AKI. Given recent studies reporting conserved cellular responses and profiling successful and failed repair genes following AKI, we sought to explore the role of lasmiditan on these repair genes. Methods: Male 8-week-old C57Bl/6 mice were administered 0.3 mg/kg lasmiditan or vehicle daily beginning 24h after ischemia-reperfusion-induced AKI (I/R-AKI) and continuing for 144h (n=6/group). The kidneys were collected and gene and protein expression of select repair genes analyzed in renal cortices. Results: Serum creatinine and kidney injury marker 1 (KIM1) were maximally elevated 24h after I/R-AKI. Lasmiditan treatment decreased serum creatinine and KIM1 compared to vehicle by 144h after I/R-AKI. qRT-PCR analysis 24h following I/R-AKI revealed decreased expression of successful repair genes ACSM2a, LR2P, SLC5A12 and HNF4A, and increased expression of failed repair genes VCAKI, LC3, RELB and KCNIP4 in the renal cortex of injured mice. Lasmiditan treatment increased successful repair gene expression compared to vehicle treatment by 144h after I/R-AKI; but had no effect on failed repair genes. These findings were confirmed using immunohistochemistry. Conclusions: While these data support lasmiditan-induced regulation of successful repair genes following I/R-AKI, contributing to increased fatty acid metabolism, reabsorption of lactate, and decreased inflammation, the mechanism remains unclear. Continued use of this approach will allow us to identify and assess key genes responsible for pathophysiological changes during AKI, other renal pathologies, and the effects of drugs stimulating repair/recovery.

Funding: Veterans Affairs Support

FR-PO176
The Novel Dual-Effect Disintegrin, ARGD-RR, Attenuates AKI to CKD in Ischemic-Reperfusion Injury Models

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Background: Acute kidney injury (AKI) can lead to the development of renal fibrosis, ultimately resulting in chronic kidney disease (CKD) and end-stage renal disease (ESRD). Platelet activation has been identified as a key factor in the pathophysiology of AKI, triggering the formation of neutrophil extracellular traps (NETs), which exacerbate tubular necrosis and renal inflammation. Previous studies have demonstrated that antagonists or inhibitors of platelet activation hold promise as therapeutic interventions in AKI models induced by ischemia-reperfusion (ER). Here, we tested whether the novel dual-effect disintegrin ARGD-RR (ARGDRR) could ameliorate AKI in I/R injury models.

Methods: In this study, we evaluated the therapeutic efficacy of a novel anti-platelet activation peptide called ARGDDR in a unilateral ischemic-reperfusion injury (uIRI) model. ARGDDR is a snake venom-derived dual-effect disintegrin-ARGDDR peptide that activates platelets with affinity for αβ<sub>3</sub> and β<sub>3</sub>-integrin thereby triggering ischemic-induced kidney injury. ARGDDR was administered, and we assessed renal dysfunction, renal fibrosis, and cell senescence after a 15-day period. Additionally, we examined the extent of platelet activation and NET formation in AKI.

Results: The mRNA levels of platelet glycoprotein Ibβ-GPⅠbα (Igα2β and Igβ3) progressively increased in the uIRI kidney from day 1 to day 15, accompanied by platelet aggregation and neutrophil infiltration. Administration of ARGDDDR ameliorated renal dysfunction, fibrosis, and cell senescence in the transition from AKI to CKD. Moreover, ARGDDDR modulated platelet-neutrophil interaction and inhibited NET formation in AKI.

Conclusions: Our findings provide compelling evidence that the disintegrin-ARGDDR peptide holds significant potential for renal protection in the transition from AKI to CKD by inhibiting platelet activation and NET formation. These results contribute to the advancement of therapeutic strategies for AKI and CKD treatment.

Funding: Government Support - Non-U.S.

FR-PO177
Renal Tubular Epithelial Cells RIPK3 Promote AKI Progression to CKD

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Background: Acute kidney injury (AKI) could increase the risk of long-term chronic kidney diseases (CKD) but its exact mechanism is still unclear. The purpose of this study was to clarify the role and mechanism of renal tubular epithelial cells RIPK3 in the AKI to CKD progression.

Methods: We evaluate the role of renal tubular epithelial cells RIPK3 through detecting its expression in renal puncture tissue and AKI to CKD progression animal model. The role of RIPK3 in promoting AKI-to-CKD transition and G2/M cell cycle arrest was evaluated using transgenic mice with specific knockout of proximal renal tubular epithelial cells RIPK3 or intervention of RIPK3 inhibitor GSK-872. Co-Immunoprecipitation and pull-down experiments were used to explore the interaction between the phosphorylated RIPK3 and CKD1. The mechanism that RIPK3 promote AKI to CKD transition through regulating G2/M cell cycle arrest were explored in vitro rescue experiments.

Results: Renal tubular epithelial cells RIPK3 was up-regulated in renal puncture tissues of CKD patients after cardiac surgery-associated AKI and AKI to CKD progression animal models. GSK-872 intervention or specific knockout of proximal renal tubular epithelial cells RIPK3 could attenuate renal interstitial fibrosis and G2/M phase cell cycle arrest. Co-Immunoprecipitation and pull-down experiments confirmed that phosphorylated RIPK3 and CKD1 could bind directly. siRNA inhibiting the expression of CKD1 could attenuate the renoprotective effect of GSK872 intervention or RIPK3 silence after intervention of TGF-β.

Conclusions: Renal tubular epithelial cells RIPK3 is up-regulated and activated during the AKI to CKD progression and drive the AKI progressing to CKD. The possible mechanism may be that RIPK3 can inhibit the activity of CKD1, and mediate the G2/M cell cycle arrest of renal tubular epithelial cell, which could provide a new theoretical and therapeutic target for delaying the AKI to CKD progression.

FR-PO178
Decoy Receptor 2 Promotes Tubular Maladaptive Repair by Inhibiting Hmgcs2-Induced β-Hydroxybutyrate Production Following AKI

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Background: Tubular maladaptive repair after acute kidney injury (AKI) leads to chronic kidney disease or end-stage renal disease. However, the underlying mechanism remains unclear. The expression of De2 was abnormally increased in renal tubules in patients of AKI, and associated with renal prognosis. Similar results were found in moderate and severe ischemia-reperfusion injury and cisplatin-induced AKI mouse models.

Methods: Similar results were found in moderate and severe ischemia-reperfusion injury and cisplatin-induced AKI mouse models. Proteomics analysis and validation study showed that De2 mediated maladaptive repair by regulating the expression of Hmgcs2 (a rate-limiting enzyme of endogenous ketogenesis) and the levels of renal beta-hydroxybutyrate (β-OHB). Hmgcs2 inhibition or deletion aggravated kidney damage and
Irisin Modulates Renal Ischemia-Reperfusion Injury by Upregulating Mitochondrial Autophagy Marker Protein LC3

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Background: Acute kidney injury (AKI) is a clinical syndrome with a high incidence and increased cost and mortality for hospitalized patients, and are still lacking of effective therapeutic drugs. Irisin has been reported to have inhibitory effects on cellular inflammation, reduced cell apoptosis, and antioxidant stress in various diseases. But it is still unknown whether Irisin has therapeutic effects after ischemic AKI.

Methods: We evaluated the serum Irisin levels and their correlation with renal function in AKI patients and healthy control groups. We constructed a mice model of ischemia-reperfusion (IR) kidney injury and administered exogenous Irisin to investigate the potential therapeutic effects and mechanisms through a series of experimental techniques such as renal tubal microperfusion.

Results: We found that the Scr level in the AKI patient was significantly higher than that in the healthy control group (256.8 ± 30.5 vs. 61.9 ± 10.5 μmol/L, P < 0.0001), the BUN level was significantly higher (17.1 ± 6.5 vs. 5.1 ± 1.0 mmol/L, P < 0.0001), and the Irisin level was significantly reduced (39.9 ± 8.2 vs. 76.7 ± 13.8 ng/ml, P < 0.0001). We found that exogenous Irisin reduced the renal damage indicators in mice model. The stability of mitochondrial JC-1 membrane potential increased and the ROS decreased after IR in the Irisin treatment group. Irisin up-regulated the expression of renal mitochondrial autophagy related proteins PINK1 and PARK2 and marker protein LC3, enhanced mitochondrial autophagy, and down regulated the activation of NLRP3 inflammasome.

Conclusions: This study suggests that Irisin may serve as a potential biomarker of ischemic AKI. Irisin has therapeutic effects on renal IR, and its protective effect may be related to enhanced mitochondrial autophagy by upregulating mitochondrial autophagy marker protein LC3. This study provides theoretical support for Irisin as a therapeutic drug for ischemic AKI.

Funding: Government Support - Non-U.S.

FR-POI180

HNF4α Links PGC1α to Quinolinate Phosphoribosyl Transferase (QPT) and De Novo NAD+ Biosynthesis

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Background: De novo NAD+ biosynthesis is suppressed in acute kidney injury (AKI), particularly the bottleneck enzyme Quinolinate Phosphoribosyl Transferase (QPT), leading to NAD+ reduction and accumulation of upstream metabolites. We previously showed that QPT is regulated by PPARγ coactivator 1 alpha (PGC1α), a transcriptional co-activator that regulates many genes involved in metabolism and mitochondrial biogenesis. A transcription factor (TF) linking PGC1α and QPT has not been identified.

Methods: The ENCODE TF Database was compared with Biogrid and the Human Reference Protein Interactome to identify TFs that interact with PGC1α and bind QPT. Expression of PGC1α, HNF4α, and QPT was assessed with qPCR. Compartment-specific NAD+ was measured using transfected biosensors. ATP and ChIP qPCR was measured via commercial assay.

Results: Analysis of public datasets identified HNF4α and RXRA as candidate TFs in regulating QPT via PGC1α. We focused on HNF4α as no RXRA mutations associate with kidney disease. HNF4α was suppressed in AKI proportionally to QPT (R² = 0.5, P < 0.01). HNF4α overexpression increased QPT expression (1.27 fold change [FC], P < 0.01), and HNF4α mirrored both QPT and PGC1α with increased cellular NAD+ and ATP with HNF4α overexpression (NAD+ in cytoplasm 1.08FC, P < 0.001; mitochondria 1.06FC, P < 0.05; nucleus 1.09FC, P < 0.05) (ATP 1.08FC, P < 0.001) and decreased NAD+ and ATP with siHNF4α (NAD+ in cytoplasm 0.86FC, P < 0.001; mitochondria 0.89FC, P < 0.05; nucleus 0.86FC, P < 0.05) (ATP 0.91FC, P < 0.01). ChIP qPCR showed that HNF4α binds QPT (QPT focus in kidney 12.72FC over IgG) proportionally with PGC1α expression (R² = 0.58 FC, P < 0.05). Finally, siHNF4α co-transfected with PGC1α plasmids prevented PGC1α induced increase in QPT expression (QPT1α overexpression = 1.34FC increase in QPT, P < 0.001; PGC1α overexpression with siHNF4α = 1.1 FC in QPT, P < 0.01).

Conclusions: HNF4α is a known regulator of metabolic pathways in the liver and a critical component of kidney cell differentiation, but few studies have examined the role of HNF4α in adult kidney. This is relevant as recent multi-omics investigations have identified HNF4α recovery after injury as a critical feature of “recovered” tubular cells. In summary, the present results identify a transcriptional mechanism for HNF4α in regulating de novo NAD+ biosynthesis suppression in AKI.

Funding: NIDDK Support, Private Foundation Support

FR-POI181

Tryptophan Metabolism in AKI: A New Target in Kidney-Brain Axis

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Background: Partial recovery following AKI could lead to long-term consequences that predispose to chronic dysfunction and may also accelerate neurocognitive decline. Kidney-brain axis seems to play a pivotal role leading to detrimental outcome for AKI patients. Several studies suggested a relationship between kidney damage and brain dysfunction even after AKI resolution. Patients who suffered AKI may afterward show a disturbance of arousal called brain-fog. Although advances in understanding the pathophysiology of AKI and brain dysfunction, there are no available preventive and therapeutic strategies. Recent findings have revealed link existing between dyslipidemia/low HDL levels and Kynurenine pathway (KP) alterations that lead to the production of neuroactive metabolites: kynurenine (KYN) and quinolinic acid (QA).

Methods: Sepsis-induced AKI (SI-AKI) was induced in a porcine model by intravenous infusion of a saline solution containing 300 μg/kg of LPS. After injection, 12 animals were treated with different doses of recombinant HDL (rHDL) (20-40mg/kg), while 6 animals did not receive treatment (LPS group). Animals were sacrificed after 24h from the start of the experimental procedure.

Results: Endotoxemic pigs developed oliguric AKI with increased tubular and glomerular damage and interstitial inflammatory infiltrate. HDL treatment decreased the inflammatory process and tubular damage, preventing AKI, especially in 40mg/kg rHDL group. The rate-limiting step of KP, the Indolamine-2,3-dioxygenase 1 (IDO1) enzyme is upregulated during inflammation in serum and brain tissue, and has been linked to cognitive dysfunction. In our model, LPS induced an increased activation of IDO-1 gene expression at brain level in endotoxemic animals; meanwhile it appears to be reduced in both treated arms (p < 0.05). Sera from the rHDL group showed a significant reduction in IDO1 activity (KYN/Trp ratio) (p < 0.05) and QA levels (p < 0.05) compared with the LPS group. Moreover, a significant decrease of both systemic and brain IL-6 levels was observed after rHDL treatments.

Conclusions: Our data indicated that HDL-enhancing therapies may decrease the inflammatory response, the retention of waste products and neuroactive compounds, improving renal and cognitive function in SI-AKI.

Funding: NIH DK-027798, NIH DK-117697, NIH NS-090402, NIH AG-012358, NIH NS-111675, NIH GM-119166.
to control MDCK cells. Conversely, Exoc5 OE cells had higher BR, MR, and SRC. Il-1β inhibited IL-6 in Il-1β knockout cells compared to control. In Exoc5 OE cells, IL-6 expression was lower in Il-1β-KO than rescue cells. A metabolomics screen showed that tryptophan increased in Exoc5 KD and Exoc5 cts-mut cells by 58- and 13-fold compared to control. In Exoc5 OE cells, tryptophan decreased by 58%. Similarly, tryptophan increased by 21% in Il-1β KO cells. Kynurenine is directly downstream of tryptophan and decreased by 83% and 20% in Exoc KD and cts-mut cells, and increased by 25% in Exoc5 OE cells. In Il-1β KO cells kynurenine decreased by 49%.

Conclusions: Kynurenine drives oxidative stress and mitochondrial dysfunction and was higher in MDRD Study participants with ADPKD compared to other CKD, and patients with ADPKD had higher plasma levels compared to healthy individuals which increased with disease progression. Nguyen et al. (2022, JCI Insight) found decreased tryptophan and increased kynurenine in PKd1 RC/RC mice. This is the opposite of what we found following cilia loss. IdO1 converts tryptophan to kynurenine. When Nguyen et al. genetically knocked out IdO1, cytisogenes decreased. In 2013 Ma et al. (2013, Nature Genet) showed that cilia loss suppresses cyst growth in ADPKD mouse models. Shao et al. (2020, Kidney Int) showed that Il-1β KO slowed cyst growth in a PKd1 model mouse. Therefore, we hypothesize that cilia loss inhibits cystogenesis by increasing tryptophan and decreasing kynurenine. These findings highlight a link between cilia and mitochondrial function and suggest that tryptophan metabolism via IdO1 could be a novel target for ADPKD treatment.

Funding: Other NIH Support - NIH Grant P30DK70438, Veterans Affairs Support, Private Foundation Treatment

FR-PO183

Loss of Pax2 and Pax8 Induces Resistance to Ischemia in S3 Proximal Tubule

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Background: Pax2 and Pax8 are two highly homologous transcription factors regulating kidney development and are re-expressed during acute kidney injury (AKI) and repair. Our aim was to determine whether Pax2 and Pax8 are necessary to regenerate new proximal tubule cells after ischemic AKI.

Methods: Pax mutations were targeted to the proximal tubule, the primary site of injury in ischemic AKI, using floxed Pax2 and Pax8 conditional alleles and a phospho-dependent Cre recombinase (PEPCK-Cre) driver. Control mice included PEPCK-Cre but wild type Pax2 and Pax8 loci. All animals expressed a GFP-Cre reporter to track Cre activity. No gross differences in kidney function or histology were observed at baseline. Mutant and control mice were subjected to unilateral ischemia-reperfusion injury (IIRI) with simultaneous contralateral nephrectomy. Samples were analyzed at various post-injury time points. Nuclei from whole kidneys of uninjured mutant and control mice were analyzed using single nucleus RNA sequencing (snRNA seq).

Results: Mice with proximal tubule Pax2 and Pax8 deletion were protected from both acute and chronic injury as measured by serum BUN, histological injury score, and expression of injury markers. Differences manifested as early as 6 h after injury, suggesting an inherent resistance to ischemia. Pre-injury mRNA seq revealed that mutant mice developed a unique population of S3 proximal tubule cells which was confirmed by immunostaining for cluster specific markers and invariably stained for GFP, marking Cre-mediated Pax2 and Pax8 deletion. The transcriptional profile of mutant S3 cells were strongly enriched in genes associated with a range of conditions that protect against ischemic injury including hypoxic preconditioning, caloric restriction, and female sex. Furthermore, our data indicate that neither Pax2 nor Pax8 is necessary for repair after ischemic AKI. On the contrary, Pax protein loss induced protection against ischemic injury by promoting a transcriptional program that strongly overlaps with other conditions that confer protection. These findings highlight critical genes and pathways that determine sensitivity to ischemic AKI and suggest a novel role for Pax proteins in the proximal tubule.

Funding: NIDDK Support

FR-PO184

Alternative Splicing Generates an Intracellular Uromodulin Isoform that Mediates Mitochondrial Function and Is Up-Regulated in AKI

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Background: Uromodulin (UMOD), a glycoprotein exclusively produced by renal tubular cells, is known to protect against acute kidney injury. Previous research has mainly focused on the secreted UMOD; however, the significance of intracellular UMOD has not been described.

Methods: We performed long-read RNA sequencing on human and mouse kidneys to explore alternative splicing variants of UMOD. RT-PCR and Sanger sequencing were conducted to validate the expression of the identified variant. The expression of the variant in mice after renal ischemia-reperfusion injury was quantified using RT-qPCR. To assess the localization and function, cDNA of the variant was overexpressed in kidney epithelial cells, and Western blotting, immunofluorescence, LDH assay, and Mito Stress Test were performed.

Results: Long-read RNA sequencing revealed a novel alternative splicing variant of UMOD, referred to as UMOD-AS, both in humans and mice. The existence of UMOD-AS mRNA was confirmed by RT-PCR and Sanger sequencing. UMOD-AS mRNA was up-regulated in renal ischemia-reperfusion injury, and UMOD-AS expression in the cell model was down-regulated. In the cellular model, UMOD-AS localized in the cytoplasm, whereas canonical UMOD localized at the membrane and was secreted extracellularly. Interestingly, UMOD-AS expressing cells showed better cell viability than control UMOD-expressing cells. Mito Stress Test suggested UMOD-AS up-regulates mitochondrial function compared to canonical UMOD.

Conclusions: UMOD-AS is an intracellularly-localized and cellular-protective isoform of UMOD. Notably, the localization and regulatory mechanisms of UMOD-AS are contrasted with canonical UMOD. Alternative splicing of UMOD may be a novel protective mechanism in acute kidney injury.

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

FR-PO185

Kidney Mitochondrial DNA Contributions to Circulating IL-6 in Sepsis-Associated AKI

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Background: Increased circulating cell-free mitochondrial DNA (ccf-mtDNA) and acute kidney injury (AKI) are associated with mortality in sepsis, but the role of ccf-mtDNA in the pathogenesis of sepsis-associated AKI (S-AKI) remains unclear. We hypothesized that ccf-mtDNA released from the injured kidney contributes to the systemic inflammatory response via IL-6 in S-AKI.

Methods: Ccf-mtDNA isolated from the plasma of mice exposed to sepsis by cecal ligation and puncture (CLP) vs sham control (N=5-6/group) were sequenced and quantified by droplet digital PCR. Single nucleotide polymorphisms (SNPs) identified in the isolated mtDNA were compared to those found in the heart, kidney, liver, and lung of individual mice to infer tissue origin. In in-vitro studies, mouse bone marrow cells were transduced with IL-6 (positive control), kidney mtDNA, or mitochondrial damage-associated molecular patterns (mdAMPs) with and without DNase or toll-like receptor-9 inhibitor. IL-6 concentrations were compared across groups. In in-vivo studies, mice were injected with saline vs kidney mtDNA with and without DNase, and IL-6 concentrations were compared. Finally, ccf-mtDNA levels were quantified in the plasma of septic human subjects with and without AKI.

Results: Ccf-mtDNA was significantly increased in the plasma of CLP mice compared to controls. Three out of five mice analyzed had unique SNPs in mtDNA fragments indicating kidney origin of release. In both in-vitro and in-vivo studies, exposure to kidney mtDNA led to increased IL-6 release, which was attenuated by treatment with TLR-9 inhibitor or DNase (Figure A). In human studies, plasma ccf-mtDNA levels were significantly increased in patients with S-AKI compared to those with sepsis without AKI, and increased ccf-mtDNA significantly correlated with plasma IL-6 (Figure B-C).

Conclusions: Ccf-mtDNA released from the kidney contributes to increased plasma IL-6 in sepsis. Preserving kidney mitochondrial integrity, preventing mtDNA release, or clearing circulating mtDNA are translational avenues to pursue to decrease mortality from S-AKI.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO186

Renal Congestion Exacerbates Sepsis-Induced AKI in Mice

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Background: Recent epidemiological studies demonstrated that renal congestion is a major factor in the development of renal dysfunction associated with heart failure. We previously established a novel unilateral renal congestion mouse model wherein the inferior vena cava was constricted between both renal veins, and reported its impact on the exacerbation of renal ischemia-reperfusion injury. However, the impact of renal congestion on septic AKI, the most common cause of AKI, is unclear.

Methods: We instigated sepsis via cecal ligation and puncture (CLP) in a unilateral renal congestion model. We comprehensively analyzed the pathophysiology of exacerbation of septic AKI by renal congestion, especially focused on the toll-like receptor (TLR) 2, a receptor of the innate immune system.

Results: After the induction of CLP in the unilateral renal congestion model, the transient decline in blood pressure was observed at 3 and 6 hours after CLP. Ultrasonography revealed the persistent dilation of renal veins in the congested kidney for a duration extending up to 7 days post-CLP. Histological analysis at day 7 exhibited marked fibrosis in the group subjected to congestive heart failure + CLP, while qPCR assays indicated upregulation of fibrosis markers including Col1a1,Acta2,Tgfb1, and Fsn1.

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

Underline represents presenting author.
FR-PO188

miR-486-5p Protects Against Ischemic AKI and Transitions toward CKD

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Background: Recovery from acute kidney injury (AKI) is associated with increased risk for progressive chronic kidney disease (CKD). We previously showed that microRNA (miR)-486-5p protects against kidney ischemia-reperfusion (IR) injury in mice, with targeting of phosphatase and tensin homolog (PTEN) and downregulation of proximal tubular genes involved in apoptosis and tissue remodeling. In cultured human endothelial cells however, miR-486-5p inhibits endothelial nitric oxide synthase (eNOS) expression. Here, we studied the effects of miR-486-5p on IR AKI and CKD development in rats with a focus on vasculature.

Methods: Kidney injury was induced in male rats by bilateral renal pedicle clamping followed by reperfusion. Lipid-encapsulated miR-486-5p (0.5mg/kg) was injected i.v. at the start of reperfusion. Outcomes were assessed after 24hr and 10 weeks. Kidney blood flow was measured by laser doppler flowmetry. Endothelium-dependent mesenteric artery relaxation was evaluated by myograph.

Results: In rats with IR AKI, miR-486-5p preserved regional kidney blood flow at 24hr (p<0.01, n=7) and prevented increases in plasma Cr (p<0.001, n=4), neutrophil and macrophage infiltration, and apoptosis. miR-486-5p had no effect on kidney PTEN expression, but inhibited IR-induced expression of eNOS and intercellular adhesion molecule (ICAM)-1. At 10 weeks, while rats with IR alone had normal plasma Cr, kidneys displayed decreased peritubular capillary density with increased interstitial collagen, α-smooth muscle actin (α-SMA) myofibroblasts, and F4/80+ macrophages. These changes were inhibited by miR-486-5p (CD31, collagen p<0.0001, n=5-6).

Conclusions: In rats, early administration of miR-486-5p prevents kidney IR injury and preserves regional blood flow despite reduction in eNOS expression. miR-486-5p also protects against CKD development and associated endothelial dysfunction. The results suggest that miR-486-5p is a promising therapy for the prevention of ischemic AKI and its sequelae.

FR-PO189

Renal-Protective Effect of Haptoglobin and Hemopexin by Inhibiting Ferroptosis in Ischemic AKI

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Background: Recent studies showed that cell free hemoglobin (CFH) increases in patients with sepsis and after heart surgery, which may cause acute kidney injury (AKI). Since CFH contains catalytically active iron, iron-dependent cell death, ferroptosis may induce AKI. This study investigates the reno-protective effect of haptoglobin (Hp) and hemopexin (Hx), which scavenge CFH, in an experimental model of AKI.

Methods: Ischemic reperfusion injury (IR) animal models were used as AKI animal models. After 2, 4, 6, 8, and 24 hours, CFH and hemin levels were evaluated in both the control and IR groups. In addition, the IRI models were treated with different doses (25, 50, 100, and 200 mg/kg) of Hp or Hx via intravenous injection 30 minutes prior to IR surgery. CFH, hemin, and kidney injury markers, as well as oxidative stress marker, and ferroptosis markers were evaluated 24 hours later. Furthermore, kidney injury score was evaluated from kidney tissues based on the percentage of cell necrosis, loss of brush border, cast formation, and interstitial edema.

Results: CFH and hemin levels increased in the IRI group at each hour compared to the control. Injection of Hp decreased CFH levels regardless of the dosage, while injection of Hx decreased hemin levels compared to the IRI group. Creatinine, BUN, and MDA levels showed increases in the IRI group compared to the control. Treatment with Hp or Hx resulted in decreases in creatinine, BUN, MDA, and kidney injury score across all dosage compared to the IRI group. MDA levels showed a decrease in all drug injection groups except for the Hp 25mg/kg group compared to the IRI group. In the IRI group, the mRNA expression of cystine/glutamate antiporter system Xc- decreased compared to the control, while ferritin heavy chain 1 increased. However, treatment with Hp or Hx resulted in an increase in cystine/glutamate antiporter system Xc- mRNA expression and a decrease in ferritin heavy chain 1 compared to the IRI group.

Conclusions: Hp and Hx, scavenger proteins, may aid as preventive agents for ischemic reperfusion AKI by inhibiting ferroptosis.

FR-PO190

Reduced Perivascular Cell Dynamin-Related Protein 1 (Drp1) Protects Against AKI and CKD in Mice

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Background: Mitochondrial dysfunction has been implicated in the pathogenesis of AKI and CKD. We have previously demonstrated that proximal tubule deletion of Drp1 attenuated progressive kidney injury and fibrosis after ischemia-reperfusion injury (IR). The role of Drp1 and mitochondrial dysfunction in kidney perivascular cells (PVCs) during AKI and CKD has not been explored.

Methods: PVC specific germline (Foxdr1-CreDR1+/-, Foxdr1-CreDr1-/-) or inducible (Pdgfr-CreERT2;Dr1+/-, Pdgfr-CreERT2;Dr1-/-) Drp1 heterozygote and knockout mice and respective littermate controls (WT) were generated. Foxdr1- CreDR1+, Foxdr1-CreDR1+/- and WT male and female mice were injected with folic acid and hemin and bim (25, 50, and 100 mg/kg, i.p.) 24, 48, and 72 hours later, mice were evaluated for kidney injury by plasma creatinine (PCr) and BUN and Kim-1 and Ngal mRNA. In another model of AKI, Foxdr1-CreERT2;Dr1+/-, Foxdr1-CreERT2;Dr1-/- and WT male mice underwent bilateral kidney IRI (bIRI, 26 min). In a model of the AKI to CKD progression, Foxdr1-CreDR1+, Foxdr1-CreDR1+/- and WT male and female mice were injected with FA and followed for 14days. Mice were evaluated for kidney fibrosis by mRNA levels of fibrosis genes (Col1a1, Fln1) and Masson’s trichrome staining.

Results: 24 hours after FA, both male and female WT mice displayed a rise in plasma creatinine (BUN) which was significantly attenuated in mice with partial deletion of PVC Drp1 (Foxdr1-CreDr1+/-). In contrast, mice with a full deletion of Drp1 in PVCs (Foxdr1-CreDr1-/-) displayed an increased susceptibility to injury in male mice and increased mortality in females. 14 days after FA, Foxdr1-CreDr1+/- mice had reduced kidney dysplasia and tubulointerstitial fibrosis compared with WT and Foxdr1-CreDr1+/- mice. After bIRI, both Pdgfr-CreERT2;Dr1+/- and Pdgfr-CreERT2;Dr1-/- mice had a decrease in plasma creatinine compared with WT controls.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
AF3 Ameliorates Ischemic Kidney Damage by Controlling the Cross-Talk Between Immune and Kidney Cells

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Background: Acute kidney injury (AKI) is a leading cause of death. The molecular pathophysiological mechanisms of AKI remain only partially understood, and targeted therapies to facilitate recovery from renal failure are still elusive.

Methods: To find central signaling pathways that drive kidney regeneration, we performed single-cell RNA sequencing (scRNA-seq) after laser-injured-induced zebrafish pronephric tubules, and explored the function of Atf3 in three different Atf3-deletion models, subjecting Atf3f/f*FosKsp-Cre, Atf3f/f*Gt3z1-Cre, and Atf3f/f*Ksp-Cre mice to unilateral nephrectomy followed by ischemia-reperfusion injury (IRI). To determine the role of Atf3 in IRI, kidney cells were subsequently analyzed by histology, flow cytometry, bulk-scRNA-seq, and CUT&RUN experiments.

Results: Depletion of zebrafish atf3 by morpholino oligonucleotides compromised the repair process after pronephros injuries. While Pax4- or Cx3cr1-mediated depletion of Atf3 did not affect renal function, Ksp-Cre-mediated Atf3 loss intensified the renal failure after IRI in mice. The absence of Atf3 in distal nephron segments reduced the expression of crucial chemokines including Ccl2, resulting in decreased numbers of infiltrating F4/80+ macrophages and deficient macrophage “M2” polarization. Using RNA sequencing and CUT&RUN techniques, we found that Atf3 directly regulates Uromodulin, and promotes its secretion via increased ROMK expression after IRI. Gene Ontology enrichment analysis of the immune cell populations confirmed the downregulation of leukocyte migration, cytokine production, and cell-cell adhesion. CellChat analysis identified a weakened interaction between immune cells and the tubular epithelial cells of the thick ascending limb (TAL).

Conclusions: Ksp-Cre-mediated excision of Atf3, primarily affecting Atf3 expression in the TAL, worsens renal failure after IRI. Loss of Atf3 affects the expression of several immune regulatory factors including Uromodulin, which is known to promote an anti-inflammatory macrophage phenotype. Our analyses reveal that Atf3 protects the kidney against ischemia by controlling the cross-talk between immune and kidney cells.

Funding: Government Support - Non-U.S.

FR-PO193
Inhibition of Histone Methyltransferase SET8 Attenuates Renal Tubular Cell Apoptosis by Restoring PTEN in Cisplatin-Induced AKI
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Background: SET8 is a histone H4K20 monomethyltransferase that regulates transcriptional and posttranslational modifications, heterochromatin formation, genomic stability, and cell cycle progression. Numerous studies have shown that SET8 is involved in various pathophysiological events, including cancer, inflammatory responses and metabolic disorders. However, its role in acute kidney injury (AKI) remains unexplored.

Methods: In this study, we aimed to investigate the role and mechanism of SET8 in cisplatin-induced AKI using a murine model and cultured renal epithelial cells.

Results: SET8 and its downstream histone H4 lysine 20 methylation (H4K20me1) expression were highly increased in cultured murine proximal tubule epithelial (TKPT) cells and kidneys from mice treated with cisplatin, along with decreased expression of phosphatase and tensin homolog (PTEN) and increased phosphorylation of p53 (p-p53). Pharmacologic inhibition of SET8 with UNC0379, a specific inhibitor, or siRNA- mediated silencing of SET8 suppressed apoptosis, p-p53 and preserved PTEN expression in TKPT cells exposed to cisplatin. Similarly, administration of UNC0379 in cisplatin- injected mice also improved renal function, attenuated tubular injury and inhibited apoptosis, which was coincident with repressing expression of SET8, H4K20me1 and p53, and restoring PTEN. Moreover, inhibition of p53 with bph (HOPic) or silence of p53 in cisplatin-aggravated cisplatin-induced apoptosis without affecting expression of SET8, H4K20me1. In contrast, inhibition of p53 with pifithrin-alpha (PFA) or silence of p53 lowered cisplatin-induced apoptosis without affecting expression of SET8, H4K20me1 and PTEN.

Conclusions: These findings indicate that SET8 relieved renal apoptosis induced by cisplatin by upregulating PTEN, which in turn repressed p53, and suggest that SET8 may serve as a novel therapeutic target for cisplatin-induced AKI by attenuating apoptosis and restoring PTEN expression.

Funding: NIDDK Support

FR-PO194
Lats2 Ablation Exacerbates Severe Ischemia/Reperfusion-Induced Renal Maladaptive Repair Through the Upregulation of p53
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Background: Incomplete recovery of AKI can lead to long-term functional deficits and CKD. The Hippo pathway plays a regulatory role in the pathogenesis and repair of AKI and CKD progression. LATS2, a negative regulator of YAP in the Hippo pathway, has been shown to be expressed in many physiological events, including cancer, inflammatory responses and metabolic disorders. However, its role in AKI repair remains unclear.

Methods: We established proximal tubule Lats2 conditional knockout (Lats2-CKO) mouse models. Then we constructed a mouse model of maladaptive kidney repair after AKI. The Hippo pathway plays a regulatory role in the pathogenesis and repair of AKI and CKD progression. LATS2, a negative regulator of YAP in the Hippo pathway, has been proved to have a strong association with cell apoptosis independent of YAP. p53 has been known to mediate the progression of cell apoptosis and maladaptive kidney repair after AKI. Nevertheless, the relationship between LATS2 and p53 in post-AKI renal maladaptive repair remains far from clear.

Methods: We established proximal tubule Lats2 conditional knockout (Lats2-CKO) mouse models. Then we constructed a mouse model of maladaptive kidney repair after AKI. The Hippo pathway plays a regulatory role in the pathogenesis and repair of AKI and CKD progression. LATS2, a negative regulator of YAP in the Hippo pathway, has been shown to be expressed in many physiological events, including cancer, inflammatory responses and metabolic disorders. However, its role in AKI repair remains unclear.

Results: At 14 days after I/R, Lats2-CKO mice represented more severe tubulointerstitial damage than WT mice. Masson trichrome, Sirius red staining, and α-SMA staining showed that fibrosis is exacerbated in post-IRI mice reduced renal fibrosis, immune cell infiltration and apoptosis in both Lats2-CKO and WT mice, and assessed the fibrotic state, inflammatory cellular infiltration, apoptosis and p53 expression in post-AKI kidney tissue. Next, we used the pharmacological p53 inhibitor Pifithrin-α (PFT-α) to treat post-IRI mice for 14 days. Hypoxia and reoxygenation (H/R) was used to mimic I/R in vitro.

Results: At 14 days after I/R, Lats2-CKO mice represented more severe tubulointerstitial damage than WT mice. Masson trichrome, Sirius red staining, and α-SMA staining showed that fibrosis is exacerbated in post-IRI mice reduced renal fibrosis, immune cell infiltration and apoptosis in both Lats2-CKO and WT mice, and assessed the fibrotic state, inflammatory cellular infiltration, apoptosis and p53 expression in post-AKI kidney tissue. Next, we used the pharmacological p53 inhibitor Pifithrin-α (PFT-α) to treat post-IRI mice for 14 days. Hypoxia and reoxygenation (H/R) was used to mimic I/R in vitro.

Conclusions: These findings indicate that Lats2 prevented recovery of AKI from inflammatory injury by regulating PTEN, which in turn repressed p53, and suggest that Lats2 may serve as a novel therapeutic target for cisplatin-induced AKI by attenuating apoptosis and restoring PTEN expression.

Funding: Government Support - Non-U.S.
FR-PO195

Renal Protection Driven by Peroxosome Activity, Proximal Tubule Park7, and Protein Succinylation

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Background: Acute Kidney injury (AKI) is an unfortunately frequent disease acquired during hospitalization with nearly 1 in 5 patients exhibiting some form of AKI. With the recent COVID-19 epidemic increasing instances of hospitalization, the burden that AKI and ensuing Chronic Kidney Disease (CKD) has on healthcare underlines the critical need for early detection, prevention, and treatment for AKI. To attenuate AKI occurrence therapeutically we need a better understanding of the physiological and cellular mechanisms underlying damage. The most pronounced effect of AKI is on the Proximal Tubule Epithelial Cells (PTECs) which have the highest metabolic activity and are therefore most susceptible to damage after ischemia, sepsis, or transplant stress. This damage causes an increase in radical oxygen species, oxidative protein stress, and decreased functionality of mitochondrial Fatty Acid Oxidation (FAO) enzymes.

Methods: Our approach to protect from long-lasting tissue damage is by modulating the metabolic regime and activating FAO in peroxisomes, a normally underused metabolic organelle. Large classes of proteins can be modulated rapidly and reversibly through the activity of enzymes that ligate Posttranslational Modifications (PTMs). We have previously shown that succinylation of lysine residues on metabolic proteins can be protective during AKI, specifically when the activity of the desuccinylase Sirtuin 5 is inhibited.

Results: Maintenance of the succinyloxy in Sirtuin 5 knockout tissue requires the activity of a second PTM ligating enzyme, the deglycase Park7. Park 7 is activated by oxidative stress and has been linked to apoptotic protection and minimizing CKD through reduction of Advanced Glycation Endproducts. Mass spectrometry analysis of kidney lysates point towards a protective combination of activated Park 7 and deactivated Sirtuin 5 increasing peroxosomal FAO. This relationship is confirmed by the use of a diet-induced peroxisome upregulation using dicarboxylic acid (DCA) supplementation. The protection seen with DCA after AKI is significantly dependent on functioning Park 7.

Conclusions: We conclude that a rapid and effective target for AKI treatment can be found by analyzing and maintaining the succinyloxy of PTECs and we hope to harness this mechanism to develop novel therapies for AKI.

Funding: NIDDK Support

FR-PO196

Scleroderma Renal Crisis: A Nephrologist’s Enigmatic Therapeutic Dilemma

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Introduction: Scleroderma Renal Crisis (SRC), occurring in 5-20% of patients with systemic scleroderma, typically presents with hypertensive urgency, acute kidney injury (AKI), microangiopathic hemolytic anemia and renal thrombotic microangiopathy. SRC is one of the few very times when AKI treatment calls for aggressive ACE inhibition, especially with Captopril. We describe fatal SRC, more than 20 years after initial diagnosis, AKI requiring hemodialysis despite escalated oral Captopril therapy for hypertension. She died 10 days after starting hemodialysis.

Case Description: A 71-year-old female with scleroderma since 2000 and treated intracranial oligodendroglioma since 2010 was admitted in late December 2022, with abdominal pain and decreased appetite. Blood pressure was 186/109 mm Hg, pulse 108/min and pulse ox 94% on room air. She was diagnosed with SRC – hypertension, microangiopathic hemolytic anemia, elevated LDH, +1 schistocytes, AKI with more than doubled creatinine to 2.21 mg/dL, UACR 935 ug/mg, >50 RBC/HPF and >50 WBC/HPF. Escalated oral Captopril was initiated. PLASMIC score was 4 points, low probability for TTP. ADAMTS13 was 53%, nondiagnostic. Hypertension was controlled on 137.5 mg Captopril TID + Nifedipine 60 mg BID. She was discharged, after 3 weeks, with stabilized blood pressure, stable creatinine at 4 mg/dL, and urine output of 1 L/day. Six days later, she was readmitted with worsening hypoxia, hyperkalemia 5.9 mmol/L, and creatinine of 5.12 mg/dL, which improved with fluid resuscitation. Potassium improved with oral sodium zirconium cyclosilicate. Kidney biopsy demonstrated thrombotic microangiopathy. She was treated for hypotension. Intermittent hemodialysis was started for worsening AKI and uremic encephalopathy. The patient passed away nine days after starting hemodialysis.

Discussion: SRC is an early complication of systemic sclerosis (SS), usually within one year of diagnosis. This case corroborates the difficulty in treating SRC-induced hypertension and resultant kidney damage. Our patient was atypical, with SRC occurring more than 20 years after diagnosis, hence the need for heightened vigilance. SRC was previously the leading cause of death in SS; the prognosis improved significantly with the introduction of ACE inhibitors. Despite adequate management of hypertension, our patient ultimately succumbed to her disease.

FR-PO197

Ascites and Bilateral Hydronephrosis

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Introduction: Tense ascites resulting in bilateral hydronephrosis documented by antegrade nephrostograms before and after large-volume paracentesis (LVP).

Case Description: A 63-year-old man presented with cirrhosis presented with ascites, confusion and oliguria. Initial laboratory evaluation revealed elevated blood urea nitrogen 91 mg/dL and creatinine 5.97 mg/dL. Three months earlier, these were 7 mg/dL and 0.97 mg/dL, respectively. Ultrasound showed massive ascites and bilateral grade 2 hydronephrosis. A urinary catheter yielded 100 mL of urine. Computed Tomography confirmed bilateral hydronephrosis. It was hypothesized that massive ascites was the cause of the hydronephrosis. Antegrade nephrostogram found absent flow and fixed narrowing at the pelvic brim. The initial left renal pelvis pressure measured 15 mmHg. After LVP of 5 liter, renal pelvis pressure was 0 mmHg and fluoroscopy demonstrated ureteral peristalsis and antegrade flow into the bladder with resolution of the narrowed segment. Retroperitoneal ultrasound four days later confirmed resolution of hydronephrosis.

Discussion: Resolution of the elevated collecting system pressure and outflow obstruction after paracentesis supported tense ascites as the etiology for the acute kidney injury.

Pre-paracentesis
Renal Cortical Necrosis in Sickle Cell Trait

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Introduction: Sickle cell disease (SCD) is a monogenic disorder characterized by an abnormal hemoglobin molecule due to a single nucleotide substitution in the β-globin gene. A homozygous inheritance causes sickling and hemolysis of erythrocytes and, subsequently, ischemia and end-organ damage. The heterogeneous inheritance results in sickle cell trait (SCT) with a milder phenotypic presentation. We report a rare biopsy-proven renal cortical necrosis (RCN) in a patient with SCT.

Case Description: A 40-year-old male presented with severe, non-radiating lower abdominal pain and had lower abdominal tenderness on examination. His creatinine was 530 mmol/L. The urinalysis showed moderate pyuria and hematuria with negative urine culture. The urine protein:creatinine ratio was 1040 mg/g and his lactate dehydrogenase was 1209 units/L. The vasculitic and viral screens were negative, with normal complement levels. His hemoglobin electrophoresis showed a hemoglobin S of 31%. A kidney ultrasound showed normal size and morphology of both kidneys. A kidney biopsy showed diffuse extensive coagulative necrosis in the cortex, where the tubules and glomeruli were lined by pale ghost cells with pyknotic nuclei, there was marked interstitial inflammatory infiltrate composed predominantly of neutrophil ghosts. The immunofluorescence stains were negative. The patient’s creatinine gradually improved over a 6-month period down to 176 mmol/L.

Discussion: Recurrent vaso-occlusive crises in SCD lead to many kidney manifestations, including RCN. Due to the relatively low levels of hemoglobin S, individuals with SCT rarely experience clinical manifestations. To the best of our knowledge, RCN has not been reported before in SCT.

FR-PO198

Plasma Cell-Rich Acute Interstitial Nephritis in VEXAS: An Under-Recognized Disease Feature


Introduction: VEXAS syndrome (Vacuoles, E1 enzyme, X-linked Autoinflammatory, Somatic) is a recently identified autoinflammatory disease with a large variety of disease manifestations. While recurrent fever, auricular chondritis, recurrent venous thromboembolism/thrombophlebitis, inflammatory skin lesions, ocular inflammation and cytopenias have been well-described, understanding of kidney manifestations is limited.

Case Description: Medical records of all patients with genetically confirmed VEXAS syndrome were reviewed for evidence of AKI or abnormal urinalysis. Patients who met the KDIGO criteria for AKI for at least two consecutive measurements of serum creatinine or cystatin C were considered as having AKI. Biopsy specimens (n = 4) were reviewed by four experienced nephropathologists. Clinical and laboratory features at disease onset and at time of AKI diagnosis were abstracted from direct chart review. Results: Among a cohort of 69 patients (all men, mean age 71 ± 9) with VEXAS syndrome, 16 (23%) developed AKI (mean age 75 ± 9) at some point during their follow-up. A review of urinary findings revealed microscopic hematuria, mild proteinuria, and pyuria in 100%, 100% and in 82% of cases, respectively. Four patients had undergone renal biopsy for AKI. One patient had features of peri-tubular capillaritis and has been previously described. Three patients were found to have biopsy confirmation of interstitial nephritis (IN). All three patients had IN (acute in 2 and active chronic in 1) with plasma cell-rich infiltrate and tubulitis. Immunofluorescence was negative and electron microscopy did not show glomerular or extraglomerular immune deposits. Prednisone was initiated in all patients with biochemical improvement in renal function and resolution of urinary findings, however, AKI recurred following reduction in prednisone dose below 10-15 mg/day.

Discussion: AKI from Plasma cell-rich IN is an under-recognized feature in patients with VEXAS. AKI in VEXAS responds well to treatment with corticosteroids. Recurrence is common with lowering corticosteroids dose. Further investigations to Identify targeted, effective therapies is necessary.
FR-PO200

Amoxicillin-Induced Crystalline Nephropathy
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Introduction: Amoxicillin-induced crystalline nephropathy (AICN) is characterized by the sudden onset of acute kidney injury (AKI) and microscopic examination of the urine revealing characteristic birefringent needles under polarized light. Surprisingly, the presence of intratubular amoxicillin crystals is not reported. We report here the first case of intrarenal deposits of amoxicillin crystals.

Case Description: A 55-year-old woman was referred for AKI within one week of the initiation of amoxicillin antibiotic therapy for mitral endocarditis. She was euvoletic and had no fever, tachycardia, or rash. Urine analysis revealed no signs of leukocyturia or hematuria. The initial serum creatinine level was 5.42 mg/dL and the urine protein/creatinine ratio was 1.1 g/g. Complement and serum electrophoresis results were within normal range. Renal ultrasound was unremarkable. Urine microscopy after amoxicillin withdrawal did not reveal any crystals. Renal biopsy detected elongated optically empty normal range. Renal ultrasound was unremarkable. Urine microscopy after amoxicillin withdrawal did not reveal any crystals. Renal biopsy detected elongated optically empty 

Discussion: Despite being one of the most frequent crystalline nephropathies, the presence of intratubular crystals of amoxicillin in situ has yet to be documented. This case highlights several important messages. First, the processing of kidney biopsies can cause dissolution of crystals, emphasizing the need for systematic analysis of frozen tissue under polarized light in suspected cases of crystalline nephropathy. Second, infrared spectroscopic analysis plays a crucial role in identifying the causative substance. Finally, the presence of crystals in urine is transient and crystalluria analyses may be negative if not performed during exposure to amoxicillin.

FR-PO201

Dual Autoimmune Processes, One IgG4 Stain
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Introduction: IgG4-related disease (IgG4-RD) is an idiopathic immune-mediated fibroinflammatory disease often targeting the pancreas, kidney, retroperitoneum, and salivary glands. Pathology shows lymphoplasmacytic infiltrate with IgG4 plasma cells, storiform fibrosis, and obliterator phlebitis. We present an atypical presentation of a disease still being elucidated.

Case Description: A 30-year-old female with cirrhosis due to autoimmune hepatitis with primary sclerosing cholangitis overlap (AIH-PSC) and CKD stage III due to previous acute kidney injury (AKI) presented with new AKI (creatinine 3.3 mg/dL) during liver transplant evaluation. Serologic studies (table 1) showed elevated IgG with IgG4 predominance. Radiologic findings included retroperitoneal lymphadenopathy and groundglass pulmonary nodules. Although liver biopsy had not shown IgG4 plasma cell predominance, kidney biopsy revealed global glomerulosclerosis, interstitial fibrosis without storiform pattern, IgG4/IgG ratio of at least 30%, and >10 IgG4-plasma cells per high powered field (fig 1). She was treated for IgG4-RD with steroids and rituximab. Kidney function and pulmonary imaging improved dramatically within 6 months.

Discussion: This is a rare case of IgG4-RD in a young female with AIH-PSC without any characteristic pathologic findings. Diagnosis should be based on clinical, serological, radiologic, and pathologic evidence. Underlying autoimmune disease may correlate with development of IgG4-RD.

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<td>Anti-erythrocyte antibody</td>
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</tr>
<tr>
<td>Anti-nuclear</td>
<td>-</td>
<td>negative</td>
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<tr>
<td>Perinuclear anti-smeared epitope antibody (p-ANCA)</td>
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<td>Myeloperoxidase (MPO) IgG</td>
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<td>Proteinase-3 (PR3) IgG</td>
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<td>IgG4</td>
<td>46.8 mg/dl</td>
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Oxalate Nephropathy: An Insidious Cause of Renal Insufficiency
Alex D. Tarabochia, Jason R. Pettus, Roy Ragan. Dartmouth Health, Lebanon, NH.

Introduction: Oxalate nephropathy is caused by urinary super saturation of calcium oxalate, crystal formation with obstruction of tubules and deposition into the renal parenchyma.

Case Description: Patient is a 73-year-old male with Crohn’s disease, distant history of oxalate renal stones 5 years ago, and hypertension referred for chronic kidney disease (CKD) with baseline serum creatinine (Cr) of 1.6 with stable Cr for more than a year, which increased to 2 over the period of six months. Blood pressure (BP) was at goal and he had not had a Crohn’s flare in four years. Renal ultrasound (US) was negative for obstruction but did show small, non-obstructing (8mm on the left, 7mm on the right) renal stones in the bilateral lower renal poles. Specific gravity was 1.015, calcium was 8.5, protein: creatine (UPC) ratio was 0.1, and urine sediment was unremarkable with light microscopy. Routine labs were obtained one month later and serum Cr was 6.5. His symptoms were remarkable for fatigue and confusion. Pertinent medical history and repeat renal imaging were unremarkable. Specific gravity was 1.014 on urinalysis; calcium, UPC and light microscopy were unremarkable. The lack of obvious findings and lack of improvement with IV hydration prompted renal biopsy which showed tubular atrophy (15%) with diffuse calcium oxalate deposition and minimal acute tubular injury. Twenty-four-hour urine collection revealed low urine citrate (113mg/day) and high urine oxalate (92 mg/day). He was started on potassium citrate and was instructed to increase fluid intake after which Cr improved to 2.5 over a period of two months.

Discussion: This case illustrates the insidious nature of oxalate nephropathy where the ongoing, mild super saturation leads to CKD and an acute super saturation leads to AKI. Risk factors include dehydration, high oxalate diet, and disorders with malabsorption.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
A 68-year-old African American female with a history of DKD, hypertension, and gout was referred to the Emergency Room for nausea and AKI. Her baseline serum creatinine (sCr) was approximately 2.6 mg/dL and increased to 4.02 mg/dL on presentation. Two months prior to presentation, the patient was initiated on allopurinol therapy for gouty arthritis. Other notable findings were elevated liver enzymes and a diffuse purpuric rash. Serologic work-up revealed negative for ANCA, normal complement levels, and negative viral serologies. Because the AKI did not improve with hydration and cessation of allopurinol, a kidney biopsy was performed. The biopsy showed focal vasculitis with fibrinoid necrosis superimposed on a background of diabetic nephropathy with severe interstitial fibrosis and hypertension related arterial sclerosis. Review of the immunofluorescence did not reveal any staining for immunoglobulins, complement, or light chains. This biopsy was most consistent with necrotizing vasculitis. A prednisone taper was initiated for presumed allopurinol induced necrotizing vasculitis. The patient had improvement of kidney function and was subsequently discharged without requiring kidney replacement therapy.

**Discussion:** Rash is a known adverse effect of allopurinol therapy, and the majority of these cutaneous reactions improve with discontinuation of allopurinol therapy. The risk of severe adverse reactions is increased in patient of African, Korean, Chinese or Thai ancestry due to the high incidence of individuals who carry the HLA-B*5801 variant allele. Allopurinol-associated renal necrotizing vasculitis is likely a presentation of this type of severe hypersensitivity reaction. Upon initiation of allopurinol, especially the patients at high risk of cutaneous reactions should be counseled regarding this risk and instructed to promptly discontinue the medication and inform the treating provider if a rash is present.

**FR-PO204**

Tubulointerstitial Nephritis and Uveitis Syndrome (TINU)


**Corewei Health, Royal Oak, MI.**

**Introduction:** Tubulointerstitial Nephritis and Uveitis Syndrome (TINU) is a rare, self-limiting interstitial nephritis and bilateral anterior uveitis. Here, we describe an interesting case of TINU.

**Case Description:** A 42-year-old woman with no significant medical history presented to the hospital with acute kidney injury (AKI). She was noted to have elevated creatinine (Cr) of 2.2mg/dL with a baseline of 0.7-0.9mg/dL. Urinalysis was positive for blood (3+) and protein (30 mg). She reported using naproxen for menstrual cramps. She was found to have an sCr of 2.2 mg/dL, an estimated glomerular filtration rate (eGFR) of 32 mL/min/1.73 m², and a urinary sediment revealing 4+ proteinuria and 3+ hematuria. She was initiated on allopurinol therapy for gouty arthritis.

**Discussion:** Recognizing the clinical presentations of rare diseases like ANCA associated vasculitis may help clinicians diagnose and promptly initiate of immunosuppressive therapy while awaiting kidney biopsy. This may yield better kidney prognosis.
Jones' silver stain 200x: Glomerulus demonstrating breaks in the GBM with associated fibrinoid necrosis.

FR-PO207
Weil Disease as a Cause of Electrolyte Wasting and AKI
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Introduction: Leptospirosis is a spirochetal illness that can manifest as a severe syndrome of Weil’s disease, characterized by oliguric AKI, liver injury, jaundice, anemia, thrombocytopenia, rhabdomyolysis and pulmonary edema. AKI in Weil’s disease is multifactorial, resulting from direct action of spirochetes on renal tissue, rhabdomyolysis, ATN and AIN.

Case Description: A 67-year-old woman from Haiti residing in the Boston area presented with lower extremity myalgias and weakness. Physical exam revealed several icterus and 4/5 muscle strength in the proximal lower extremities. She was found to have oliguric AKI with creatinine of 5.9 mg/dL, potassium of 4.3 mEq/L, phosphorus of 1.3 mg/dL and calcium of 8.2 mg/dL. LFT abnormalities included ALT 187 IU/L, AST 278 IU/L, total bilirubin 10.6 mg/dL and direct bilirubin 9.5 mg/dL. CPK was elevated at 3439 IU/L. CIBC was remarkable for white blood cell count 19.8 K/uL, hemoglobin 8.9 g/dL, platelet count 23 K/uL. Reticulocyte count was low at 0.3% with haptoglobin 364 mg/dL and LDH 313 IU/L. INR and PT were normal. ANA was negative. U/A revealed 1+ glucose, 3+ blood and 3+ protein (quantified at 4.7 g/g) with 10-15 isomorphic RBC/lpf, few granular casts and several renal tubular epithelial cells on microscopy. Infectious Diseases was consulted, and initially had low pre-test probability for infection given that the patient was afebrile and had been living in Massachusetts for 6 months, however recommended testing for leptospirosis, Dengue, chikungunya and tick-borne diseases. Leptospira IgM returned positive with high titer of 12,800 for L. interrogans on MAT confirmatory testing. The patient was diagnosed with Weil’s disease and was treated with ceftriaxone with normalization of laboratory parameters and symptoms.

Discussion: This patient’s presentation of oliguric AKI with relatively preserved potassium and hypophosphatemia is characteristic of leptospirosis-associated renal injury, which is often preceded by electrolyte wasting that is thought to result from leptospire-induced changes in expression of tubular transport proteins along the nephron. It is important to maintain a high index of suspicion for leptospirosis in patients with AKI and evidence of electrolyte wasting, and in patients who present with direct hyperbilirubinemia out of proportion to other LFT abnormalities, even in the absence of exposure and recent travel history.

FR-PO208
Putting the Pieces Together: A Multifaceted Elevation in Creatinine
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Introduction: Goody Powder is OTC medicine containing aspirin, caffeine, and acetaminophen. When taken in excess and combined with alcohol it can induce undesirable elevations in blood pressure that can exacerbate renal dysfunction in an already compromised kidney. It can also cause severe gastric irritation with the risk for gastrointestinal bleeding. GI bleed could lead to blood loss, uremia, and dehydration. Furthermore, caffeine and alcohol exhibit diuretic properties intensifying dehydration and exacerbate AKI through the reduction of blood volume. Although aspirin and alcohol have been linked to kidney damage, there are few case reports demonstrating the rapid progression to ESRD.

Case Description: A 33-year-old African male BMI 37 and no reported PMH presented with complaints of fatigue, generalized weakness, nausea, vomiting, and diarrhea x 1 month. Reported daily episodes of vomiting with intermittent hematemesis. He also complains of dizziness, abdominal pain, decreased urine output. He denies fever, chills, chest pain, or dysuria. The patient also reports prior heavy drinking with multiple alcoholic beverages/day till recently, and combining it with Goody powders for his abdominal pain. BP 175/88, HR 96. Lab Na 131, K 6.0, bicarb 238, creatinine 50, and eGFR 1, Hb 6.6. The patient was admitted for further workup where electrolytes were replenished, his hypertensive emergency was appropriately controlled, and he underwent dialysis. A renal biopsy demonstrated accelerated hypertension as one of the prime causes for his renal failure.

Discussion: Even though Goody Powders’ controlled use is generally safe, its combined use with alcohol possibly accelerated the progression to ESRD in our patient. This patient possibly had baseline CKD due to uncontrolled hypertension that was never controlled but in the setting of above, he progressed to ESRD rather quickly. Also, he had concurrent hemolysis secondary to severe hypertension on top of potential GI bleed. It is important to note that combining caffeine with alcohol can have contradictory CNS manifestations especially when uremia sets in. Therefore, timely identification of metabolic abnormalities along with prompt management is crucial. Patient education should be emphasized to avoid prior behaviors and to avoid further damage.

FR-PO210
Acute Hyperoxaluria in Setting of Hereditary Spherocytosis Presenting as a Rapidly Progressive Glomerulonephritis (RPGN)
Barbara C. Mcmullen, Anna M. Burgner. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Hereditary spherocytosis (HS) is the most common inherited hemolytic anemia. Characteristic symptoms include anemia, jaundice, and splenomegaly. Clinical severity is variable with most remaining well compensated. Common complications include cholelithiasis, hemolytic episodes, and aplastic crisis. Despite causing hemolytic anemia, kidney injury is rarely associated with this disease.

Case Description: A 12-year-old female with HS developed hemolytic crisis and AKI and was aggressively resuscitated. She had evidence of a rapidly progressive glomerulonephritis (RPGN) by labs, see Table 1. She was treated empirically with steroids and underwent kidney biopsy on hospital day 5. Biopsy results showed diffuse calcium oxalate crystals with minimal glomerular injury, see figure 1. Day 1 post biopsy

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she required dialysis for metabolic derangements. With normalization of electrolytes and clearance of oxalate, she was able to cease dialysis with excellent kidney recovery.

Discussion: The source of acute oxalosis was unknown. Erythrocytes carry oxalate but intact red blood cells do not increase risk of crystal formation. Red cell membrane fragments have been shown to promote oxalate crystal growth and aggregation up to 2.5-fold. However, she had a history of prior hemolytic episodes without AKI or nephro lithiasis. We ruled out causes of oxalate including history of bariatric surgery and ethylene glycol poisoning. We learned that 2 days prior to admission she had received an infusion containing 2500mg vitamin C (Myers cocktail). We postulate that hypervitaminosis C in setting of hemolytic anemia caused acute oxalate crystal deposition with subsequent kidney failure. Various infusions have become readily available with minimal medical oversight, thus history taking remains paramount to patient care.

Red – RRT day

Diffuse tubular injury with oxalate crystal deposition and focal hemosiderin tubulopathy

FR-PO212

Intraperitoneal Urinary Leak Presenting as Severe AKI After Robotic-Assisted Laparoscopic Radical Prostatectomy (RALRP)

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Introduction: About one in five hospitalizations is complicated by AKI, and patients with urological diseases are at higher risk of developing AKI but severe AKI is a rare event after prostate surgery. We present a unique case of AKI following RALRP.

Case Description: A 60-year-old male with hypertension, type 2 diabetes, prostate cancer and normal kidney function at baseline, presented with severe lower abdominal pain six days after RALRP. His surgical drains were removed a day prior to presentation, but his urinary catheter was maintained. Abdominal exam revealed a tender right lower abdomen and clean surgical sites. He was afebrile, blood pressure was 149/86 mmHg, and pulse was 94 beats/minute. A non-contrast abdominopelvic computed tomography (CT) showed a pelvic hematomata to the right of the urinary bladder with small locules of gas. There was also a lower density fluid collection in the surgical bed. His serum creatinine was 1.72 mg/dL, potassium was 4.2 mEq/L, and blood urea nitrogen was 22 mg/dL. Hemoglobin was 10 g/dL. WBC, platelet count, creatinine kinase and coagulation profile were all within normal limits. Urinalysis was positive for blood, but negative for infection. The patient had worsening abdominal distension and pain and an abdominal ultrasound showed a new development of moderate ascites. At that time, patient also had doubling of his serum creatinine to 4.21 mg/dL while maintaining adequate urine output. Abdominal paracentesis performed in the left lower quadrant aspirated 2 liters of bloody fluid. Analysis of the peritoneal fluid showed creatinine of 10.4 mg/dL. A CT cystography confirmed a vesicourethral urinary leak with expansion into the peritoneal cavity. A pelvic drain was placed, resulting in normalization of serum creatinine and resolution of abdominal ascites.

Discussion: RALRP has become the dominant surgical approach for radical prostatectomy in the United States. Vesicourethral urinary leak is a common complication following RALRP, but the reported incidence of expansion of those leaks into the peritoneum was 1% and <0.5% required CT-guided drainage. Our case is unique given the acute presentation of severe non-oliguric AKI after RALRP with development of ascites after removal of the surgical drain resulting in pseudo-AKI from increased creatinine absorption through the peritoneal membranes.
AKI: Mechanisms - Case Reports

Poster/Friday

FR-PO214
AKI and Hypercalemia: A Complicated HIV Story
Yara Bilan, Ali Mehdi, George Thomas, Dania Salih Bacha, Michael W. George, Cleveland Clinic, Cleveland, OH.

Introduction: HIV causes kidney injury through direct viral effects, antiviral therapies, immune reconstitution, and superimposed infections. We report a case of kidney dysfunction in the setting of HIV/AIDS and disseminated mycobacterial avium complex (MAC) infection.

Case Description: A 23-year-old male with history of HIV/AIDS was admitted with acute kidney injury (AKI) and hypercalemia (hyperCa) after outpatient evaluation for failure to thrive and lymphadenopathy. Creatinine peaked at 2.48mg/dL from a baseline of 0.8. HyperCa and hyperphosphatemia were noted at 13.5 and 5.2mg/dL respectively. Urinalysis showed 2+ protein with a UPCR of 0.6. Sediment analysis revealed mucky brown casts. Kidney US showed non-obstructing renal calculi without hydronephrosis. Workup showed low PTH levels, 25-OH Vitamin D of 26.8ng/mL (nl 30-80) and 1,25-Dihydroxyvitamin D of 58.4pg/mL (nl 19.9-79.3). PTHrP was elevated at 4.1pmol/L (nl 0.2-3). Per chart review, patient had a diagnosis of disseminated MAC and a recent kidney biopsy that showed acute on chronic interstitial nephritis. At that time, his AKI was attributed to MAC and antibiotics were started. Subsequently, patient had worsening adenopathy concerning for lymphoma, but a follow up biopsy could not be obtained. His symptoms were suggestive of uncontrolled MAC so the antibiotics and HIV therapy were adjusted. His AKI was thought to be related to the hyperCa which in turn was hypothesized to be related to the granulomatous infection due to activated vitamin D. The elevated PTHrP remained of concern. The hyperCa was managed with IV fluids and pamidronate. Patient was discharged on optimized HIV and MAC therapy with improvement of calcium level and kidney function. 9 months after admission, creatinine was down to 1.23 with a calcium of 9.7.

Discussion: HyperCa is a rare but potentially serious complication of disseminated MAC infection, with incidence ranging from 5 to 20%. The mechanism is thought to be due to increased 1-alpha hydroxylase expression in activated macrophages. A similar mechanism explains hyperCa seen with lymphomas. In the setting of HIV in general, and AIDS particularly, hyperCa should trigger an in-depth evaluation for an underlying granulomatous or lymphomatous disorder. Improvement generally follows treatment of the underlying pathology.

FR-PO215
Nivolumab-Induced Acute Interstitial Nephritis
Zaid A. Elkarni, Tina Kochar, Muhammad Rawala, Alokiya Patel. The University of Texas Medical Branch at Galveston, Galveston, TX.

Introduction: Nivolumab, an anti-programmed death – 1 (PD-1) monoclonal antibody, is an immune checkpoint inhibitor that has recently been approved for use as treatment for various cancers including melanoma, renal cell carcinoma, non-small cell lung cancer and squamous cell carcinoma. However, immune checkpoint inhibitors have been linked to a different array of immune related side effects affecting dermatological, gastrointestinal, endocrinological, hematopoietic, and renal systems. There have been a few documented occurrences of nephrotoxic side effects.

Case Description: We present a case of a 73-year-old male patient who was diagnosed with clear cell renal cell carcinoma with extensive necrosis, lung metastasis and renal vein thrombosis in 08/2021. The patient was started on Cabozantinib chemotherapy with initial good response. The patient was started on Nivolumab in 01/2023 in combination with lower dose of Cabozantinib as the response to cabozantinib was suboptimal. Two months after starting Nivolumab the patient was admitted with c/o right flank pain. He was found to have evidence of acute kidney injury (AKI). BMP showed a creatinine of 7.21 mg/dL, BUN 57, Na 134 mg/dL, K 5.7 mg/dL. Urinalysis showed 30 mg / dl proteinuria, 4+ albumin, +1 blood, and urine spot protein to creatinine ratio was 1 gm / gm. CBC revealed a normal white blood cell count and no eosinophilia. Soon after admission the patient developed urticarial symptomatology and had to be initiated on Hemodialysis and a renal biopsy was planned. Renal biopsy report was consistent with signs of acute interstitial nephritis with associated tubulitis, normal appearing glomeruli, negative immunofluorescence, and minimal intimal fibrosis. The patient was started on intravenous methylprednisolone 2 mg / kg for a total of 3 days followed by oral prednisone 1 mg / kg. Kidney function slowly improved and stabilized after 2 weeks with a creatinine of 4.4 mg / dl with no need for further hemodialysis sessions.

Discussion: It is challenging to differentiate between cases of AIN versus acute tubular necrosis (ATN), which occur commonly in patients with cancer. The following case report highlights AIN as a cause of AKI in patients receiving Nivolumab and how good clinical judgement along with timely intervention can lead to reversal of dialysis dependent AKI

FR-PO216
Giant Abdominal Aortic Aneurysm (AAA): A Rare Cause of Obstructive Nephropathy
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Introduction: Obstructive nephropathy (ON) accounts for 5-10% of all cases of AKI. The most common causes include benign prostatic hyperplasia, kidney stones or malignancy. Only few cases have been reported of ON caused by a large abdominal aortic aneurysm (AAA) producing ureteral compression. We present the case of a patient whose severe renal failure only became evident after presenting to the hospital with impending AAA rupture.

Case Description: A 72-year-old male with long-term tobacco use and no medical care for >15 years presented with abdominal pain and dyspnea. He denied any fever, chills, nausea, vomiting, diarrhea, or poor oral intake. In ED, blood pressure was 163/93, but otherwise stable. Blood work showed a creatinine 14.0 mg/dL, BUN 149 mg/dL, K 5.3 mmol/L, CO2 6 mmol/L, anion gap 29, and normal LFTs. CT without contrast revealed an impending aortic rupture with aneurysmal dilation measuring 8.6 x 10.6 cm in axial diameter causing severe right-sided hydronephrosis and mildly atrophic left kidney. Dialysis was initiated for optimization of acid-base status for emergent endovascular repair. The next day he underwent percutaneous stent graft repair and had a right nephrostomy tube placed resulting in complete resolution of right hydronephrosis. Urine output improved, however, clearance was still impaired so dialysis was restarted and continued without adequate renal recovery.

Discussion: AAA is a rare and potentially fatal cause of ON. AAAs larger than 8 cm carry an annual rupture risk of 30-50%. Once this occurs mortality risk is extremely high, making emergency surgery the only alternative. Our patient’s case posed an added level of complexity as he was found to have acute renal failure requiring emergent dialysis for pre-op optimization. Although exceedingly rare, it is important to keep in mind aortic aneurysms as a cause of ON with the major difference from most other causes being the critical role prompt treatment plays in patients’ survival.

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Underline represents presenting author.
Point-of-Care Ultrasound (POCUS) in Metastatic Ovarian Carcinoma: FR-PO218

Image 1. Diagnosis of IgG4-TIN is challenging without the presence of other extra-renal manifestations of IgG4-RKD. Kidney biopsy revealed diffuse interstitial fibrosis and tubular atrophy involving 90% of the cortical parenchyma, and immuno-labeling showed diffuse IgG4-positive plasma cells in the interstitium with 17-31 cells/HPF in most concentrated areas (Image 1).

Discussion: Tubulointerstitial nephritis (IgG4-TIN) is the most common renal manifestation of IgG4-RKD, it may present as acute or chronic renal insufficiency. Diagnosis of IgG4-TIN is challenging without the presence of other extra-renal manifestations of IgG4-RKD. Focal glomerulosclerosis should be considered in TIN with presence of plasma cell infiltrates. To the best of our knowledge, this case is first to be reported in literature for isolated IgG4-TIN. Greater clinical awareness of this entity will lead to early diagnosis and early intervention.

FR-PO219

Severe Hypothyroidism May Contribute to AKI but Not Hyponatremia: A Case Report
Nicholas J. Carballo, Swetha Rani Kanduri. Ochsner Health, New Orleans, LA.

Introduction: Hypothyroidism is commonly encountered in patients with chronic kidney disease but rarely contributes to acute kidney injury. Majority of the published cases of acute kidney injury (AKI) have associated rhabdomyolysis secondary to severe hypothyroidism. In addition, hypothyroidism work up is typically included as a standard practice in the etiology of hyponatremia. Herein, we report a severe case of hypothyroidism resulting in AKI without associated rhabdomyolysis or hyponatremia.

Case Description: An 89-year-old woman presented to emergency department with a chief complaint of left-sided hip pain following mechanical fall. Review of systems positive for fatigue and constipation. Medical history was pertinent for CKD IIIb, hypothyroidism and hypertension. Physical examination revealed persistent bradycardia (HR 30-50 bpm) and 2+ bilateral lower extremity edema. Telemetry additionally demonstrated intermittent sinus pauses. Laboratory data at the time of admission revealed serum creatinine (Scr) of 1.8 mg/dL (baseline 1.3 mg/dL), thyroid stimulating hormone (TSH) of 298 IU/mL, free T3 < 0.40 ng/dl and total T4 < 40 ng/dl, creatinine phosphokinase (CPK) was 404 U/L and serum sodium was 136 mmol/L. Urine analysis consistent with 1+ protein, no blood and urine sediment notable for waxy and granular casts. Urine protein:creatinine ratio (UPCR) was 0.28 mg/dL and a kidney ultrasound revealed a 3.8 cm cyst in the left parenchyma. She was started on IVF resuscitation and was started on empirically on plasma exchange pending her ACAT level. The patient was discharged with daily furosemide for symptom management and volume status optimization.

FR-PO220

An Atypical Case of Typical Hemolytic Uremic Syndrome (HUS) Mark N. Massoud, Gurbir S. Schmby, Josephine Abraham. University of Utah Health, Salt Lake City, UT.

Introduction: Typical hemolytic uremic syndrome (HUS) is a rare cause of thrombotic microangiopathy in adults. Predominantly a pediatric disease, typical HUS is caused by Shiga toxin producing Escherichia Coli. We present the case of an adult with typical HUS.

Case Description: A 60 year old woman with history of type 2 Diabetes Mellitus and no kidney disease was admitted to the ICU with a 5 day history of nausea, vomiting and bloody diarrhea. Her workup revealed colitis with sepsis, AKI, and thrombocytopenia. Platelet count was 61,000/mL and plummeted to 31,000/mL during the course. Serum creatinine on admission was 2.8 mg/dL and peaked to 6.0 mg/dL with progression to anuric renal failure over 3 days. Hemoglobin dropped from 16.9 g/dL on admission to a nadir of 6.6 mg/dL over 6 days requiring RBC transfusion. Features of non immune hemolytic anemia were detected including low haptoglobin level (<1 mg/dL), elevated LDH level of 2301 IU/L and negative Coombs’ test. Peripheral smear was notable for schistocytes. DIC panel with coagulation studies and fibrinogen levels were normal. The patient received IVF resuscitation and was started on antibiotics with IV ceftriaxone and metronidazole. Shortly after admission she developed severe and required intubation. She received hemodialysis for renal failure. The combination of MAHA, thrombocytopenia and AKI warranted consideration for TTP. ADAMTS 13 level was ordered and the patient was started empirically on plasma exchange pending ADAMTS 13 level. Urine microscopy showed extensive granular casts. ADAMTS 13 came back normal (45%) and plasma exchange was discontinued. Sheiga toxin-producing E Coli PCR was positive in the stools. Renal function improved and dialysis discontinued after 3 sessions. Thrombocytopenia completely resolved with improvement in anemia and a creatinine at discharge of 3.42 mg/dL.

Discussion: Typical HUS caused by shiga-like toxin producing enteric organisms is most commonly encountered in children but can affect all ages and should be suspected when a patient presents with bloody diarrhea, MAHA, thrombocytopenia, AKI and neurological symptoms. The differential should always include TTP and empiric plasma exchange should be pursued while awaiting ADAMTS 13 levels as delaying treatment for TTP could be devastating. It is important to note that AKI, especially severe, is not a prominent feature of TTP and should warrant consideration of alternative diagnosis.
Oliguric AKI Developed After Toxic Ingestion of Tribulus/Drug-Induced Liver Injury (DILI)

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Introduction: Liver disease is associated with multiple mechanisms of acute kidney injury (AKI). Bile cast nephropathy is a relatively rare (but potentially underdiagnosed) cause without great treatment options. Also, many non-tested supplements are available and may be used—some which may have a toxic effect on the kidneys and lead to AKI.

Case Description: A 46 year old male with AFib, bipolar disorder, and normal baseline kidney and liver function was admitted with severe cholestatic liver injury and developed an oliguric AKI. He had 5 weeks of progressive jaundice, fatigue, weight loss, and poor oral intake. Total bilirubin peaked at 48.5 mg/dL. Liver biopsy was consistent with drug induced liver injury suspect to be from a supplement obtained on Amazon called Tribulus used a “testosterone booster”. Kidney function consistently worsened after admission as the patient became nearly anuric. Urine Na 62 meq/L and multiple reviews of the urine sediment showed bile casts without other granular casts. Kidney biopsy was deferred due to patient preference. Patient’s mental status worsened and hemodialysis was initiated for potential uremic symptoms. Workup was initiated for potential liver transplantation. In an attempt to decrease inflammatory mediators contributing to liver disease, plasmapheresis was started which also had the effect of significantly reducing the serum bilirubin level. urine output drastically improved after plasmapheresis and no further hemodialysis sessions were needed as renal function recovered. Liver function also improved with supportive care.

Discussion: This case demonstrates a severe oliguric AKI in the setting of Tribulus ingestion and DILI with eventual recovery that was caused most likely by one of two mechanisms: 1. Direct tubular damage due to toxic drug effects or 2. Bile cast nephropathy. that interesting may have resolved after plasmapheresis significantly decreased the serum bilirubin level. Further investigation into the toxic effects on renal tissue from the over the counter supplements is warranted. It is unclear if improvement in renal function was the direct result of plasmapheresis—though if the clinical findings are highly concerning for bile cast nephropathy in a severe AKI, plasmapheresis may be considered to lower serum bilirubin and potentially improve renal function when AKI is caused by bile cast nephropathy.

FR-PO222

Bartonella Endocarditis-Associated Glomerulonephritis Presenting as Acute Renal Failure

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Introduction: Acute kidney injury (AKI) in the setting of mitral valve endocarditis is often due to cardiac tamponade secondary to mitral valve regurgitation. We report a case of acute renal failure caused by Bartonella endocarditis-associated glomerulonephritis.

Case Description: A 28-year-old man from Nicaragua with a history of mitral valve replacement presented with left arm weakness. Brain MRI revealed a subacute right parietal lobe infarct. TTE and TEE showed thickened mitral valve leaflets and a high transvalvular pressure gradient, consistent with prostatic valve endocarditis. Empiric antibiotics were initiated. Cultures remained negative throughout admission. On hospital day (HD)13, Bartonella henselae IgG was >1:25600, and antibiotics were changed to rifampin and doxycycline. Creatinine on admission was 1.3 baseline 0.8) and stabilized at 1.1. On HD13, the patient’s Cr uptrended to 1.5. Concurrently, he developed acute hypoxic respiratory failure with evidence of volume overload, initially thought to be cardiorenal syndrome and the patient was diuresed. Despite reaching euvalucemia, his Cr continued to uptrend to 6.4. UA with moderate hematuria and proteinuria. 24-hour protein was 1.3g. FeUrea was 47% which was less consistent with pre-renal AKI and prompted an intrinsic AKI workup. Results notable for positive ANA, low C3 and C4, and positive PR3, which led to the clinical diagnosis of infectious glomerulonephritis. Renal biopsy to confirm the diagnosis was deferred in favor of definitive treatment with mitral valve replacement. The patient’s creatinine improved to 2.9 after surgery, and he was discharged with a presumed diagnosis of C3-mediated Bartonella glomerulonephritis. He continued 3 months of doxycycline and 6 weeks of rifampin and his creatinine normalized within 2 weeks of discharge.

Discussion: Acute renal failure in the setting of endocarditis can be multifactorial, and it can be challenging to determine the etiology. The concomitant development of respiratory failure, valvular dysfunction, and acute renal failure was initially compelling and it can be challenging to determine the etiology. The concomitant development of AKI: Mechanisms - Case Reports

FR-PO224

Thrombotic Microangiopathy from Chafing Fuel Intoxication

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Introduction: Diethylene glycol (DEG) is widely used as an industrial diluent in chafing fuel, brake fluids, wallpaper strippers etc. Mass poisonings with high fatalities have been reported. Here we report a rare and unusual case of Thrombotic Microangiopathy (TMA) in a patient who ingested chafing fuel.

Case Description: A 58-year-old male with alcohol use disorder presented with 5 days of vomiting, diarrhea and altered mental status. His wife reported severe alcohol cravings and ingestion of hand sanitizer (isopropyl alcohol) and chafing fuel (DEG). He was anuric with creatinine of 8.2, a pH of 6.87, bicarb of 2 mmol/L, anion gap of 44 and osmolal gap of 45. Toxicology screen was negative. He was admitted to the intensive care unit for emergent hemodialysis. Hemodialysis was continued as there was no evidence of renal recovery. He then developed hypertension and thrombocytopenia. Peripheral smear was without schistocytes, LDH was elevated and haptoglobin was low. C3 was mildly decreased. C4, CH50, HIT antibody panel and ADAMTS13 activity were within normal limits. A kidney biopsy was performed on day 5 (see figure) which showed thrombotic microangiopathy and diffuse acute tubular injury. On day 6, he developed severe neurological defects including slurred speech, facial droop and progressive cranial neuropathies. He required mechanical ventilation for airway protection. He failed an empiric trial of steroids and expired on day 19.

Discussion: AKI in DEG toxicity is linked to high mortality rates and dialysis dependency. Typical Kidney biopsy lesions are extensive necrosis of the proximal tubule, severe interstitial hemorrhage and hyaline casts. In our case, TMA can be attributed to DEG in the absence of other causes. Vascular injury from necrotic glomeruli or direct endothelial injury from DEG are possible mechanisms. In DEG poisoning, TMA should be considered as a potential life-threatening complication.
FR-PO226
Lysozyme Nephropathy: A Rare Cause of Progressive Kidney Disease
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Introduction: A progressive decline in renal function with sub-nephrotic proteinuria in a diabetic is usually attributed to DKD. Lysozyme nephropathy is a rare cause of progressive decline in renal function with only a few underreported cases in the literature mostly in patients with hematological malignancy. AKI is seen in one-third of patients with hematological malignancy and has a negative impact.

Case Description: An 84-year-old male with stage 4 chronic kidney disease, type 2 diabetes mellitus, and chronic anemia on ESA was admitted with an upper GI bleed. He had hemorrhagic shock leading to acute tubular injury. Urinalysis showed trace protein with no RBCs on the microscopic sediment exam. A senologic workup was negative except for positive ANA and hepatitis B surface antibody, which had been previously negative. He had anemia and severe leukocytosis (WBC > 65 K/mm3). His kidney function gradually improved over 2 weeks. Following hospital discharge, the patient was readmitted with worsening kidney function and a high anion gap metabolic acidosis. The urine sediment showed granular casts. A kidney biopsy was performed, which showed moderate (30-40%) tubulointerstitial scarring and patchy proximal tubular degenerative changes, consistent with acute and chronic tubulointerstitial nephropathy. Refractory, hypertensive, intracytoplasmic protein droplets were noted in the proximal tubular cells, which showed immunohistochemical reactivity for lysozyme. Immunofluorescent staining for kappa and lambda was negative.

Discussion: Lysozyme, also called muramidase, is a basic, cationic protein, primarily produced by monocytes/macrophages, salivary gland acinar cells, Paneth cells, and other cell types. Lysozyme is filtered by the glomerulus and reabsorbed by the proximal convoluted tubule where tubular injury occurs. Lysozyme nephropathy is seen with myeloid leukemias, myeloproliferative, myelodysplastic disorders, granulomatous disease, inflammatory bowel disease, and malignancy. This patient had leukocytosis with myelocytes on the smear which might have reflected underlying hematologic malignancy. A diagnostic evaluation was deferred as he was not a candidate for therapy based on age and comorbidities. Subsequently, his kidney function continued to decline. He opted for conservative management of end-stage kidney disease and hospice care.

FR-PO227
Thrombotic Microangiopathy from Metastatic Signet Ring Cell Carcinoma
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Introduction: Thrombotic microangiopathy (TMA) as a paraneoplastic syndrome is rare and outcomes can be devastating. We present a case of TMA as an initial presentation of metastatic signet ring cell carcinoma (SRCC).

Case Description: Our patient is a 36-year-old female with a history of type 2 diabetes mellitus who presented with 3 weeks of dyspea, cough and hemoptysis, then respiratory failure requiring intubation. Chest CT scan showed bilateral parenchymal mosaic attenuation. Her hemoglobin and platelets decreased to 7.8 g/dL and 68,000/µL, respectively. Other work up include: MCV 82.1, WBC 13,100/µL, LDH 18, 238 U/L, haptoglobin <10 mg/dL, Coomb's negative, schistocytes on peripheral smear, fibrinogen 80 mg/dL, prothrombin time 12.2, aPTT 40 seconds, potassium 8.4 mmol/L, creatinine 2.61 mg/dL, bicarbonate 9 mmol/L and lactate 19.1 mmol/L. She received FFP, PRBC and platelets. AKI with urea > 80 mg/dL was diagnosed and patient was initially treated with hemofiltration which was subsequently changed to plasmapheresis immediately. She was anuric and required CRRT. Despite the transfusions, her hemoglobin and platelets worsened at 5.3 mg/dL and 19,000/µL. She developed diffuse guttate and critical limb ischemia. After the 3rd hospital day, she was no longer on comfort measures only. The autopsy showed metastatic poorly differentiated colon adenocarcinoma with signet-ring cell component, with diffuse bone marrow involvement.

Discussion: The management of secondary TMA, such as DIC, pre-eclampsia, severe hypertension, are focused on the underlying cause. Metastatic carcinoma with bone marrow involvement can be an obscure differential and can prove fatal if undetected. The mechanism of how TMA occurs is not clear but there may be a role in mucin production from the signet ring cell subtype which causes endothelial cell dysfunction and thus causing thrombus formation. Bone marrow involvement generates abnormal angiogenesis that damages blood vessels in a similar fashion to ulcerative and Pseudomonas sepsis. This leads to ultrasound findings of metastatic carcinomas, which has been implicated in the pathogenesis of MAHA. Metastatic malignancies have been misdiagnosed as TTP as does not respond to plasmapheresis, had more respiratory symptoms and higher LDH. TMA as a paraneoplastic syndrome ultimately requires prompt chemotherapy and/or resection. Mucin producing tumors have been reported to present initially as TMA but by the time the diagnosis is made, it has widely metastasized and prognosis is notably poor.

FR-PO228
Metformin-Associated Lactic Acidosis: A Mimicker of Acute Mesenteric Ischemia
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Introduction: Metformin-associated lactic acidosis (MALA) is a rare life-threatening complication of metformin. Metformin is renally excreted with a major precipitating factor for MALA being acute kidney injury (AKI). The clinical presentation of MALA is similar to that of acute mesenteric ischemia though imaging is usually negative. Here we present a case of MALA masquerading as acute mesenteric ischemia and intra-abdominal sepsis.

Case Description: A 52-year-old female with a history of HTN, Type 2 DM on metformin, CKD of unclear baseline presented with vomiting, poor oral intake, and abdominal pain for 2 days with finger-stick glucose of 35 mm/dL. She denied fever, chills, urinary symptoms, diarrhea, or overdose of metformin. Her initial vitals were T 95.6 degree Fahrenheit, BP 171/96, HR 91, RR 16, and SpO2 100% on room air. The physical examination showed only dry oral mucosa. Laboratory values were significant for potassium 6.8 meq/L, serum creatinine 7.9 mg/dL, blood urea nitrogen 49 mg/dL, glucose 49 mg/dL, bicarbonate 5.0 meq/L, anion gap 45.9 meq/L, venous blood gas with pH 7.0, PCO2 21 mmHg, lactate <17 mmol/L, white blood cell 17.7 xL. CT of the abdomen showed thickened small bowel loops and a questionable single loop of small bowel with pneumatisis. The patient was admitted for sepsis in the setting of presumed ischemic bowel. However, the surgery service discounted this diagnosis as they felt that there was no pneumatosis upon their review and that the thickened loops of bowel can be due to enteritis. She was empirically treated with intravenous piperacillin/tazobactam. Given AKI and severe lactic acidosis, a metformin level was sent. The patient was treated with 2 sessions of hemodialysis. When blood and urine cultures returned negative, antibiotics were discontinued. Her renal function improved to a serum creatinine of 1.6 mg/dL 2 weeks later, at which time the metformin level returned to be elevated at 27 mg/cL. Finally, her creatinine level was 1.2 mcg/ml.

Discussion: Our case highlights that MALA can be confused with ischemic bowel on clinical presentation with abdominal pain, lactic acidemia and suggestive CT findings of pneumatosis intestinalis. Thus, high clinical suspicion and prompt treatment with renal replacement therapy is needed to avoid unnecessary surgery even without resulted metformin levels.

FR-PO229
Severe Hypothyroidism Presenting as Rhabdomyolysis and Acute Tubular Necrosis

Introduction: Hypothyroidism often manifests with a broad range of muscular symptoms: cramping, generalized weakness, and diffuse myalgias. Rhabdomyolysis is a rare manifestation of severe hypothyroidism resulting in profound acute tubular necrosis
via myoglobin induced renal vasoconstriction, proximal tubule necrosis, and distal tubular obstruction. We present a case of acute tubular necrosis caused by rhabdomyolysis secondary to severe hypothyroidism.

**Case Description:** A 62-year-old female with past medical history of coronary artery disease, type II diabetes mellitus and hypothyroidism presented with fatigue, shortness of breath, fifteen pound weight gain and decreased appetite for a month. She reported myalgias and non-compliance with oral synthroid for seven months. Vital signs revealed normothermia without bradycardia. Physical exam was unremarkable. Laboratory work revealed elevated creatinine kinase (CK) 59.952 U/L, creatinine 6.37 mg/dL (baseline 0.8-1), very low free T4 -0.1 and very high TSH >1000. Urimaysis was positive for blood with minimal red blood cells, and urine sediment revealed granular casts. Treatment with intravenous fluids and synridhod significantly improved the TSH (75.9 mIU/L) and CK (10,791 U/L) on admission day ten. Renal function slowly improved over the hospitalization course with serum creatinine trend 6.37 mg/dl to 3.8 mg/dl on discharge with concurrent non-oliguric urine output. She was discharged home with oral thyroid hormone replacement therapy. She demonstrated complete renal recovery on outpatient follow up with serum creatinine 0.72 mg/dl, normal CK levels 31 U/L and thyroid function panel (TSH 0.97, free T4 1.5).

**Discussion:** The precise mechanism of hypothyroidism-induced rhabdomyolysis is unclear, however, it is thought to be related to impaired glycogenolysis or mitochondrial oxidation. This case is unique as there are no previously reported instances of patient sustaining such severe hypothyroidism-induced rhabdomyolysis (serum CK 400K upper limit of normal), and ATN in the absence of underlying chronic kidney disease. Therefore, prompt diagnosis, identification of causative factor, and timely treatment are crucial to prevent long-lasting renal injury in this disease. It also emphasizes medication compliance, patient education, and considering hypothyroidism in the differential diagnosis of rhabdomyolysis for improved patient outcomes.

**FR-PO230**

### Oxalate Nephropathy: A Studied Case of AKI

**Introduction:** Oxalate nephropathy (ON) is a rare manifestation of hyperoxaluria which can present as acute kidney injury (AKI) with the possibility of rapid progression to end stage kidney disease. We present a case of AKI with ON on biopsy.

**Case Description:** A 64-year-old male with obesity, type 2 diabetes mellitus and hypertension presented with nausea and unsteady gait. He has AKI with a serum creatinine (Cr) of 9.4 mg/dL on admission with a baseline Cr of 0.8 mg/dL 3 months prior. Clinical history did not reveal a cause for AKI. Urine studies showed the occasional granular cast but no dysmorphic RBCs, proteinuria or pyuria. Serological workup including antinuclear antibody, anti-neutrophilic cytoplasmic antibody, and serum monoclonal testing were unremarkable. He underwent kidney biopsy due to inadequate improvement of renal function with intravenous fluids. Kidney biopsy (Figure 1) showed widespread calcium oxalate deposition in the tubules (renal oxalosis) with associated mild acute tubular injury and mild interstitial nephritis. Genetic testing did not show a known mutation associated with Primary Hyperoxaluria.

**Discussion:** Primary Hyperoxaluria is due to a genetic defect leading to abnormal oxalate handling. Secondary Hyperoxaluria (SH) occurs due to excessive dietary oxalate intake and/or gastrointestinal disorders that increase absorption of oxalate or oxalate precursors, such as inflammatory bowel disease. Both diabetes mellitus (DM) and obesity have also been associated with increased urinary oxalate excretion. We assume that our patient suffered from SH with both obesity and DM playing a role. Although significantly less common than other causes of acute kidney injury, ON should be included in the differential for AKI of unclear etiology, especially in patients with concurrent DM and obesity.

**FR-PO231**

### Say “No” to the DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

**Hannah R. Miller, Tyler Sims, Sam Beavin. University of Kentucky College of Medicine, Lexington, KY.**

**Introduction:** Healthy 25-year-old with rash due to DRESS and acute kidney failure due to granulomatous acute interstitial nephritis in the setting of EBV and RMSF infection.

**Case Description:** A 25-year-old woman with history of paroxysmal SVT and migraines was seen outpatient and treated with amoxicillin/clavulanic acid for suspected bacterial pharyngitis with lymphadenopathy. Four days later, she developed a pruritic rash on hands and shins that spread diffusely. Hospital workup showed positive IgM titers for Rocky Mountain Spotted Fever and IgG titers for Ebstein-Barr Virus. Patient started on topical steroids and doxycycline for suspected RMSF. She then developed flu-like symptoms and oliguria with severe kidney failure. Kidney function worsened to a peak creatinine of 11.71 mg/dL. Kidney US demonstrated increased parenchymal echogenicity, and UA was unremarkable. Hospital day 4 kidney biopsy showed severe tubular interstitial nephritis with substantial eosinophils in interstitium and formulation of granulomas. She was treated with IV methylprednisolone for 3 days and then switched to oral prednisolone with significant improvement in kidney function.

**Discussion:** This case revealed the rare pathological finding of granulomatous tubulointerstitial nephritis on kidney biopsy and rapid improvement of kidney function with high dose steroids. The presentation was mostly likely due to DRESS from the amoxicillin with associated AIN. Cases of AIN with granulomatous inflammation are not common and account for < 1% of all kidney biopsy findings (1). Most often this pattern is associated with antibiotics, NSAIDS and diseases such as sarcoidosis, TB, fungal infections and GPA (Shah S. 2015). Glucocorticoids were the treatment of choice as patient achieved resolution of both her DRESS and acute kidney failure with avoidance of dialysis.

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**Figure 1:** Widespread calcium oxalate deposition within the renal tubules under polarized light (arrows).
Unresolving AKI Diagnosed as a Case of Tubulo-Interstitial Nephritis with Uveitis Syndrome

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Introduction: Tubular-interstitial nephritis and uveitis (TINU) is a very rare condition and till now around 250 cases have been reported so far. The pathogenesis of TINU syndrome remains unclear. Patients usually present with non-specific symptoms like nausea, vomiting and the ocular symptoms of uveitis might not always coincide with the diagnosis of acute kidney injury (AKI). The diagnosis can be easily missed with the clinical picture overlapping with perrenal etiology of AKI.

Case Description: We report a case of a 67-year-old female with a past medical history of diabetes mellitus, hypertension, and uveitis. She presented with nausea and vomiting for a few weeks. She was found to have acute kidney injury (AKI) with creatinine level of 2.06 mg/dl and was initially treated with intravenous hydration. Admission urinalysis showed proteinuria and negative leukocyte casts. Renal US was normal. Initial laboratory work up were unremarkable to determine the etiology of AKI. Complete blood count showed a slightly raised eosinophil percentage of 10%. Her serum calcium was 12.9 mg/dl on admission with PTH of 7 pg/ml (15-65 pg/ml) and 1.25 Vitamin D of 87 pg/ml (19.9-79.3 pg/ml). CT chest revealed patchy ground glass opacities throughout the lungs. Infectious work up revealed Beta-D-Glucan >500. A bronchoscopy with BAL was performed and returned positive for PJP on PCR. She was started on atovaquone with oral prednisone.

Discussion: AKIN criteria is a general tool for assessment of AKI, it does not give etiological information which is vital for the management to prevent long term complications.

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FR-PO237
Incidence of AKI with Immune Checkpoint Inhibitors: A Five-Year Retrospective Review
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Background: Immune checkpoint inhibitors (ICPs) are one of the most commonly prescribed cancer treatments. ICPs prolong overall & progression-free survival in patients with a wide range of malignancies, but also cause AKIs. This can lead to dose delays, discontinuation of therapy, and prolonged courses of immunosuppression. The reported rate of AKI with ICPs is substantial ranging from 3%-7%. Use of ICPs has increased significantly in recent years. The aim of this study was to describe the incidence & stages AKI associated with ICPs, over a 5 year period.

Methods: Patients receiving ICPs between 2016-2021 in University Hospital Waterford (UHW), were identified using the UHW oncology database. Data were then linked to our institutional electronic patient record to obtain laboratory data and kidney biopsy results. Medical charts were reviewed to obtain data on concurrent medications and treatment received for ICPI-AKIs. AKI was defined as per the KDIGO criteria.

Results: 202 patients commenced ICPs, with a mean age of 69 & a male predominance (1:6:1). 20.3% of patients experienced an AKI, & of those, 19.5% had eosinophilia. The incidence of AKI & eosinophilia differed by agent. AKI rates differed by agent; Pembrolizumab 21.2%, Nivolumab 20.9%, atezolizumab 10.8%, durvalumab 33.3% & ipilimumab 33.3%. Anti-CTLA4 ICPs had a higher rate of AKI compared to PD-1 ICPs at 25% & 21%. 83% had a stage 1 AKI, 7% had a stage 2 AKI & 10% had a stage 3 AKI. Stages differed by agent. 71.4% with a stage 2 or 3 AKI received steroids, & 1 patient received infliximab. Only 1 patient had a renal biopsy, reporting ATN. The average time to develop an AKI was 85.7 days (ranging 7 to 314 days).

Conclusions: This demonstrates a considerable burden of AKI in patients on ICPs. Incidence of AKI in our cohort is higher than previously reported, at 20.3%, but the majority were stage 1. Only 1 patient underwent a biopsy. Previously, biopsies were the standard of care, however current ASCO guidelines recommend empiric treatment. A high index of suspicion should be maintained throughout duration of treatment, even in patients established on ICPs, due to the variation in time to develop an AKI after treatment initiation. The use of ICPs is increasing & it is important to monitor for renal toxicity. Close monitoring of renal function, early recognition & management of AKI can prevent long-term renal damage and improve outcomes.

FR-PO238
AKI and Acute Kidney Disease After Radical Cystectomy for Muscle-Invasive Bladder Cancer: Two Underestimated but Dangerous Threats
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Background: Radical cystectomy (RC) represents the first line surgical treatment for muscle-invasive bladder cancer (MIBC), a worldwide increasing malignant neoplasm. However, RC represents the most complex and invasive surgery in urology, characterized by significant morbidity and mortality. Among RC patients, the incidence of post-operative acute kidney injury (AKI) and Acute kidney disease (AKD) is still not clear, due to the paucity of data. Aim of the study was to evaluate the incidence of AKI and AKD after RC.

Methods: A consecutive cohort of 839 patients who underwent RC for MIBC in a tertiary institution between 2010 and 2022 was collected. All clinical variables, comorbidities, surgeries techniques and oncological regimen were reported pre and after surgery. Serum creatinine and eGFR using CKD-EPI formula were collected at baseline preoperative and in the ats day 48, 37, 12, 8, 6 days for the AKI once and after 9,12,15,18,21,24,27,30,45, 60, 75, 90 days for the AKD establishment. Fisher’s exact test; Wilcoxon rank sum test; Pearson’s Chi-squared test were used for the statistical analysis.

Results: General characteristics of patients included in the study are summarized in Table 1. Surprisingly, a very high rate of both AKI (30%) and AKD (50%) was reported in the total cohort of patients, with an augmented incidence in the elder pts, low pre-operative eGFR, pre-existing CKD, BMI > 24, robotic surgery and hypertensive pts in the multivariate analysis (table 2). Moreover, stage II and III of both AKI and AKD affected a non-negligible percentage of patients, requiring advanced nephrological medical treatments and prolonged hospitalization.

Conclusions: AKI and AKD are very common but hidden side effects in the RC for MIBC. Therefore, a personalized nephrological counseling both in the pre and post-surgery asset is necessary to reduce morbidity and mortality.

FR-PO239
GFR in the Era of Precision Medicine: A Face to Face Between Measured GFR (mGFR) and Estimated GFR (eGFR) in Onconephrology
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Background: Onco-nephrological patients deserve the highest attention in term of personalized medicine. Acute and chronic renal damages represent common major side effects, often as a results of drugs renal toxicities due to false dosage based on GFR. Therefore, a reliable assessment of renal function is mandatory. Aim of this study was to determine the extent of the error of eGFR common formulas compared to mGFR in onco-nephrology.

Methods: A consecutive cohort of 701 onco-nephrological patients (pts) was collected to compare the most used eGFR formulas (MDRD, CKD-EPI SCR 2012, CKD-EPI 2021 SCR, CKD-EPI Cys 2012, CKD-EPI Cys 2021, CKD-EPI Cys/Scr, Cockcroft-Gault) with mGFR method (iohexol Plasma Clearance). True positives and False positives were classified in CKD stages based on eGFR and mGFR. Comparisons between groups were performed using Wilcoxon ranks sum test for numerical variables and Pearson’s Chi square test for categorical ones.

Results: Clinical data: overall median age was 66 years, median BMI 25, Male: 53.6, F: 46.5, Diabetes: 10.9%, Hypertension: 53.8%, CKD stage I: 1.7%, II: 25.5%, IIIA: 28.3%, IIIB: 27.5%, IV: 13.4%, V: 1.74%, mean Creatinine: 1,44 mg/dl, cystatin: 1,24. We reported a huge discrepancy between the eGFR formulas and mGFR values, suggesting the essential role of mGFR in the clinical decision making algorithm (Figures 1 and 2).

Conclusions: eGFR formulas showed a non-negligible error in all CKD stages classification in comparison to mGFR. In the onconephrological asset, the use of mGFR should be mandatory to obtain a tailored management.

FR-PO240
Myeloma Cast Nephropathy in an HIV Patient with AKI
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Introduction: HIV is associated with a multitude of renal pathologies that can involve the glomeruli, tubule, and interstitium. HIV is rarely associated with monoclonal gammapathy. We present a case of myeloma cast nephropathy in an HIV patient presenting with an AKI.

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Case Description: 58-year-old male patient with a past medical history of well controlled HIV and CKD with a baseline creatinine of 1.3 mg/dL presented to the hospital with abnormal labs. His creatinine was 7.1 mg/dL. Hemoglobin was 7.1 g/dL. Patient reported generalized weakness of 2 weeks duration. On presentation, patient’s vital signs and physical exam were unremarkable. Repeat labs revealed a BUN of 61 mg/dL, creatinine of 6.9 mg/dL, and hemoglobin of 6.7 g/dL. Patient received IV hydration in the ER with no significant improvement in creatinine and was admitted for further workup. Workup included SPEW which showed a monoclonal band in the gamma region; 9.2 g/dL. IgG was 10703 mg/dL and serum free kappa/lambda was 733.43. Renal biopsy showed light chain cast nephropathy, kappa light chain type in addition to minimal global glomerulosclerosis, mild interstitial fibrosis and mild to moderate arterioclerosis. Multiple myeloma was suspected and was confirmed on bone biopsy which showed myeloma with kappa-restricted plasma cells, involving 80-90% of cellularity. Patient was started on daratumumab/horzumab/dexamethasone for treatment of multiple myeloma. After a month, his creatinine has steadily decreased down to 2.6 mg/dL.

Discussion: HIV can commonly cause focal segmental glomerulosclerosis, collapsing variant. It is also known to cause pan-nephropathy including glomerular, interstitial, and tubular pathology. HIV can also be associated with polycythemia vera and HIV-associated myelomatosis. Treatment of underlying multiple myeloma can help improve kidney disease. Clinicians should have a broad differential for AKI, including multiple myeloma, in HIV patients especially if they present with anemia as treating the underlying etiology is essential in treating the kidney disease.

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

Underline represents presenting author.
Results: 595 patients were included, mean age 65.9 ± 9.7, 51.4% female. 28.6% met CT-criteria for sarcopenia. 66.9% had one or more AEs. Patients with sarcopenia had increased odds of AKI and anemia (Figure 1), adjusted for confounders. Patients with concomitant sarcopenia and CKD had the highest rates of AEs (Figure 2).

Conclusions: Patients with anNSCLC and sarcopenia are at increased risk for AEs from triplet therapy, possibly due to eGFR overestimation and failure to appropriately dose-reduce chemotherapy.

FR-PO245
Role of Leukapheresis in the Management of AKI Associated with Hyperleukocytosis of Acute Myeloid Leukemia (AML)

Introduction: The rates of AML patients with hyperleukocytosis range from 8–12%. Due to very high early mortality rates, as high as 50% during 30 days after presentation, hyperleukocytosis—especially if complicated by leukostasis—is a hematologic emergency that requires prompt treatment. The role of leukapheresis remains controversial due to the lack of strong data. Hereby, we report a case of acute kidney injury (AKI) that resolved after one session of leukapheresis.

Case Description: A 73-year-old male presented to the hospital with abdominal pain, nausea, vomiting, and generalized fatigue of 2 weeks duration. He was found to have a WBC count of 159,000/μL with 98% peripheral blasts concerning for acute leukemia. On admission, nephrology was consulted for oliguric AKI without evidence of sepsis or hypotension. Urine microscopy revealed a few granular casts suggestive of ATN. The patient did not meet Cairo-bishop criteria for tumor lysis syndrome (TLS). The patient was initiated on hydroxyurea. Due to a lack of improvement in oliguric AKI after four days of presentation and without any other identifiable cause than cytostasis, he underwent one session of leukapheresis (Figure 1). This was followed by two consecutive sessions of dialysis for uremic encephalopathy. Two days later, his urine output increased to about 1.8 L with remarkable kidney function improvement, and he didn’t require further dialysis. Unfortunately, the patient passed away after six weeks of a complicated hospital course with remarkable kidney function improvement, and he didn’t require further dialysis.

Discussion: Renal failure can occur due to leukostasis from hyperleukocytosis in acute leukemia as a result of tubular and glomerular dysfunction. The exact mechanism is unknown but possibly due to mechanical obstruction from less deformable leukemic blasts, the release of proinflammatory cytokines, and matrix metalloproteinases that damage endothelial cells. No current guidelines exist for the treatment of renal injury in this setting. Our case suggests leukapheresis should be considered a therapeutic option for such patients.

FR-PO246
AKI due to Chronic Lymphocytic Leukemia Infiltration with Necrotizing Granulomas
Erika D. Critelli, Amy Yau, Laura Biederman. The Ohio State University, Columbus, OH.

Introduction: Chronic lymphocytic leukemia (CLL) can commonly affect the kidneys. In autopsy findings, leukemic infiltration can be seen in up to 64-90% of cases, but direct involvement to the renal parenchyma causing acute kidney injury (AKI) is rare. In addition to leukemic inflammation, non-necrotizing granulomatous interstitial nephritis has been described.

Case Description: A 61 year old male with a past medical history of type 2 diabetes mellitus, ulcerative colitis, and immunoglobulin heavy chain variable region gene (IgHV) mutated CLL (not previously requiring therapy) presented in the outpatient setting with creatinine elevation from 1.0 mg/dL to 1.9 mg/dL. Work up revealed normal kidney size and new proteinuria of 493mg/24 hours. The creatinine rise was seen alongside a rise in his white blood cell (WBC) count from baseline 13-19 K/μL to 24-39 K/μL. Renal biopsy revealed leukemic infiltration with cells staining positive for CD20 and CD5 indicating direct involvement of the renal parenchyma along with necrotizing granulomas. The granulomas were found to be non-infectious, indicating a severe form of inflammation.

He was started on acalabrutinib and obinutuzumab with hopes for AKI resolution.

Discussion: Other case reports note the appearance of necrotizing granulomatous inflammation seem to affect younger men; additionally, there is no correlation with WBC. Most cases have complete to partial renal recovery after initiation of chemotherapy, however case reports suggest patients with granulomatous inflammation may have a poorer response. The mechanism of renal injury is not clear. Some suggest leukemic cells secrete monoclonal immunoglobulins whereas others suggest renal damage from a hypersensitivity reaction to leukemic cells. Of note, previous case reports did not classify IgHV mutation status, which is now routinely evaluated for. Renal biopsy remains critical to diagnose this potentially reversible, specific, and rare cause of acute renal failure and dictate initiation and guidance of chemotherapy.

FR-PO247
Association Between Cancer and AKI Among Medicare Fee-for-Service Beneficiaries, 2006-2014
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Background: Acute kidney injury (AKI) is a heterogeneous syndrome characterized by an abrupt decline in kidney function. Although patients with cancer are likely to be susceptible to AKI, population-based incidence of AKI in patients with cancer is not well understood in the US.

Methods: We conducted a population-based retrospective cohort study among Medicare fee-for-service beneficiaries who were continuously enrolled for six-years, including an initial one year cancer-free window before the index year. The index year was defined by a new cancer diagnosis. Follow-up started with the index year and ended at the time of AKI, death, or censoring at the end of five years. We defined incident cancer
by the presence of two ICD-9 CM diagnosis codes in an outpatient setting or one ICD-9 CM diagnosis code in an inpatient setting without a history of cancer diagnoses in the same patient. The main outcome was time to AKI or death. All-cause death date was ascertained using the National Death Index. Association between cancer and AKI was assessed by cause-specific Cox proportional hazards modeling.

**Results:** We identified 5,613,285 Medicare fee-for-service beneficiaries with incident cancer diagnoses over the same time period, matched on age, sex, and race and ethnicity. The cumulative incidence of AKI indicated by SHR was not notable. The association of cancer with death was stronger than that with AKI, impact of cancer on risk of AKI, compared with those without cancer. However, because the cause-specific association of cancer with death was stronger than that with AKI, impact of cancer on cumulative incidence of AKI indicated by SHR was not notable.

**Funding:** Other U.S. Government Support

**FR-PO248**

**Mortality of Patients with Cancer and AKI: What Are the Lessons?**


**Hospital das Clínicas, Recife, Brazil.

**Background:** Acute kidney injury (AKI) is a prevalent complication in cancer patients contributing to mortality. This study aimed to assess factors associated with the mortality of patients with cancer and AKI monitored in the onconephrology clinic of a university hospital.

**Methods:** This was a cross-sectional, retrospective study. Medical records were reviewed of patients monitored from January 2018 to December 2022. Patients with COVID-19 were excluded. AKI was defined according to KDIGO criteria. The final creatinine (CrF mg/dL); last value measured before discharge or death; oliguria: diuresis <400 mL/24h. A comparative analysis was performed of patients who died and survivors. Univariater and multivariate analyses were used in the search for risk factors for death. The impact of baseline assessed of hyperphosphatemia (phosphorus-4.5 mg/dL) and hypothyroidism (sodium<135mEq/L) on mortality.

**Results:** A total of 340 patients (50% male), with an median age of 62 years, were studied. The mean follow-up time was 15 days. Most patients (78%) presented solid tumors. Type of AKI were: intrinsic renal (38%), prerenal (30%), and obstructive (27%). Outcome data were available on 336 patients. One hundred and eighteen patients (35%) died. Patients who died differed from survivors by being in ICU (55% vs 17%; p<0.001), intrinsic renal AKI (57% vs 27%; p<0.001), sepsis (58% vs 19%; p<0.001), urine output (mL) (500 x 1050; p<0.001), need for renal replacement therapy (RRT) (60% x 25%; p<0.001), ICD-9 (3.2 x 1.5; p<0.001), phosphorus (4.6 x 4.0; p=0.018) and albumin (g/dL) (2.8 x 3.0; p=0.046). In the univariate analysis, the following were associated with mortality: not being in ICU (OR 0.17; p<0.001), CrF (OR 2.26; p<0.001), intrinsic renal AKI (OR 3.47; p<0.001), sepsis (OR 0.17; p<0.001), non-obstructive (OR 0.31; p<0.001), phosphorus (OR 1.2; p=0.023) and no need for RRT (OR 0.22; p<0.001). In the multivariate analysis, only CrF was an independent risk factor for death (OR 7.51; p=0.009). Hyperphosphatemia was associated with mortality (p=0.006), but hypothyroidism was not.

**Conclusions:** We confirmed the high mortality rate of patients with cancer and AKI. The severity and persistence of AKI are determinants of mortality. Hyperphosphatemia seems to be a predictor of mortality in cancer patients with AKI.

**FR-PO249**

**Lymphocytic Infiltrates on Kidney Biopsy of a Patient with AKI and Chronic Lymphocytic Leukemia: Intestinal Neoptilrisis or Infiltration by Leukemia?**

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**Introduction:** Chronic lymphocytic leukemia (CLL) is the most common adult leukemia and has been identified in patients with an inflammatory syndrome, or obstructive nephropathy. Infiltration of organs by CLL can occur, however, kidney involvement is unusual.

**Case Description:** A 60-year-old female with history of hypertension on treatment with lisinopril and HCTZ, proteinuria, hyperphosphatemia and on esomeprazole and CLL with trisomy 12 and 14; 19 translocation, on treatment with biurbanil for 5 years, is found to have worsening kidney function. In the ER, she reported abdominal discomfort and bloating for one month. On physical exam she had bilateral lower extremity edema. Three months earlier, she had a creatinine of 0.9 mg/dL. On current presentation, her creatinine was 5.27 mg/dL and potassium was 2.9 mmol/L. UA revealed proteinuria and pyuria. Spot UPCR was 400 mg/g. A kidney ultrasound showed normal size kidneys. A kidney biopsy was performed which showed acute granulomatous tubulointerstitial nephritis (TIN) with extensive interface infiltrate and scattered interstitial infiltrate. Evaluation by a hematopathologist confirmed involvement of renal parenchyma by CLL. By immunohistochemistry, lymphoma cells were positive for PAx5, CD20, and CD5. Treatment was initiated with prednisone. Ibrutinib was discontinued and she was started on Obinutuzumab and Venetoclax. 4 weeks later, her creatinine improved to 1.26 mg/dL and urinalysis was negative for proteinuria or pyuria.

**Discussion:** This case illustrates the importance of a multidisciplinary collaboration and critical thinking in suspicion of lymphocytic infiltration of the kidney in the setting of CLL in a patient with AKI. Mechanistically, AKI secondary to infectious disease secondary to CLL is poorly understood with one report hypothesizing tubular microvascular compression and infiltration-associated inflammatory response. Recognition of this phenotype of infiltrative disease in patients with CLL is vital for timely treatment.

**FR-PO250**

**Clonal Hematopoiesis of Indeterminate Potential Is Associated with Kidney Disease Progression in a Multi-Cohort Meta-Analysis of Individuals with CKD**

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**Background:** Clonal hematopoiesis of indeterminate potential (CHIP) is a common inflammatory condition of aging caused by acquired mutations in blood stem cells. CHIP causes myriad end-organ damage, including a doubling of the risk of cardiovascular disease independent of traditional risk factors. We have recently shown associations for CHIP with acute kidney injury and with kidney function decline in the general population, with a greater effect for CHIP driven by mutations in genes other than DNMT3A (non-DNMT3A CHIP). Longitudinal kidney function endpoints in individuals with pre-existing chronic kidney disease (CKD) and CHIP have been examined in two previous studies, which reported conflicting findings and were limited by small sample sizes.

**Methods:** In this study, we examine the prospective associations between CHIP and CKD progression events in four cohorts of CKD patients: the Chronic Renal Insufficiency Cohort (CRIC), the African American Study of Kidney Disease (AASK), the Canadian study of prediction of death, dialysis and intercurrent cardiovascular events (CanPRE DiCT), and BioVU (total N = 4853). The primary outcome was CKD progression (composite of 50% kidney function decline or end-stage kidney disease). Analyses were adjusted for age, sex, self-reported race, and the following baseline parameters: eGFR, proteinuria, smoking status, BMI, diabetes status, hypertension, and cardiovascular disease history.

**Results:** Across all cohorts, the average age was 67.4 years, the average baseline eGFR was 41.2 ml/min/1.73m2, and 25% had LID. In a random-effects meta-analysis, across all cohorts, the association between CHIP was HR 1.59, 95% CI: 1.01-2.51). This effect was slightly more pronounced in the subgroup with baseline eGFR ≥30 ml/min/1.73m2 (HR 1.77, 95% CI: 1.06-2.98).

**Conclusions:** Non-DNMT3A CHIP is a potentially targetable novel risk factor for CKD progression in a multi-cohort meta-analysis.

**Funding:** NIDDK Support, Other NIH Support - Canadian Institutes of Health Research Project Grant (application # 427810, R01DK132155, R01DK125782, Government Support - Non-U.S.

**FR-PO251**

**SHT-1F-Agonist-Mediated Protection Against Cisplatin-Induced Nephrotoxicity Is Abolished in a Murine Model of Lung Cancer**

Andrey Orwick, Leah J. Siskind. University of Louisville, Louisville, KY.

**Background:** Anti-cancer drug-induced acute kidney injury (AKI) is a persistent problem. Cisplatin is a prominent example of this, 30% of patients develop AKI after a single chemotherapy cycle. There is a need to identify strategies to identify patients at risk for cisplatin-induced AKI. Previous studies have shown that cisplatin driving the AKI to CKD transition in the repeated low-dose cisplatin (RLDC) model is not fully understood. Mitochondrial dysfunction plays a critical role in the transition from AKI to CKD. The role of kidney mitochondrial dynamics/quality control in the RLDC model is currently unknown. Preclinical cisplatin toxicity studies have been completed in mice without cancer. The lack of appropriate preclinical models has led previous research down doomed pathways.

**Methods:** The objective of this study was to determine if neoprotective strategies in mice with lung cancer will still protect mice with lung cancer. Eight-week-old B6129 mice with and without lung cancer were administered Cisplatin (7mg/kg) or saline via intraperitoneal (i.p.) injection once a week for four weeks. Following the first dose of cisplatin, mice were administered LY344804 (2mg/kg) or saline 6 days a week via i.p. injection. We pharmacologically induced mitochondrial biogenesis in a mouse model to determine if this pathway will protect from cisplatin-induced nephrotoxicity.

**Results:** Stimulating mitochondrial biogenesis increased kidney mitochondrial content and reduced loss of kidney function, kidney injury, inflammation, and...
development of fibrosis from RLDC in mice without cancer. However, these effects are nullified when the experiment was repeated in mice with subcutaneous lung cancer.

Conclusions: Previous clinical trials on nephroprotective agents have failed, and we propose that poorly representative mouse models may be responsible for misleading preclinical research. Our development of clinically relevant models of cisplatin-induced nephrotoxicity provides a foundation for developing nephroprotective agents that can be used as adjunctive therapy for cancer patients receiving cisplatin.

Funding: NIDDK Support

FR-PO252

Gut Microbiota and Kidney Injury After Allogeneic Hematopoietic Cell Transplantation (allo-HCT)
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Background: Acute kidney injury (AKI) is a common complication of allo-HCT associated with an increase in non-engraftment mortality. In contrast, higher diversity of gut microbiota at neutrophil engraftment is associated with lower mortality. We aimed to study the association of changes in gut microbiome diversity in an allo-HCT cohort who developed post-transplant AKI or CKD.

Methods: We performed a single-center study of 419 allo-HCT recipients from 2014-2017 at Memorial Sloan Kettering Cancer Center with analysis of gut microbiome diversity. We defined AKI and CKD based on KDIGO criteria and eGFR using the CKD-EPI equation. We defined gut microbiome diversity using Shannon and Simpson reciprocal diversity indices (DI), with higher levels indicating more diverse microbiota. We used Wilcoxon rank-sum test to compare baseline DI (within 7 days of HCT conditioning) between patients who did and did not develop AKI by 100 days post-HCT, and peri-engraftment DI (median DI in days 7-21 post-HCT) between those who did and did not develop CKD at 6 months.

Results: Simpson reciprocal and Shannon DI were 21.8 (IQR: 13.7, 35.2) and 3.7 (IQR: 3.2, 4.2) at baseline, and 6.3 (IQR: 3.7, 10.4) and 2.3 (IQR: 1.7, 2.8) at peri-engraftment, respectively. Of the 419 patients, 263 (63%) developed AKI; 114 (27%) did not develop CKD at 6 months.

Conclusions: Our findings do not support the existence of a link between baseline or peri-engraftment gut diversity and the risk for development of AKI or CKD in patients undergoing allo-HCT. This study highlights the complex and multifactorial etiology of AKI in allo-HCT recipients and the need for additional prospective and mechanistic studies.

Figure 1. Baseline and peri-engraftment Simpson reciprocal and Shannon diversity indices by any AKI in 106 days post-HCT and CKD at 8 months.

FR-PO253

Multiple Cancers Alters Renal Physiology and Induces Kidney Injury and Inflammation
Dana Hammour, Leah J. Siskind. University of Louisville, Louisville, KY.

Background: The altered physiology of cancer patients and their unique susceptibility to kidney disease has led to the rapidly growing specialty of Onconephrology. Cancer patients often have decreased kidney function, and drug-induced acute kidney injury (AKI) is common and remains a hurdle. Drug-induced AKI can interrupt therapy and reduce overall survival. Our lab has recently shown that lung-cancer enhances the nephrotoxicity of cisplatin. Additionally, we were able to show that lung-cancer alone alters kidney physiology. However, we are unaware if this phenomenon is exclusive to the model we tested. In this study we used multiple cancer types to determine if kidney function, injury, and inflammation are being altered by subcutaneous cancer alone.

Methods: Eight- to ten-week-old B6.129 mice were randomly assigned into six group of non-cancer and various other cancer types. In the cancer groups, cancer cells were injected subcutaneously and followed for tumor size. Animals were euthanized once tumor size met necessary endpoint per IACUC protocol.

Results: Different cancer types have varying effects on altering kidney function, injury and inflammation. Metastatic lung cancer induces the largest changes, compared to non-metastatic lung cancer. Additionally, melanoma increased urinary NGAL, but did not increase KIM-1 expression.

Conclusions: The presence of subcutaneous tumors is sufficient to alter kidney biology, induces renal injury and inflammation and reduce renal function. Further studies will need to be conducted to elucidate the mechanism behind these changes. Understanding the tumor-kidney crosstalk may provide mechanistic insights and uncover novel therapeutic targets for onconephrology patients.

Funding: NIDDK Support

FR-PO254

Urine EGF and TNFR2: A Pilot Study of Novel Biomarkers to Predict Long-Term Renal Outcomes in Pre-Clinical Model of Cisplatin-Induced Chronic Kidney Injury
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Background: Cisplatin is associated with development of chronic kidney disease (CKD) and hypertension affecting around 45% of pediatric oncology patients. Novel urine biomarkers may allow earlier identification of patients at risk of CKD progression. Urine EGF (uEGF) has been shown to be an independent predictor of CKD progression in humans with an inverse correlation between uEGF and estimated glomerular filtration rate (eGFR). Tumor Necrosis Factors Receptor 2 (TNFR2) is a promising biomarker of inflammation with higher levels associated with increased risk of CKD progression. Murine cisplatin pre-clinical models result in long-term renal function decline and could facilitate identification of biomarkers to predict CKD progression.

Methods: Ten-week-old C57Bl6J male mice received 3 weekly intraperitoneal (IP) injections of cisplatin 8 mg/kg/dose vs 0.9% NaCl control (n = 18/group). Urine was collected at 14 days and 3 months after initial cisplatin dose, and transdermal GFR (GFR) measurements were performed at 3 and 6 months after initial cisplatin dose. uEGF (ELISA, MEGCO, RD&D Systems) and uTNFR2 (R-PLIX assay, Meso QuickPLIX SQ instrument) were measured according to manufacturer’s instructions. GFR analysis was performed calculating FITC-sinistrin clearance after retroorbital injection. Veterinarian Pathologist quantified tubular injury, inflammation and fibrosis in kidney sections (score 0-4).

Results: Survival was 98% (control 94% vs 83% cisplatin). At 6 months, cisplatin treated mice had lower GFR, and higher tubular injury, interstitial fibrosis, and inflammation on histological analysis. Cisplatin treated mice had significant reduction in uEGF at 14 days, and 3 months and a significant increase in uTNFR2 at 14 days compared to control group (p<0.05 2-way ANOVA). There is a significant negative correlation between uEGF at 3 months and tubular injury, inflammation, and fibrosis at 6 months and a positive correlation with GFR at 6 months. There is a significant positive correlation between uTNFR2 at 14 days and tubular injury, glomerular changes, and fibrosis at 6 months (Pearson, p<0.05).

Conclusions: uEGF and uTNFR2 could be promising early biomarkers to predict CKD in pre-clinical models of cisplatin-induced CKD.

FR-PO255

Atypical Presentation of Renal Amyloidosis in a Patient with Plasma Cell Dyscrasia (PCD)
Prival Sakhuja, Randolph A. Henningar, Rula A. Abdulrahman. Stony Brook University Hospital, Stony Brook, NY.

Introduction: Amyloidosis (AD) is deposition of abnormal proteins that can lead to organ dysfunction. Light chain AD (AL amyloidosis) is the most common systemic form. This is commonly associated with PCDS such as multiple myeloma (MM). This case focuses on a patient with IgA PCD who develops an atypical presentation of renal AD.

Case Description: 76-year-old male with hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, atrial fibrillation, urinary bladder AD and chronic kidney disease (CKD) was seen at CKD clinic. Cr was 1.8-2.0 mg/dl. Urinalysis with no hematuria, protein or creatinine ratio (PCR) was 821 mg/g. SPEP specified M-spike and immunofixation with IgA-kappa monoclonal protein bands. Patient was referred to
is atypical due to the absence of massive proteinuria and predominance of kappa light chains with nephrotic syndrome. When amyloid deposition is found in the tubulointerstitial (TI) compartments, proteinuria is not a common feature. Additionally, lambda light chains are seen more often than kappa light chains as they are more amyloidogenic. Our case is atypical due to the absence of massive proteinuria and predominance of kappa light chains. Insignificant proteinuria can often be due to deposits confined to the TI or vascular compartments, however our patient had deposits in the glomeruli. Thus, it is important to note that even in the absence of significant proteinuria, a patient with known PCD with renal dysfunction, may still undergo renal biopsy. The histological findings can also vary despite the degree of proteinuria.

FR-PO256

Use of Radioactive Iodine in the Management of Thyroid Cancer in Those with Low-Clearance CKD/ESKD

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Background: Radioactive iodine (RAI) is a key adjuvant treatment of differentiated thyroid cancers. Iodide is cleared by the kidney which leads to complexities in the treatment of patients with end-stage kidney disease (ESKD) due to prolonged circulation half-life.

Methods: A structured multidisciplinary care pathway was created for those receiving RAI with ESKD, involving Nephrology, Radiation Oncology, Medical Physics, and Biomedical Engineering. A shielded room is used for RAI with the addition of mobile shielding for staff to reduce staff exposure during dialysis. Alterations for water treatment were made to deliver ultrapure water suitable for HD. Patients were dialyzed in isolation until levels <30MBq (1.5 µSv/hr). Safety protocols for radiation protection for staff and dialysis waste management were implemented.

Results: Case One: 47 year old man with invasive follicular thyroid carcinoma in the setting of CKD stage 4 (eGFR of 17 ml/min/1.73m2). Following thyroidectomy, an avid focus present in left thyroid bed requiring treatment with RAI. He underwent radioactive iodine ablation therapy with a reduced dose protocol of 1.1 GBq. Levels were closely monitored and graphed compared to a normalised dose rate for those without renal impairment. His clearance was in line with the expected rate. Case Two: 50 year old man with recurrent papillary thyroid carcinoma on a background of ESKD on HD. Initial treatment with surgery and RAI in 2017. He represented with recurrent nodal disease and underwent a neck dissection. RAI treatment was planned. Dialysis was arranged prior to treatment to familiarise staff with the new unit. He received a 50% reduction in RAI with a dose of 1.850 GBq. Following treatment, he underwent dialysis at 14 hours post treatment then every 48 hours. His levels were reduced by >50% with each dialysis session (Figure).

Conclusions: RAI can be safely administered to patients with low clearance CKD/ESKD with the implementation of a structured care pathway utilising a multidisciplinary approach.

FR-PO257

Non-Proteinuric CKD: An Atypical Presentation of Multiple Myeloma

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Introduction: Light chain deposition disease (LCDD) is characterized by overproduction and deposition of monoclonal light chain immunoglobulins. LCDD usually has prominent kidney involvement; including proteinuria and kidney failure characterized by nodular glomerulosclerosis and tubular basement membrane thickening. Here we highlight an atypical presentation of biopsy proven kappa type LCDD without significant glomerular proteinuria in a patient found to have Kappa restricted Multiple myeloma (MM).

Case Description: Our patient is a 64-year-old male with medical history of asthma, hyperlipidemia, and tobacco use disorder (remission for 9 y). He presented to nephrology clinic for evaluation of confirmed isolated elevation in creatinine of 2.1 (BUN 21) with normal CBC, electrolytes, total protein and albumin. History was negative for NSAI use, OTC supplements, frequent UTI or nephrothiasis. There was no family history of CKD or ESKD. His only medication was Fluticasone-Vilanterol. His vital signs and physical exam were unremarkable. Urinalysis was negative for protein, but trace blood was noted. ANA, ANCA, C3/C4, RF, and viral hepatitis serologies were negative. UACR 10mcg/mg and UPUR 0.2mg/mg. SPEP was normal. Kappa FLC 273 mg/L, Lambda FLC 26.1 mg/L, Ratio 10.46. Renal imaging was noted to be normal for bilateral cysts without evidence of enhancing lesion, stones or hydronephrosis. Renal biopsy was ultimately performed, and it revealed LCDD Kappa type, interstitial fibrosis/tubular atrophy of 70-80% with moderate arterio- and arteriolosclerosis. Bone marrow biopsy revealed normal cellular marrow with trilamellar hematopoiesis and increased plasma cell mass (20% by CD 138 immunostaining). Flow cytometry revealed monoclonal kappa restricted plasma cell population. PET/CT was normal, implying that the kidneys were the sole site of the disease. He was started on cyclophosphamide, bortezomib and dexamethasone (CyBorD) and creatinine eventually improved. UACR increased slightly to 25mcg/mg.

Discussion: Kidney biopsy is almost always essential when the origin of CKD is unknown. Among patients newly diagnosed with MM, 20-50% have either AKI or CKD at the time of diagnosis. Early recognition and treatment of an underlying plasma cell disorder is important in preserving kidney function. This case highlights the importance of thorough workup for monoclonal gammapathy despite absence of typical presenting features.
FR-PO259

Daratumumab Monotherapy in Severe Patients with AL Amyloidosis and Biopsy-Proven Renal Involvement

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Background: Daratumumab is an anti-CD38 monoclonal antibody recently approved as a first-line therapy on top of standard therapy for the treatment of multiple myeloma and AL amyloidosis. The following data describe the good results reported by our group and the long-term experience achieved in recent years on the efficacy of daratumumab used in monotherapy.

Methods: We described 17 patients (pts) treated with Daratumumab alone, 24 iv administration at a dose of 16 mg/kg. All of them had an histological confirmation and staging of renal involvement and were ineligible for ASCt. Pts could either be naïve or refractory. When feasible, the patient who underwent the whole cycle of therapy underwent a second kidney biopsy at the end of the treatment.

Results: The mean age at diagnosis was 73 years. 16/17 pts had proteinuria that was associated with renal function impairment in 11. 2 pts were on dialysis at the time of therapy initiation. 9 pts completed the treatment, 13 over 17 underwent at least 12 infusions. At the 12th administrations 84.6% of pts had an overall hematological response, 46.6% of pts achieved a complete hematological response, 38% had a very good partial response, and 15.5% were non responders. 5/13 had already achieved an organ response.; the 2 pts who were in dialysis at the time of therapy initiation, remained on dialysis. 7/9 achieved a renal response. Proteinuria decreased from 6.02 to 1.28 g/dl (p = 0.005) with stabilization/improvement of eGFR. 8/9 pts with cardiac involvement obtained at least amelioration. At the end of follow-up 5 pts have persistent hematological and renal response. 1 pt with initial partial response had a relapse. The last pt is still alive and is being treated with daratumumab monotherapy plus immunotherapie at the end of the treatment. Histological findings showed stable deposits in 6 over 7 cases, while the last one showed a reduction in the extent and amount of amyloid deposits.

Conclusions: Our data, based on the real life experience of our center, suggest that daratumumab monotherapy may represent an effective therapeutic option, capable not only of inducing a substantial improvement in the renal status in pretreated or naïve pts, while the last one showed a reduction in the extension and amount of amyloid deposits.

FR-PO260

Onconeurology: The Role of Kidney Biopsy in the Management of Side Effects of Targeted Therapies

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Background: The introduction of innovative therapies, resulting from revisiting cancer as a disease of the immune system, has changed the scenario of complications. These new classes of drugs, such as targeted therapies and immune checkpoint inhibitors, assure substantial advantages in cancer therapy, despite some side affecting various organs, including the kidney. Histological evaluations of kidney disorders induced by targeted/immunotherapy are limited.

Methods: In this study we examined the histological features of patients treated with new cancer agents who underwent kidney biopsy for new onset kidney failure and/or urinary abnormalities.

Results: The cohort included 30 adult patients. The most frequently administered therapies were immunotherapy (30%), targeted therapy (26%), chemotherapy plus targeted therapy (13.3%), targeted therapy plus immunotherapy (13.3%), targeted therapy plus chemotherapy (16.7%). The most common histological finding was tubular interstitial nephritis (30%) that was associated with acute tubular necrosis in 4 cases, and thrombotic microangiopathy (23.3%). After kidney biopsy, 16 of the 30 patients were treated according to the histological diagnosis. Fourteen patients were treated with steroids. One patient with membranous nephropathy was treated with a single dose of rituximab. A patient with severe thrombotic microangiopathy requiring dialysis received a treatment with eculizumab for 3 months. Overall some renal response was obtained in all patients treated with glucocorticoids, while complete kidney response was achieved in the patient treated with rituximab. Cancer therapy was resumed without change in 21 out of 30 patients.

Conclusions: Kidney biopsy is critical for the management of kidney toxicities and should be strongly encouraged for patients showing adverse kidney effects of novel cancer agents.

FR-PO261

Cancer Status and Mortality in Older Hemodialysis Patients: Data from a Korean Society of Geriatric Nephrology Retrospective Cohort

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Background: Our study probed the correlation between cancer presence and mortality rates in elderly patients on hemodialysis, a link that is currently underexplored despite established associations between cancer, age, and chronic kidney disease (CKD).

Methods: We conducted a retrospective, multicenter cohort study through the Korean Society of Geriatric Nephrology. This study encompassed 2,085 patients aged 70 or above who commenced hemodialysis from 2010 to 2017. We employed the Kaplan-Meier survival estimator and Cox proportional hazards regression analysis to assess all-cause mortality.

Results: Among our cohort, 262 patients (12.6%) had a cancer history, while 55 patients (2.6%) were managing active cancer. Over a median follow-up period of 3.2 years, 1,357 deaths (65.1%) occurred. The active cancer group revealed significantly higher all-cause mortality in comparison to those with a cancer history or no cancer (85.5% vs 68.3% vs 64.9%; p<0.002). Kaplan-Meier analysis underscored this mortality disparity among the groups (p < 0.001, log-rank test). Further, the multivariate Cox regression analysis, post-adjustment for clinical variables, evidenced a strong correlation between active cancer and all-cause mortality (HR:1.89; 95%CI: 1.36-2.64; p < 0.001).

Conclusions: Elderly patients on hemodialysis with active cancer demonstrated a higher mortality rate compared to those with a history of cancer or no cancer. Interestingly, cancer survivors exhibited a mortality risk akin to those never diagnosed with cancer. Thus, elderly cancer survivors may be viable candidates for dialysis.

FR-PO262

Cancer Screening for Dialysis Patients

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Background: Routine cancer screening is not recommended for end stage renal disease (ESRD) patients due to their high mortality rate. The current status of cancer screening in this population remains uncertain, and routine screening is deemed cost ineffective. False-positive test outcomes may lead to unwarranted medical interventions, overtreatment, and psychological distress, highlighting the need for careful consideration in implementing such screening measures.

Methods: Among 340 ESRD patients at UPMC Harrisburg, 136 were ineligible, resulting in a cohort of 204 patients. Descriptive analysis reported categorical variables as number (percent). Group differences were assessed using chi-square tests, employing Fisher exact test for frequencies ≤5. A p-value ≤0.05 indicated statistical significance. SAS 9.4 (SAS Institute, Cary NC) was used for all analyses.

Results: Among the cancer screening rates examined, including breast cancer, colon cancer, prostate cancer, and cervical cancer, there was no statistically significant difference observed between patients who died from cancer-related causes and those who died from non-cancer-related causes. However, a history of cancer did not significantly raise overall mortality (HR=1.07; 95%CI: 0.90–1.28; p = 0.448).

Pairwise log rank test showed all between-group comparisons significant.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
died from non-cancer related causes. However, it is worth noting that the screening rate for lung cancer displayed a statistically significant difference between these two groups.

**Conclusions:** Cancer screening in ESRD patients should be tailored on anticipated survival, transplant eligibility, and cancer risk. However, this study is limited by small sample sizes. Larger patient cohorts are needed to provide more representative results. A personalized approach to cancer screening, considering specific risk factors and projected lifespan, is crucial in ESRD patients. Further retrospective studies are necessary.

**FR-PO263**

**Futility of Dialysis in Patients with Tumor Lysis Syndrome in Advanced Hematological Malignancy: A Case Series**

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**Background:** Acute kidney injury (AKI) can occur as result of tumor lysis syndrome (TLS) in patients with an underlying hematological malignancy. In TLS, hyperuricemia and hyperphosphatemia can cause crystal nephropathies. In patients with advanced malignancies, excess lactic acid production occurs as neoplastic cells preferentially undergo anaerobic glycolysis, known as the Warburg effect, resulting in type B lactic acidosis. These patients typically are hemodynamically stable. While dialysis is frequently used in the management of TLS, data on outcomes of these patients with advanced hematological malignancy would aid in deciding utility of dialysis. The purpose of our study is to assess mortality outcomes in patients with an advanced hematological malignancy with TLS, type B lactic acidosis, and AKI to better determine the utility and outcomes of dialysis in this cohort.

**Methods:** For this case series we used the TriNetX search, then refined our cohort to only include patients with type B lactic acidosis and excluded patients with AKI also due to hypotension/hypoperfusion. We identified 10 patients admitted to the Medical University of South Carolina between 2014 and 2022 with an underlying hematological malignancy with type B lactic acidosis, TLS, and AKI. Renal outcomes were assessed based on death, dialysis, and transfer to hospice through 6 months.

**Results:** Death occurred in 100% of patients with an underlying hematological malignancy presenting with TLS, type B lactic acidosis and AKI, with median time from onset of TLS to death of 4.5 days (SD 55). 70% of patients began dialysis with median time to initiation following TLS diagnosis of 1 day (SD 1.3), and median time to death following dialysis initiation of 2 days (SD 25.4). Median pH was 7.29 (SD 0.08), median lactate 8.6 (SD 5.6), LDH 5817 (SD 7558), uric acid 15.45 (SD 7.34), peak Scr 3.7 (SD 1.53), phosphorous 8.6 (SD 3.5).

**Conclusions:** Patients in our cohort had very poor rates of survival and dialysis did not appear to change outcomes. Given poor outcomes in these patients we suggest dialysis may have limited utility in our cohort and the focus of care should be comfort.

**FR-PO264**

**Type B Lactic Acidosis Secondary to Metastatic Liver Cancer in the Setting of Normal Renal Function: A Case Report**

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**Introduction:** Lactic acidosis occurs when lactate levels are greater than 4 mmol/L. It is due to an overproduction of lactate or decreased metabolism. There are two types, Type A and Type B. Type B is more common in hematological conditions, such as multiple myeloma, leukemia, and lymphoma.

**Case Description:** We present a case of a 43-year-old male with Type B lactic acidosis secondary to stage IV colon cancer with metastasis to the liver. Computed Tomography scan of the abdomen and pelvis showed extensive hepatic metastasis with marked hepatoplenomegaly and mild ascites. He had a lactic acid of 16.5 mmol/L, glucose of 52 mg/dl, and bicarbonate of 8 mEq. He received aggressive fluid resuscitation, IV antibiotics, and bicarbonate supplementation. However, his lactic acid worsened, requiring urgent dialysis. Despite dialysis, he showed no significant improvement, and was placed on hospice.

**Discussion:** Type B lactic acidosis can arise as a complication of solid and, more commonly, hematological malignancies, such as multiple myeloma, lymphoma, and leukemia. It is a rare complication that requires prompt diagnosis and treatment of the underlying condition. Treatment modalities, such as hemodialysis and chemotherapy, have been studied, but the prognosis remains poor. Our patient with type B lactic acidosis received hemodialysis, sodium bicarbonate, and glucose supplementation with marginal initial improvement, followed by worsening lactic acidosis. Due to the late stage of his cancer, chemotherapy was not beneficial. There is a paucity of information due to the rarity of studies on severe lactic acidosis. More studies are needed to better understand the pathogenesis of type B lactic acidosis secondary to hematological malignancies to improve patient outcomes.

**Figure 1.** Median peak arterial pH, serum lactate, and LDH of each patient.

**FR-PO265**

**Beyond Tumor Regression: Exploring the Fatal Consequences of Immune Checkpoint Inhibitor (ICI)-Induced Triple M Syndrome and Myoglobin Nephropathy**


**Introduction:** Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. Despite showing remarkable tumor regressions and anti-tumor efficacy, these agents can also lead to life-threatening immune-related adverse events (irAEs). One exceedingly rare irAE is ICI-induced myocarditis with myositis/myasthenia overlap, also known as Triple M Syndrome. We present a case of Triple M Syndrome with acute kidney injury and provide a review of the clinical course.

**Case Description:** A 76-year-old male with melanoma was treated with a single dose of adjuvant Nivolumab. Two weeks later, he was admitted with sudden-onset angina, respiratory failure requiring emergent intubation, and neurological symptoms.

**Imaging showing extensive liver metastasis with significant hepatoplenomegaly and ascites.**
Physical exam revealed bilateral pitting, diopla, and proximal muscle flaccid paralysis. Lab tests revealed no biochemical abnormalities or increase in transaminases to 4783 UI/L, but no liver enzymes, and elevated creatinine kinase (CK) of 6800 U/L. Serum myoglobin was elevated to 3799 mcg/L, aldolase was 100 U/L, and acylcholine receptor antibodies were detected. EKG did not show ischemic features. Electromyography demonstrated significant abnormalities. The patient was diagnosed with ICI-induced myositis, myotonia, and myopathy. The patient exhibited profound elevation in troponin and myoglobin levels, while CK levels were less remarkable. This suggests a predominant myocardial injury with a lesser extent of skeletal muscle involvement. Important to note is that the diagnosis of myositis relied on troponin and CK, while CK and myoglobin were necessary for diagnosing myoglobin pigmentation. In summary, recent experience of triple M syndromes in an iRAE causing renal injury from myoglobin, and not necessarily only interstitial disease, is crucial.

FR-PO266
Ifosfamide-Induced Fanconi Syndrome: A Complication That Cannot Be Overlooked
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Introduction: Fanconi syndrome (FS) is a severe dysfunction of the proximal tubule, which causes urinary loss of glucose, amino acids, phosphorus, bicarbonate and potassium. Ifosfamide (IFO)-induced FS is reported in 1.4-5% of children being treated for solid tumors, but few cases have been reported in adults. We describe a case of FS in an adult who was taking IFO for sarcoma treatment.

Case Description: A male, aged 29, diagnosed with cervical fibrosarcoma at the age of 13. In September 2021, with the third recurrence of the disease, he initiated chemotherapy (CT) with IFO, vincristine and actinomycin D. On the 24th week of CT, an adult who was taking IFO for sarcoma treatment.

Discussion: This case presents Triple M Syndrome, an iRAE characterized by myositis, myotonia, and myopathy. The patient exhibited profound elevation in troponin and myoglobin levels, while CK levels were less remarkable. This suggests a predominant myocardial injury with a lesser extent of skeletal muscle involvement. Important to note is that the diagnosis of myositis relied on troponin and CK, while CK and myoglobin were necessary for diagnosing myoglobin pigmentation. In summary, recent experience of triple M syndromes in an iRAE causing renal injury from myoglobin, and not necessarily only interstitial disease, is crucial.

FR-PO267
Prevalence of Cisplatin-Induced Nephrotoxicity in an Inner-City Population in the Bronx, New York
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Background: Cisplatin is a commonly used chemotherapy agent with known nephrotoxicity. Studies evaluating its nephrotoxicity in minorities are limited. We assessed the incidence of kidney injury among our adult patients receiving cisplatin.

Methods: Retrospective review of records for adult patients receiving cisplatin from Jan 2021 to Jan 2023 was conducted. Serum Creatinine (SCr) and estimated glomerular filtration rate (eGFR) were obtained at baseline and within 30 days after cycles 1, 2, and 3 of Cisplatin. KDIGO definition was used to diagnose AKI.

Results: Of the 47 patients included in the analysis, 51.1% were male (n=24), median (range) age was 58 years (19-78), 42.6% were Black (n=20), 21.3% White (n=10) and other racial-ethnic groups. American Indian, Asian and others. Cisplatin was most used in Whites (n=17), 80% of whites were Hispanic. The median number of cisplatin cycles was 4 (range: 1-11). Median baseline eGFR and Scr were 99.74 ml/min and 0.80 g/dl, respectively. Blacks had a mean baseline GFR of 86.1 ml/min, while non-Blacks had a mean of 100.86 ml/min (p=0.02). Cisplatin was administered to patients 3 and 4, but FS was not diagnosed at the time. We emphasize the importance of monitoring renal function and electrolytes in cancer patients undergoing CT, mainly because a wide range of old and new drugs is available.

FR-PO269
Abiraterone-Associated Syndrome of Mineralocorticoid Excess (SAME) Chandra Kumar Mallick Kodavanti,1 Raja Ravender,1 Saeed K. Shafi,2 University of New Mexico Health Sciences Center, Albuquerque, NM; 2Raymond G Murphy Department of Veterans Affairs Medical Center, Albuquerque, NM.

Introduction: We present a patient with abiraterone-associated SAME and discuss its pathophysiology and treatment.

Case Description: A 77-year-old man with metastatic prostate adenocarcinoma was treated with abiraterone 1 gram daily. Prednisone 5 mg daily was added 3 months later. Soon after chemotherapy initiation, his plasma potassium declined (Figure 1), and did not improve despite potassium replacement requiring hospitalization. He was volume overloaded with signs of urinary potassium wasting (Table 1). Further investigations revealed an ACTH (adrenocorticotropic hormone) mediated SAME. Discontinuation of abiraterone with amiloride use improved serum potassium and decreased kaliuresis.

Discussion: Abiraterone is a drug that irreversibly inhibits Cytochrome P450c17 with the suppression of 17α-hydroxylase (17α-OH) and C17,20-lyase and is used for the treatment of prostate cancer. The inhibition of 17α-OH in the Zone A of the adrenal cortex causes an ACTH-mediated SAME due to accumulation of corticosterone and deoxycorticosterone. Therefore, it is co-administered with prednisone to inhibit ACTH. However, low-dose prednisone may not effectively suppress ACTH in all the patients on abiraterone. High dose steroids or spironolactone use is discouraged as they may be associated with worse outcomes. Potassium wasting can be managed effectively with measured before cisplatin, after 1st, 2nd, and 3rd cycle. The results indicated a statistically significant decrease in eGFR at each level following cisplatin therapy [Wilks’ Lambda = 0.003, F (1, 26) = 13.7, p = 0.04].

Conclusions: Our retrospective study in a minority based, low socioeconomic status adult population highlights the progressive risk of kidney injury following each cycle of cisplatin therapy, indicating risk for chronic dose-dependent cisplatin-induced nephrotoxicity. Patients from low socioeconomic backgrounds and minority populations may be at higher risk for renal dysfunction and progression to CKD. Further prospective studies targeting this specific population are warranted to validate these findings and develop tailored interventions to reduce cisplatin-induced nephrotoxicity.

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amirolide and low-dose steroids. Despite prednisone use, the possibility of abiraterone inducing SAMA should be entertained in patients with hypertension, volume-overload, and/or hypokalemia.

Laboratory values

J Am Soc Nephrol 34: 2023

Figure 1: A graph showing plasma K (LOESS smoothed) and total CO₂ in (mEq/L) since prostate-cancer diagnosis.

FR-PO270

Lysozyme Toxicity Causing Proximal Tubulopathy in Patient with Acute Monocytic Leukemia

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Introduction: Acute leukemia is a common malignancy that is often associated with acute kidney injury. While rare, lysozyme-induced nephropathy can occur in patients with monocytic leukemia. This condition is caused by overproduction of lysozyme, which is released into blood circulation, filtered by the glomerulus, and reabsorbed by the proximal tubule. The resulting tubular injury can lead to renal insufficiency and electrolyte imbalances.

Case Description: 22 years old male was admitted to the hospital with fever. Upon admission, labs revealed marked leukocytosis, white blood cell count of 114,94 k/uL. Bone marrow biopsy confirmed a diagnosis of acute monoclastic/monocytic leukemia. The patient was noted to have acute kidney injury with serum creatinine of 1.48 mg/dL. Urine microscopy was with numerous granular casts and few eumorphic red blood cells. Kidney ultrasound showed normal-sized kidneys, increased parenchymal echogenicity and no hydronephrosis. After rapid resolution of AKI to a baseline creatinine of 0.6mg/dL patient was noted to have hypokalemia with serum potassium of 3.2 mmol/L, hypophosphatemia with phosphorus of 1.4 mg/dL (normal range 2.2-4.5mg/dL) and uric acid levels of 1.3 mg/dL (normal range of 3.5-8.5mg/dL). Given the high percentage of blasts and monocytes, lysozyme-induced nephropathy with Fanconi syndrome was considered. Fractional excretion of potassium was > 10%, indicating increased renal loss of potassium. Additional testing revealed elevated serum lysozyme levels (>100 µg/mL; normal range 0.2-7.5 µg/mL), supporting a diagnosis of lysozyme-induced nephropathy. Patient was started on aggressive fluid hydration; electrolytes were replaced. The patient was eventually started chemotherapy with normalization of white blood cell count and renal function.

Discussion: Lysozyme-induced nephropathy is a rare complication of acute or chronic monocytic neoplasms associated with overproduction of lysozyme resulting in elevated serum and urine levels. Lysozyme is freely filtered by the glomerulus and reabsorbed in the proximal tubule. Lysozyme can be toxic to proximal tubule cells leading to acute tubular injury, renal insufficiency, hypokalemia due to renal potassium wasting and Fanconi syndrome. Kidney biopsy can be helpful to establish a diagnosis. Recognition of this rare etiology for AKI is important and may guide management of acute and chronic leukemias.

FR-PO271

Imatinib-Associated Fluid Retention

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Background: Imatinib is one of the first tyrosine kinase inhibitors and is used in several conditions based on effects on receptors like BCR-ABL, the platelet-derived growth factor receptor (PDGFR), and stem cell factor (SCF) receptor tyrosine kinases. It has been associated with fluid retention (FR) and the mechanism behind this is largely unknown. Here we provide laboratory data that suggests imatinib affects aquaporin 2 (AQP2) expression proposing a theory behind imatinib associated FR.

Methods: Mouse kidney inner medullary collecting duct cell line (IMCD-3) cells are grown on coverslips in 24-well plate with DMEM containing 10% fetal bovine serum to 95% confluency. The cells are starved in 1ml/well plain DMEM F12 medium for 2 hours prior to treatment. They are then treated with DMSO as control or with either 5 µM imatinib for 1 hour or 100 nM AVP for 1 hour. The cells were then fixed, permeabilized, and incubated with anti-aquaporin 2 antibody and Alexa Fluor Goat anti-rabbit IgG 488. The cells are counter-stained by DAPI to visualize nuclei and stained coverslips then are mounted to slides and visualized under fluorescence microscope.

Results: IMCD-3 cells express AQP2 with an even distribution in cytosol and membrane in untreated control cells. Stimulation of IMCD-3 with vasopressin promotes a dramatic membrane distribution of AQP2. Similar to vasopressin, treatment of IMCD-3 cells with imatinib also induced a profound membrane distribution.

Conclusions: To our knowledge, this is the first evidence that treatment of IMCD-3 cells with imatinib enhances AQP2 membrane distribution. The bidirectional control of AQP2 trafficking from cytoplasm to the apical plasma membrane is regulated by vasopressin/vasopressin receptor (VP/VPVR) pathway and filamentous actin (F-actin) polymerization/demembranization. The signaling pathways can be activated by growth factor receptors such as EGFR and PDGFR which also cross-talk to VP/VP. Abi tyrosine kinases likely play important roles as downstream regulators in regulating actin skeleton remodeling and intracellular trafficking. Activation of Abi tyrosine kinases increases cell surface expression of EGFR. Therefore, inhibition of Abi tyrosine kinases by imatinib may lead to blockade of the EGF/EGFR signaling that regulates AQP2 distribution and FR. Further study of Abi signaling as a potential regulator in AQP2 trafficking is warranted.

Funding: Private Foundation Support

FR-PO272

The Conundrum of Normal Kidney Endothelial HLA-DR Clarified by Checkpoint Inhibitor Toxicity: A Role for Microvascular Endothelium in Peripheral Tolerance

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Background: Years ago we reported high constitutive expression of HLA-DR on microvascular endothelial cells of normal human kidney in the absence of inflammation. This surprised us and seemed incongruent with what is known about HLA class II antigen processing. Peptides bound to class II molecules are derived from the uptake of extracellular proteins which get processed intracellularly and then exported to the cell surface bound to HLA-DR where they can be recognized by specific T cell receptors. We asked, therefore, not be dangerous to have kidney endothelial cells constitutively express HLA-DR on their surface where they might encounter and activate circulating T cells?

Methods: We used flow cytometry and T cell activity assays to investigate the role of HLA-DR on human microvascular endothelial cells (KMEC).

Results: First, we show T cell proliferation and gamma interferon secretion of sensitized T cell when influenza hemagglutinin peptide is presented by KMEC of the appropriate HLA-DR specificity. Blockade of CD86 or HLA-DR reduces T cell activation while blockade of CD274 (PD-L1) enhances activation. Second, T cell co-stimulatory and inhibitory molecules on normal native and transplanted kidneys are identified by flow cytometry. CD274 expression is high on all KMECs and T cells within the kidney express CD274 (PD-1). Third, biopsies of acute kidney injury associated with checkpoint blockers that block the PD-1, PD-L1 axis show an intense perivascular lymphocytic infiltrate. Finally, human fetal kidneys express endothelial HLA-DR and CD274 at a similar time in development suggesting a fundamental property of the endothelial cells rather than resulting from an immune response.

Conclusions: Taken together, we propose a mechanism of peripheral tolerance whereby KMEC HLA-DR limits activation of sensitized T cells, even if a bound peptide is recognized, because of the constitutive high co-expression of CD274 (PD-L1).

Funding: Private Foundation Support

FR-PO273

Acute Interstitial Nephritis and Its Recurrence due to BRAF-MEK Inhibitors: Inhibitors for Melanoma

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Introduction: The efficacy of BRAF – MEK inhibitor therapy on survival in advanced melanoma has resulted in its widespread use. We describe two cases of biopsy proven Acute Interstitial Nephritis from BRAF-MEK inhibitors.

Case Description: Case One 51 year-old with melanoma, on binimetinib and encorafenib for two years developed acute kidney injury with creatinine of 2 mg/dL from...
baseline of 0.76 mg/dL two weeks ago. Labs revealed leukocytosis to 17,000, urinalysis with 41 WBC, 3 RBC, urine protein-creatinine 1.5 g/g, urine albumin-creatinine 44 mg/g and a negative urine culture. Encorafenib and binimetinib were held. Other workup revealed total protein 7 g/dL, elevated globulin 4.9 mg/dL, 1, ANA 1:640, anti-dsDNA 1:80, anti-RF 23 IU/mL. Kidney biopsy revealed AIN. Prednisone was initiated at 1mg/kg/day, with return of baseline kidney function in four weeks, at which time prednisone was tapered off. She is undergoing surveillance monitoring for melanoma off BRAF-MEK inhibitors, with plan to switch to alternative drug within the class should there be recurrence of disease. Case Two 64-year-old with metastatic melanoma on vemurafenib and cobimetinib for six months developed AKI with creatinine of 4 mg/dL from baseline of 1.2 mg/dL. Kidney biopsy revealed AIN. She was treated with prednisone 1 mg/kg/day and switched to encorafenib and binimetinib. Two months later, she developed another AKI, presumably AIN and steroids were prescribed. She was switched to immunotherapy, however due to progression of melanoma dabrafenib and trametinib was initiated, this time with prophylactic low dose of steroids given at the time of re-initiating treatment with a BRAF-MEK inhibitor.

**Discussion:** We report the first case series of AIN after BRAF-MEK inhibitors for advanced melanoma. We describe our approach to therapy which includes initial treatment with steroids to suppress the immune response, followed by switch to alternative drug, possibly within the same class. However, as described in case two, our patient developed an immune reaction to the second agent as well suggesting that the reaction is likely a class effect. This was offset by prophylactic low dose of steroids given at the time of re-initiating treatment with a BRAF-MEK inhibitor.

**FR-PO274**

**An Unusual Case of Acute Tubulointerstitial Nephritis (ATIN) with CD8-Positive Cytotoxic T Cell Infiltrate**

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**Introduction:** ATIN is a cause of acute kidney injury (AKI) characterized by tubulointerstitial inflammatory infiltrate, primarily lymphocytic and eosinophilic. We present a case of ATIN with an almost exclusive CD8+ cytotoxic T-cell infiltrate.

**Case Description:** A 65-year-old man with history of hypertension, nephrolithiasis, prostate cancer treated with brachytherapy, smoldering myeloma, thymoma s/p thymectomy, CD8+ granulomatous lymphadenitis on lymph node biopsy 2 years earlier and family history of autoimmune presented with AKI amid NSAID use. Exam was normal. Patient discontinued NSAIDs. Work-up revealed proteinuria 378mg/d, serum creatinine 2.6(baseline 1.3)mg/dL, free lambda light chains on UPEP, serum lambda 15mg/dL, K/L ratio 0.03 (stable). Urinalysis depicted protein 100mg/dL without abnormal cells or casts. HIV, hepatitis B/C, HTLV-U1 serologies, Parvo, CMV, AAV and EBV PCR were negative. c-ANCA was positive, ANA, dsDNA, PR-3, MPO antibodies negative, complements were normal. Kidney biopsy showed severe ATIN with CD8+ dominant T cell infiltrate, moderate interstitial fibrosis, no immune complex or amyloid deposition or glomerular crescents. Suspicion for a T-cell lymphoproliferative disorder was entertained. Hematologic workup was negative for thymoma recurrence or myeloma progression including flow cytometry. T-cell receptor studies were polyclonal. Patient was started on prednisone, creatinine improved to 2mg/dL after 2 weeks.

**Discussion:** This is a case of ATIN with an almost exclusively, atypical CD8+ cytotoxic T-cell infiltrate. Based on prior history, we suspect the underlying cause may be autoimmune dysregulation or T cell disorder. A careful workup to rule out active viral infections and underlying hematologic disorder was performed before starting immunosuppression with close follow up.

**Figure 1. Renal biopsy illustrating tubulointerstitial nephritis with CD8 cytotoxic T cell infiltrate, CD8 IHC x20**

**FR-PO275**

**Pauci-Immune Necrotizing and Crescentic Glomerulonephritis due to Pembrolizumab**

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**Introduction:** Immune checkpoint inhibitors (ICI) have trailblazed the treatment of cancer in the past decade. However, these drugs are marred with occurrence of Immune-related Adverse Effects (irAEs). Most commonly reported renal irAE is acute tubulointerstitial nephritis(AIN). Lately, cases of acute kidney injury(AKI) from podocytopathy and glomerulonephritis with ICI are noted but true incidence is likely underestimated from missed diagnosis and under-reporting. We present an illustrative case of an elderly female with a rare manifestation of AKI during treatment with pembrolizumab(Keytruda) with complete recovery due to prompt diagnosis and effective therapy.

**Case Description:** 74-year-old female undergoing treatment for metastatic squamous cell carcinoma of head and neck presented to Nephrology clinic for evaluation of AKI, hematuria and new-onset proteinuria. 15 days ago, she received a third dose of Keytruda. Creatinine had rapidly risen to 2.8mg/dL from baseline 0.5mg/dL. Urine protein-creatinine ratio of 1.6g/g, urine sediment with numerous acanthocytes and RBC casts. Renal biopsy showed acute pauci-immune focal necrotizing glomerulonephritis with 30% cellular crescents, granular mesangial staining for IgM and C3 on immunofluorescence and foot process effacement by electron microscopy. Keytruda was discontinued; she was treated with methylprednisolone, cyclophosphamide and rituximab. Kidney function normalized within 8 weeks.

**Discussion:** The case highlights importance of clinical suspicion and knowledge of the heterogeneity of pathological findings with renal irAEs on ICI therapy. Emerging data suggest incidence of AKI from 2-20% with Keytruda, a highly selective monoclonal IgG4-κ antibody against PD – 1 receptor. Renal irAEs can occur during and upto 2 months after therapy cessation. Many times, AKI is presumptively treated with steroids for AIN. The presence of glomerular hematuria, proteinuria or persistent AKI despite steroids warrants a renal biopsy as most patients can recover completely with early diagnosis and prompt treatment and possibly tolerable rechallenge of ICI.

**FR-PO276**

**Membranoproliferative Glomerulonephritis (MPGN) Associated with Atezolizumab**

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**Introduction:** Immunotherapy is a revolutionary approach to cancer management, particularly in advanced malignancies that have progressed despite traditional chemotherapy. Atezolizumab is a humanized monoclonal antibody immune checkpoint inhibitor that binds to programmed death ligand 1 (PD-L1) to selectively prevent the interaction between the PD-1 and B7.1 receptors. We present a unique case of a patient with acute kidney injury associated with nephrotic syndrome after starting atezolizumab for metastatic pancreatic carcinoma.

**Case Description:** 64 year old female with a past medical history significant for stage 1A endometrial cancer status post (s/p) total abdominal hysterectomy, biliary obstruction s/p stent for locally advanced unresectable pancreatic duct adenocarcinoma FOLFIRINOX and foot process effacement by electron microscopy. Her had hypertensive urgency with anasarca on clinical exam. Labs showed acute kidney injury with urinalysis positive for protein and blood. Further work up revealed nephrotic range proteinuria with UPCR 8 g/g, ANA, complements, Urine electrophoresis were negative. Serum electrophoresis showed IgG kappa monoclonal band. Anti-PLA2R receptor normal. Renal vein doppler was negative for renal vein thrombosis. Renal biopsy showed MPGN with full house pattern, immune complex deposit in sub endothelium thought to be from atezolizumab. She was taken off the immunotherapy trial and started on diuretics and steroids with significant improvement in her proteinuria and anasarca.

**Discussion:** Nephrotic syndrome (NS) in this patient was thought to be related to atezolizumab as secondary work up for MPGN was all negative. NS resolved after stopping atezolizumab and starting steroids which is suggestive of atezolizumab related nephrotoxicity.
the development of MCD with concurrent ATIN on a background of minimal NSAID use. NSAIDs can cause our knowledge, there is only one case report of MCD associated with lenalidomide

administration in a patient with Waldenström macroglobulinemia. Immunotherapy-Related Renal Sarcoidosis in a Patient with Metastatic FR-PO277

Acute Tubulointerstitial Nephritis and Minimal Change Disease After Administration of Lenalidomide Xuanling Du, Charles Russell, Naveen Punchayil Narayankutty. University of South Florida, Tampa, FL.

Introduction: Several case reports have raised concern regarding association between lenalidomide and acute tubulointerstitial nephritis (ATIN) or minimal change disease (MCD), mostly described in patients with plasma cell dyscrasia. Here we report a case of concomitant ATIN with MCD after lenalidomide initiation for a patient with myelodysplastic syndrome (MDS).

Case Description: A 68-year-old male with a history of MDS, hypertension, and coronary artery disease presented with a 2-week history of right flank pain, anasarca, and dark urine. He reported a 40-pound weight gain since the symptoms began. He had been taking lenalidomide for 7 months and was awaiting allogeneic hematopoietic stem cell transplantation. He was taking ibuprofen 2-3 tabs (200mg) per week over the last few years and denied other medication changes or contrast exposure. On admission, serum creatinine was 6.9 mg/dl (baseline 0.6-0.8 mg/dl) with albumin of 1.5 g/dl (baseline 3.5 g/dl). A urinalysis showed a specific gravity of 1.045, 51-100 WBC/hp, 51-100 RBC/hp, and many granular casts. Urine protein quantification was > 2000 mg/dl. Renal ultrasound showed medical renal disease. Hospital course was complicated by continued renal deterioration requiring initiation of hemodialysis. His renal biopsy showed mild acute tubulointerstitial nephritis with scattered eosinophils and some chronic ischemic changes. Ultrastructural studies revealed diffuse podocyte injury and extensive foot process effacement consistent with minimal change disease. The patient was started on prednisone 60mg daily with an ensuing taper initiated at discharge. At 13 weeks the patient reported near total renal recovery with cessation of hemodialysis needs.

Discussion: Lenalidomide has been reported to induce ATIN. To the best of our knowledge, there is only one case report of MCD associated with lenalidomide administration in a patient with Waldenström macroglobulinemia. NSAIDs can cause acute renal failure, ATIN, and nephrotic syndrome, including MCD. NSAID-associated MCD may be present with or without ATIN, usually after long-term use. The elements of the history in our case suggests that consistent use of lenalidomide might have triggered the development of MCD with concurrent ATIN on a background of minimal NSAID use. Furthermore, rarely has MCD been reported in the setting of both MDS and lenalidomide exposure.

FR-PO278


Introduction: Immune checkpoint inhibitors (ICIs) are widely used as standard of care therapy in management of metastatic melanoma. There have been various reported kidney complications associated with these treatments, though immunotherapy-related sarcoid-like reactions (SLRs) with kidney involvement are rare.

Case Description: A 57-year-old lady was diagnosed with metastatic melanoma stage IV and received first line Iplimumab/Nivolumab followed by Nivolumab monotherapy q3 weekly. Her therapy was interrupted by an asymptomatic rise in serum creatinine (sCr) from a baseline of 0.9 mg/dl to 2.14 mg/dl with an incidentally detected serum calcium (sCa) of 13.23 mg/dl. She was managed with hydration & bisphosphonates. As sCr and sCa remained elevated with further ICI challenges, her treatment was changed to targeted therapy with oral Dabrafinib/Trametinib. Her melanoma remained in remission, but she persisted to have high sCr and sCa. Metabolic work-up revealed presence of hypercalciumia and elevated serum 1,25(OH)2 vitamin D. A CT chest was suspicious for granulomatous disease, but bronchoalveolar lavage result was equivocal. The patient underwent a kidney biopsy which revealed findings consistent with sarcoidosis. She initially responded to oral steroids. As her disease remained steroid dependent, therapy was switched to oral mycophenolate mofetil. Patients' sCr has remained stable at 1.5 mg/dl after 4 months of follow up.

Discussion: In the presented case, it appears that renal SLR was related to immunotherapy as kidney dysfunction and hypercalcemia occurred after the patient was initiated on treatment. Renal SLR may also have been perpetuated with continuation of the treatment with targeted therapy, as Dabrafinib/Trametinib treatment has also been associated with SLR. In such situations, treating SRIs with steroids or immunosuppressive agents may be a reasonable option to allow continuation of therapy.

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

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FR-PO280

A Case of Acute Interstitial Nephritis Associated with Belvarafenib, a Novel pan-RAF Kinase Inhibitor for Metastatic NRAS Mutant Melanoma

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Introduction: Belvarafenib is a potent oral type II pan-RAF kinase inhibitor that inhibits B-Raf V600E- and C-Raf-mediated signal transduction pathways and mutated Ras proteins, thereby demonstrating growth suppression of cancer with RAF or RAS mutation. This novel therapy has limited known adverse effects, with no reported kidney-related adverse events. Here, we present a case of interstitial nephritis associated with Belvarafenib treatment.

Case Description: A 79-year-old woman was diagnosed with stage IV melanoma (wild-type BRAF) with NRAS mutation on the pan-RAF agent (Belvarafenib). Eight months into the treatment, she presented to the melanoma clinic with nausea, fatigue, and severe weakness. The patient was pale on physical examination, and her vital signs were normal. Laboratory investigations revealed a serum creatinine of 260 µmol/L (from baseline 90 µmol/L) and protein trace in urinalysis with no leukocyturia or hematuria.

Discussion: Acute renal injury, particularly acute interstitial nephritis, is not a recognized side effect of Belvarafenib. This is the first reported case of a pan-RAF agent kidney adverse effects manifested by AIN and ATI. A literature review reported no renal adverse effects associated with pan-RAF agents. Belvarafenib is a novel agent; further research and time are required to determine its adverse effects incidence. However, clinicians must remain vigilant about the potential kidney adverse effects of this agent and consider a kidney biopsy to assess AIN in patients whose AKI does not respond promptly to discontinuing Belvarafenib and supportive care.

FR-PO281

Gemcitabine Hemolytic Uremic Syndrome (HUS) Associated with a New Complement Factor B (CFB) Mutation Successfully Treated with Eculizumab

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Introduction: Gemcitabine(G) HUS often causes chronic kidney disease or ESRD. We describe a patient(p) who received a large cumulative dose of G who had a CFB mutation which caused dialysis dependency treated with eculizumab(E) successfully allowing cessation of dialysis.

Case Description: A 46 yr old woman with ER/PR positive & HER2 negative breast cancer metastatic to her spine, liver and thoracic nodes was given G, 1500 mg on days 1 & 8 of ever 3 week cycle. After receiving 28040 mg/m2 of G she developed a BP of 160/100mmHg, dyspnea, an increase in serum creatinine from 1.3 to 3.7 mg/dl and MAHA with a Hg of 5.4 gm/dl, platelets 100,000, haptoglobin < 10 mg/dl, and LDH of 1046 IU/L & schistocytes on blood smear. C3 & C4 and ADAMTS15 were normal. Hepatitis A & B, ANA, anti-DNA, cryo, ANCA, Shiga toxin, cardiolipin ab, rheumatoid factor, immunofloxation, INR, PTT, platelet antibodies, DAT, & direct coombs were all normal. After 2 plasmaphereses a renal biopsy showed Light: endothelial swelling, thickening of glomerular basement membranes, with double contours & intraluminal thrombi. If no tissue, EM: corrugated basement membranes with total foot process fusion and no immune deposits. She rapidly progressed to hemodialysis. Complement gene sequencing (Invitae, San Francisco, CA) showed a CFB mutation c.1937A>C (p.Tyr646Ser). She then received E 900 mg iv weekly x 4 & 1200 mg every other week for 4 months. MAHA quickly abated & after 3 months dialysis was stopped with a creatinine of 1.8 mg/dl. She died 4 months later from her cancer.

Discussion: We believe G-HUS occurs from a 2 hi hypothesis. G induces apoptosis & cell death in cultured bovine endothelial cells (AJ van Hall Cell Signal 34:86, 2017). The rapid renal vessels contraction mutation in CFB could be enough to induce HUS. Several studies suggest E can treat G-HUS but they did not study complement mutations. Any pt with G-HUS should have complement gene testing performed & if positive E can induce MAHA remission & reverse dialysis dependency.

FR-PO282

Hyperacute Immune Checkpoint Inhibitor-Associated Acute Tubulointerstitial Nephritis (ICI-ATIN) Followed by ICI-Renal Tubulus Acidosis (RTA): A Case Report

Hui Zhuang Tan,1 Ravindran Kanesvaran,2 Yi Chye Law,2 Joycelyn Jie Xin Loo,2 Singapore General Hospital, Singapore, Singapore; 2National Cancer Center Singapore, Singapore, Singapore.

Introduction: Hyperacute renal immune-related adverse events (irAEs) are rare. Immune checkpoint inhibitor related renal tubular acidosis (ICL-RTA) has been described, but its true incidence is unknown. We report a case of biopsy proven hyperacute ICl-related acute tubulo-interstitial nephritis (ICI-ATIN) with probable ICI-RTA developing after completion of steroid therapy.

Case Description: A 67-year-old Skih male was referred for non-oliguric KDIGO 3 AKI (sCr 219µmol/L; baseline sCr 62 µmol/L) and fever occurring 9 days after his first cycle of ipilimumab and nivolumab for treatment of metastatic clear cell renal cell carcinoma. Investigations showed pyuria (urinary leukocytes 168/L) and subnephrotic range proteinuria (uPCR 2.42g/g). C-reactive protein was raised at 205mg/L. Renal obstruction was excluded. There was no exposure to nephrotoxic drugs. Empirical broad-spectrum antibiotics was commenced. Progression of AKI (peak sCr 351µmol/L) prompted the initiation of prednisolone (60mg/day) for treatment of presumptive ICI-ATIN, once infection screen returned negative. ATIN was subsequently confirmed on kidney biopsy. Favourable response was observed, and prednisolone was tapered over 6 weeks. ICI was not resumed. Tyrosine kinase inhibitor was commenced. Gradually worsening hypokalemia, normal-gap metabolic acidosis, hypophosphatemia were observed shortly after completion of steroid therapy. RTA was clinically suspected. However, concurrent pulmonary infection contraindicated further steroid therapy. Electrolyte/alkal replacement was commenced. Gradual dose de-escalation, but not cessation, of replacement was successful during 8 months of follow-up.

Discussion: ICI-ATIN should be suspected in all patients on ICI with AKI, regardless of timing of presentation. Differences of AKI with fever in this context include sepsis-associated AKI, cytokine release syndrome and ICI-ATIN. Diagnosis may be challenging without kidney biopsy. An early, empiric trial of steroids may be considered as soon as infection is excluded. Limited evidence suggests that patients with hyperacute irAEs may develop further toxicities despite steroid therapy and cessation of ICI. ICI-RTA was a probable differential in our case. Steroid therapy remains the mainstay of treatment of ICI-RTA. It is uncertain if ICI-RTA can be transient or will persist as a chronic toxicity in patients managed without steroids.
FR-PO283

Colony-Stimulating Factor 1 Receptor Inhibitor (PLX3397) Attenuates Kidney Injury and Fibrosis Caused by Repeated Low-Dose Cisplatin
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Background: Cisplatin is a standard drug to treat many solid organ cancers. However, cisplatin can cause significant side effects including irreversible hearing loss and short-term (AKI) and long-term (fibrosis) renal impairment. Fernandez et al found that a mouse model of repeated low dose cisplatin (RLDC) treatment exhibited significant hearing loss and loss of cochlear mechanosensory hair cells. The colony-stimulating factor 1 receptor inhibitor PLX3397 ablated cochlear macrophages (>95% of immune cells in cochlea) and prevented hearing loss and hair cell loss. A recent report suggested that depletion of resident macrophages may mitigate renal fibrosis in the RLDC model. Therefore, we hypothesized that PLX3397 also would protect against cisplatin-induced nephrotoxicity.

Methods: CBAJ/C57BL16F1/GFP (het) mice were used to label macrophages with GFP. Mice underwent three cycles of cisplatin treatment (3 mg/kg/day i.p. cisplatin for 4 days followed by a 10-day recovery). We fed mice with vehicle- or PLX3397-formulated chow one week prior, and then via oral gavage during the cisplatin cycles. We harvested kidneys, blood, and inner ears at 20 days after the last cisplatin injection for histological and biochemical analyses. Tissue platinum (cisplatin) was measured by inductively coupled plasma mass spectrometry.

Results: Mice that received cisplatin had increased plasma BUN and NGAL levels. In addition, cisplatin-treated mice had significant tubular injury and fibrosis, while administering PLX3397 significantly improved all parameters. We found that cisplatin increased CX3CR1+ cells in the kidney (without vs. with cisplatin, 8.6 ± 1.3 vs. 20.2 ± 2.6 cells/high-power field (HPF), n = 4-5/group, p = 0.001). We confirmed that PLX3397 treatment ablated CX3CR1+ cells in the kidney (Cisplatin without vs. with PLX3397, 20.2 ± 2.6 vs.1.5 ± 0.6 cells/HPF, n = 4-5/group, p < 0.001). Moreover, PLX3397 markedly prevented the accumulation of platinum in the kidney.

Conclusions: PLX3397 treatment mitigated cisplatin-induced kidney injury and renal fibrosis via ablation of renal CX3CR1+ cells. Additionally, PLX3397 treatment also demonstrated decreased accumulation of cisplatin in the kidney. The pathogenetic roles of CX3CR1+ cells in cisplatin-induced nephrotoxicity of the RLDC model need to be elucidated in future studies.

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

FR-PO285

Allograft Rejection Following Immune Checkpoint Inhibition After Renal Transplantation: An In-Depth Analysis of PD-1, PDL-1, and CTLA-4 Checkpoint Inhibitors
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Background: Immune checkpoint inhibitors (ICIs) have emerged as one of the most pivotal therapeutic agents in tumor immunotherapy, and now used in solid-organ transplant recipients as salvage therapy post-tumor recurrence or for management of secondary tumors. However, ICI-associated allograft rejection has surfaced as a particular concern in solid-organ transplant recipients.

Methods: We performed a retrospective multi-center cohort study using TruEra, a global federated health research network providing access to electronic medical records across large healthcare organizations (HCOs) grouped into a network called Global Collaborative Network of 105 HCOs from 14 countries. We identified 164,034 post-renal transplant recipients without ICI use and 247 patients receiving ICI after transplant until May 11 2023 from 37 HCOs. Post-kidney transplant recipients in propensity-matched groups receiving either ICI or non-ICI regimen (n=247 each) were assessed for allograft rejection within first year of ICI exposure as compared to first-year allograft rejection in non-ICI group, with risk analysis and Kaplan-Meier survival analysis as relevant, with further analysis of renal allograft rejection in propensity-matched cohort comparisons with PD-1, PDL-1 and CTLA-4 inhibition.

Results: Kidney allograft rejection within 1 year occurred in 14.9% of patients in the non-ICI cohort as compared to 11.3% in the ICI exposure group (RR=1.32; 95%CI 0.83-2.09). In renal transplant recipients on PD-1 versus CTLA-4 checkpoint inhibition, allograft rejection was confirmed in 30.3% of patients in each cohort (RR=1; 95%CI 0.48-2.08). Allograft rejection noted in 71% patients in CTLA-4 vs. PDL-1 cohorts(RR=1; 95%CI 0.63-1.59), and 50% of patients in PD-1 vs. PDL-1 cohort (RR=1; 95%CI 0.54-1.86). Our study demonstrates there was no significant difference in renal allograft rejection between ICI and non-ICI cohort.

Conclusions: After propensity matching, ICI exposure post-renal transplant was not associated with acute allograft rejection within one year of ICI exposure. Our analysis of allograft rejection with one-year exposure of either of three ICI classes did not reveal superior (or inferior) association as compared to first-year allograft rejection post-renal transplant in non-ICI cohort.

FR-PO286

Focal Segmental Glomerulosclerosis (FSGS) Associated with Chimeric Antigen Receptor T-Cell (CAR-T) Therapy
Paloma C. Orozco Scott, Matthew Abramson. Icahn School of Medicine at Mount Sinai, New York, NY.

Introduction: CAR-T therapy was first used to treat pediatric leukemia, and has since expanded to other hematologic malignancies. The most common adverse reactions include cytokine release syndrome (CRS) and neurotoxicity. Acute kidney injury (AKI) has been reported in up to 30% of adult patients post CAR-T. Treatment for CRS is non-standardized but may include tocilizumab or steroids. However, ICI-associated allograft rejection has surfaced as a particular concern in solid-organ transplant recipients as salvage therapy post-tumor recurrence or for management of secondary tumors. However, ICI-associated allograft rejection has surfaced as a particular concern in solid-organ transplant recipients.

Methods: We performed a retrospective multi-center cohort study using TriNetX, a global federated health research network providing access to electronic medical records across large healthcare organizations (HCOs) grouped into a network called Global Collaborative Network of 105 HCOs from 14 countries. We identified 164,034 post-renal transplant recipients without ICI use and 247 patients receiving ICI after transplant until May 11 2023 from 37 HCOs. Post-kidney transplant recipients in propensity-matched groups receiving either ICI or non-ICI regimen (n=247 each) were assessed for allograft rejection within first year of ICI exposure as compared to first-year allograft rejection in non-ICI group, with risk analysis and Kaplan-Meier survival analysis as relevant, with further analysis of renal allograft rejection in propensity-matched cohort comparisons with PD-1, PDL-1 and CTLA-4 inhibition.

Results: Kidney allograft rejection within 1 year occurred in 14.9% of patients in the non-ICI cohort as compared to 11.3% in the ICI exposure group (RR=1.32; 95%CI 0.83-2.09). In renal transplant recipients on PD-1 versus CTLA-4 checkpoint inhibition, allograft rejection was confirmed in 30.3% of patients in each cohort (RR=1; 95%CI 0.48-2.08). Allograft rejection noted in 71% patients in CTLA-4 vs. PDL-1 cohorts(RR=1; 95%CI 0.63-1.59), and 50% of patients in PD-1 vs. PDL-1 cohort (RR=1; 95%CI 0.54-1.86). Our study demonstrates there was no significant difference in renal allograft rejection between ICI and non-ICI cohort.

Conclusions: After propensity matching, ICI exposure post-renal transplant was not associated with acute allograft rejection within one year of ICI exposure. Our analysis of allograft rejection with one-year exposure of either of three ICI classes did not reveal superior (or inferior) association as compared to first-year allograft rejection post-renal transplant in non-ICI cohort.
Discussion: This is the second case report of biopsy-proven FSGS after CAR-T in the literature. In contrast to the first case, our patient did not have interstitial inflammation or complete podocyte foot-process effacement, suggesting against primary FSGS, nor did he develop oliguria or edema. The presentation of new-onset proteinuria was temporarily related to the CAR-T infusion, possibly representing either a CRS-related global or an off-target local inflammatory response. This case highlights the importance of understanding CAR-T's effects on the kidney. A limitation of our case is the lack of APOL-1 testing to investigate as a second-hit phenomenon.

Targeting therapy by blocking the MRA receptor with spironolactone and inhibiting the renin-angiotensin-aldosterone system with ketocorticoide ultimately lead to improvement in serum potassium levels in addition to oral repletion.

FR-PO287
Preliminary Open-Labeled Study to Evaluate the Effect of Ciclasatin on the Pharmacokinetics of Cisplatin in Patients with Lung Cancer Undergoing Cisplatin-Based Chemotherapy
Hideyuki Kabasawa,1 Michihiro Hosojima,2 Sawako Goto,1 Satoshi Watanabe,3 Takahiro Tanaka,1 Nobutaka Kitamura,4 Ichiei Narita,5 Toshiaki Kikuchi,1 Akihiko Saito.2 1Department of Clinical Nutrition Science, Niigata University, Niigata, Japan; 2Department of Applied Medical Science, Niigata University, Niigata, Japan; 3Department of Respiratory Medicine and Infectious Diseases, Niigata University, Niigata, Japan; 4Clinical and Translational Research Center, Niigata University Medical and Dental Hospital, Niigata, Japan; 5Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan.

Background: In animal studies, the nephrotoxicity of cisplatin (CDP) is reduced by clastatin (CS), which is thought to be related to the function of the endocytosis receptor mediated by CS, and CS mediated neurotoxicity may be nephrotoxicity of CDP. CS is approved as a combination drug (Thienam®, imipenem-clastatin sodium), not as a single agent, and its effects on the pharmacokinetics of CDP in humans have not been examined. To evaluate the pharmacokinetics and safety of CDP when Thienam® is administered during chemotherapy including CDP in patients with advanced NSCLC, we evaluated the pharmacokinetics in this setting. The majority of referrals were for CKD, with multiple myeloma as the most common malignancy. These findings underscore the importance of collaboration between oncology and nephrology specialists to provide optimal care for patients with cancer-related kidney diseases. Further studies may provide insight into the long-term outcomes and best practices for managing these complex patients.

Results: Patients were sequentially administered 0, 0.5, and 1.0 g of Thienam®, and a total of nine patients, three in each group, were enrolled in the study. The median age was 65 years, 47–70 years (89%) years patients were men. The stages were unresectable stage III in one, stage IV in four, and stage IVB in four patients. The Cmax was 2.4±0.09, 2.6±0.34, and 2.4±0.26 μg/mL, T1/2 was 114±3.5, 114±3.2, and 114±3.4 h, and area under the curve (AUC) was 857±414, 818±244, and 776±1217 μg/mL/min in the 0.5, 1.0, and 1.0 thienam groups, respectively. No severe adverse events occurred; only one case of grade 3 or higher adverse event (leukopenia) occurred, which was thought to be due to chemotherapy.

Conclusions: In chemotherapy, including CDP administered to chemotherapy-naive patients with advanced NSCLC, the T1/2 and AUC of serum platinum concentration were decreased, particularly in the high-dose thienam group. It might be due to the suppression of microRNA-mediated renal uptake and retrieval of CDP by CS (Trial registration: jRCTs031180329).

Funding: Clinical Revenue Support

FR-PO288
Refractory Hypokalemia due to a Rare Paraneoplastic Syndrome
Ajman Ajaz, Muhammad S. Ajmal. Baylor College of Medicine, Houston, TX.

Introduction: Renal potassium wasting can occur due to a variety of etiologies. Understanding the pathway resulting in potassium wasting is critical to treating and ultimately correcting the acid-base and electrolyte derangements seen in these cases.

Case Description: We present a case of a 54 year old female with newly diagnosed high grade metastatic neuroendocrine tumor (NET) admitted for intractable diarrhea improving after octreotide administration. Her labs, however, showed persistence of severe hypokalemia and metabolic alkalosis despite aggressive repletion. Urine electrolytes suggested renal potassium wasting with undetectable renin and aldosterone levels, and elevated urine and serum cortisol levels with elevated adrenocorticotropic hormone (ACTH) which failed to be suppressed with dexamethasone suppression testing (DST), suggesting a paraneoplastic etiology for ACTH release. Due diligence was taken to ensure that ACTH release was not from a primary pituitary tumor in addition to determining the cause for cortisol and the MRA receptor in the adrenal and the steroid synthesis pathway. Cortisol, at high levels, acts upon the MRA receptor resulting in hypokalemic metabolic alkalosis.

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

Current and future areas of inquiry for onconephrology clinics

FR-PO290
Association of Proton-Pump Inhibitor Use and Immune Checkpoint Inhibitor-Associated AKI: Evidence from a Meta-Analysis
Arjunmohan Mohan,1 Pujaree Krisanapun,2 Supawit Tangpanthi,3 Charat Tangpanthi,4 Charat Tangpanthi,4 Sandra Herrmann,2 Mayo Clinic Rochester, 1Zareath Hospital, Philadelphia, PA; 2Mayo Clinic Minnesota, Rochester, MN.

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but their use is associated with immune-related adverse events (irAEs), including kidney injury. Proton pump inhibitors (PPIs) are commonly prescribed medications independently associated with kidney injury. Understanding the relationship between irAEs and acute kidney injury (AKI) and PPI use is crucial for optimizing patient management and minimizing complications.

Methods: To explore the association between ICI-AKI and PPI use, a comprehensive literature review was conducted. Databases including MEDLINE and EMBASE were systematically searched for articles published until January 2023. Studies reporting the incidence and risk of ICI-AKI in patients receiving ICIs, with or without concomitant PPIs, were identified and included in our analysis. Pooled odds ratios (ORs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.

Results: A total of 13 studies, involving 9371 patients, were included. The overall incidence of AKI from all-cause was 51.0% (95%CI, 32.6-69.8%) among patients on PPIs and 49.0% (95%CI, 31.1-67.1%) among those not on PPIs. Focusing specifically on ICI-AKI, the incidence was 59.0% (95%CI, 49.9-67.8%) among patients on PPIs, compared to 38.7% (95%CI, 30.3-47.4%) in those not on PPIs. Importantly, our analysis revealed a significant association between PPI use and the risk of ICI-AKI, with a pooled OR of 2.51 (95% CI 1.24-5.11). These findings indicate a higher likelihood of developing ICI-AKI when using PPIs.

Conclusions: In conclusion, our meta-analysis provides further evidence of an increased risk of ICI-AKI associated with the use of PPIs. Clinicians should exercise caution when prescribing PPIs to patients receiving ICIs.
caution and try to avoid prescribing PPIs in patients undergoing ICI therapy, as these
influences renal electrolyte handling by modulating renal reabsorption of phosphate (PO
in membrane-bound and soluble forms. Membrane- Klotho acts as a co-receptor for
fibroblast growth factor (FGF23), while the soluble form of Klotho circulates and acts
systemically on distant organs. Known secretes to create the membrane Klotho to produce
the soluble forms of circulating Klotho. The relative contribution of the two forms of
Klotho as a co-receptor is not known as the conformation of Klotho affects both forms. Low circulating levels of Klotho are associated with numerous disorders, including chronic kidney disease, cardiovascular disease, and cognitive impairment. To dissociate the function of two forms of Klotho, we aim to generate a non-
cleavable form of the Klotho protein (NCK), which will provide us with the means to
create a transgenic mouse model to study physiology and pathophysiology.

Methods: Using previously published data and our own mutational analysis of the
putative cleavage sites, we finalized on one mutant called non-cleavable Klotho (NCK)
mKd 5 956.5958L, with the replacement of 9 aa at 956.5GTLGFR to GDLGGGGG
and expressed it in HEK293 cells.

Results: We proceeded to test that NCK is: 1. Expressed normally and trafficked
to cell surface, 2. Functionally intact. 3. Indeed, NCK expression in cells and cell surface
is comparable to WT Klotho (immunoblot, immunocytochemistry, and surface
biotinylation), and, NCK is functionally intact as evident by its ability to sustain FGF23
signaling (FGF23-induced phospho-ERK/total ERK. There is no detectable NCK in the
supernatant despite abundant cell surface expression. The data supports a NCK that is
trafficked to the cell membrane, functionally intact, but not released from the cell surface.

Conclusions: A mouse model of NCK replacing WT Klotho is being generated
which will provide a valuable tool for studying the physiological and pathological roles
of membrane vs. soluble Klotho protein.

Funding: Other NIH Support - Charles Pack Foundation, Private Foundation Support

FR-PO292
Partial Klotho Deletion in the Renal Distal Segment Does Not Affect Ca2+ Handling
Teodora Grigore, Malou Zuidschweroude, Caro Bos, Hannes Olausson, Joost Hoenderop, Radoudumc, Nijmegen, Netherlands.

Background: Klotho is a protein important in health and disease, as decrease of circulating Klotho levels is correlated with age increase and chronic kidney disease (CKD) progression. This highlights Klotho as a potential early biomarker for CKD, as well as a potential therapeutic strategy to improve health and lifespan of patients. Klotho influences renal electrolyte handling by modulating renal reabsorption of phosphate (PO4
3-
) and calcium (Ca2+)
through Ca2+
channel TRPV5 and Na+/Pi co-transporter NPT2a, and by interacting with renal phosphaturic hormone fibroblast growth factor-23 (FGF23).

Methods: The mouse model with a partial deletion of Klotho (Ksp-KL -/ ) in the distal convoluted tubule (DCT) was generated using the Cre-Lox recombinase system, and was characterized by a disrupted mineral metabolism, with hyperphosphatemia, elevated FGF23 levels and decreased parathyroid hormone levels. An interventional study was performed on Ksp-KL-/- mice by subjecting the mice to a 0.02% Ca2+ diet for 3 weeks immediately after weaning. 24-hour urine and blood samples were collected using metabolic cages, and kidney and intestines were processed and relevant gene expression levels were analysed (qPCR). This study aimed to assess Ca2+ handling in Ca2+-deficient Ksp-KL-/- mice to increase our understanding of electrolyte handling.

Results: Urinary, serum and fecal Ca2+ levels were not significantly different in Ksp-KL-/- mice compared to Ksp-KL+/+ mice. Intestinal expression of Trpv6 and Npt2b did not indicate a compensation towards intestinal electrolyte handling.

Conclusions: Partial deletion of Klotho (21%) in the DCT does not affect renal or intestinal Ca2+ handling, contrary to the global deletion of Klotho. We speculate that this may be due to insufficient challenge on the Ca2+ metabolism of the mice, as well as residual Klotho amounts that are sufficient to maintain normocalemia and normocalcuria.

FR-PO293
Molecular Characterisation of Novel Klotho Variants Identified in Patients with Ca2+ Disturbances

Background: Klotho is the long-term loss of kidney function, which exerts multiple repercussions on other organs, including the cardiovascular system. The progression of CKD is significantly associated with decreased serum levels of Klotho and elevated serum levels of FGF23, however the precise underlying molecular mechanisms are yet unsolved. Although CKD has a high heterogeneity in molecular changes, the disruption of the Klotho-FGF23 axis is a common feature, considering that the decline in serum levels of Klotho as the disease progresses is constant in all stages of CKD. Klotho is a protein with a large ectodomain that can be cleaved and released into circulation. Expressed in the proximal and distal tubules, Klotho is demonstrated to affect renal P2O4 excretion by interacting with NPT2a and reabsorption of Ca2+ by anchoring TRPV5.

Methods: The Klotho variants (c.1151T>C, c.1489T>C, c.1819A>G, c.2069C>T, c.2590G>A, c.2620G>A, c.3008A>G) were identified in a cohort by whole-exome sequencing. The variants were transiently transfected in HEK293 cells. The variants were characterized by investigating the shedding pattern, conditional cleavage, presence on the cell surface, cellular localization and co-localisation with TRPV5.

Results: Full-length shed Klotho (c.1130 kDa) and Klotho domains (c.60 kDa) can be cleaved and identified by Western blotting. All results are compared to the wild-type Klotho variants.

Conclusions: Our study indicates that the novel identified Klotho variants have an effect on the expression and shedding of Klotho, which directly affect the serum levels of FGF23, leading to a decrease in circulating Klotho levels. These recent findings should allow for novel investigations on the effect of Klotho shedding in CKD.

FR-PO294
Bone-Specific Overexpression of Membrane Klotho Induces FGF23
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Background: Klotho, either membrane-bound or soluble (or cleaved) form, acts as a coreceptor that enhances the binding affinity of FGF23 to FGF receptors (FGFRs). Soluble Klotho has been shown to potentiate FGF23 production in osteocytes through a yet unknown mechanism, but little is known about the role of membrane Klotho in the regulation of FGF23 production.

Methods: We generated and characterized a novel mouse strain with targeted overexpression of membrane Klotho in the osteoblast lineage, driven by the 2.3-kb Colα1 promoter.

Results: The transgenic mice are born alive and initially indistinguishable from their control littermates, but they show growth delay and die within a few days. Overexpression of membrane Klotho in osteoblasts/osteocytes resulted in a tremendous increase in serum levels of FGF23 (up to 485-fold) and cranial bFGF mRNA (~600-fold) compared to wild-type mice. Remarkably, elevated levels of 1,25-dihydroxyvitamin D and PTH, reduced Nap2a, and elevated Cyp24a1. Treatment of these mice with an FGF-receptor blocker markedly and dose-dependently suppressed the increased bone Fg23 expression. Using primary osteoblasts isolated from the transgenic mice, we also show that the increased Fg23 expression during osteogenic differentiation is primarily mediated by FGFR-dependent activation of the MAPK pathway.

Conclusions: These results suggest that membrane Klotho stimulates FGF23 production in osteoblasts/osteocytes, presumably by forming a positive feedback loop mediated by the FGF23-Klotho-FGFR signaling complex. Thus, membrane Klotho expressed in bone cells functions as an amplifier of FGF23 production.

FR-PO295
Merged In Vitro/In Vivo RNAseq/ATACseq Pinpointed FGF23 Target Genes Dysregulated with Klotho Deletion in Kidney Single-Cell Subpopulations
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Background: FGF23 controls phosphate and vitamin D synthesis in the kidney via its co-receptor eKlotho (KL), however, the cellular responses to FGF23 during normal and disease states are not fully understood. We hypothesize that FGF23 induces unique and generalized changes in transcription and genomic accessibility within specific nephron cell populations.

Methods: HEK293 cell line stably expressing membrane Klotho (HEK-mKL cells) was treated with FGF23 (50 ng/mL) for 4 and 16 hours, then processed for ATACseq and

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-P0296
Skeletal Muscle Is a Novel Source of FGF23 in Mouse Models of CKD
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**Background:** Fibroblast growth factor 23 (FGF23) increases renal phosphate (Pi) excretion, and in early stages of CKD, FGF23 levels rise progressively in an attempt to maintain normal Pi levels. Pi is a potent inducer of FGF23 in bone. Previous studies suggested that muscle might not be the sole source for systemic FGF23 elevation in CKD. Here we study whether muscle models of hyperphosphatemia express FGF23 in skeletal muscle (SM) and whether Pi treatments of cultured myotubes (MT) induce FGF23 expression.

**Methods:** C2C12 MT & primary mouse MT were treated with 1-12 mM Pi for 24 hours, followed by qPCR expression analysis of FGF23. MT were grown in chamber-slides, treated with Pi, & immunostained with anti-FGF23. We analyzed four models of hyperphosphatemia: two CKD models, i.e. mice with global deletion of collagen 4a3 (Col4a3-/-), & wildtype mice receiving an adenine diet (1.5% of diet) at 3 days and 3 weeks. We also studied Col4a3-/- mice receiving a low Pi (0.2%) diet for 7 weeks. Furthermore, we generated mice with SM-specific deletion of FGF23 (FGF23fl/fl;HSA-Cre+) & administered an adenine-rich or a high Pi diet for 14 weeks & 7 weeks. Furthermore, we detected FGF23 in SM tissue of Pi-treated mice, compared to control mice on the same diet.

**Results:** Mouse models with hyperphosphatemia produce FGF23 in SM tissue in the presence & absence of CKD. SM-derived FGF23 significantly contributes to the hyperphosphatemia-associated elevations in serum FGF23 levels. Our ongoing studies aim to determine whether SM-derived FGF23 has paracrine effects, & for example contributes to SM atrophy that we have detected in these mouse models. Furthermore, we will determine if SM-derived FGF23 has endocrine effects & increases renal Pi excretion.

**Funding:** NIDDK Support

FR-P0297
Glycerol-3-Phosphate Is an Independent Predictor of FGF23 Levels in Hemodialysis Patients
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**Background:** Glycerol-3-phosphate (G-3-P) is a determinant of FGF23 levels, independent of known regulators of FGF23 such as serum phosphorus, calcium, PTH, iron metabolism, and inflammation. We measured serum G-3-P levels by LC/MS in 35 healthy individuals and 108 HD patients. We found that higher G-3-P was associated with increased G-3-P levels in HD patients. We next examined whether serum G-3-P is a determinant of FGF23 levels, independent of known regulators of FGF23.

**Methods:** We measured serum G-3-P levels by LC/MS in 35 healthy individuals and 108 HD patients. We found that higher G-3-P was associated with increased G-3-P levels in HD patients.

**Conclusions:** We measured serum G-3-P levels by LC/MS in 35 healthy individuals and 108 HD patients. We found that higher G-3-P was associated with increased G-3-P levels in HD patients.

**Funding:** NIDDK Support

FR-P0298
Multi-Trait Analysis of Mineral Metabolism Markers Identifies Novel Genetic Associations for FGF23
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**Background:** Genome-wide association studies (GWAS) have identified numerous genetic loci associated with mineral metabolism markers but have exclusively focused on single-trait analysis. In this study, we performed a multi-trait analysis of GWAS data of mineral metabolism markers, exploring overlapping genetic architecture between the traits, to identify novel genetic associations for fibroblast growth factor 23.

**Methods:** We applied multi-trait analysis of GWAS (MTAG) to genetic variants common to GWAS of 5 genetically correlated mineral metabolism markers (phosphorus, calcium, and PTH) in European-ancestry subjects. We integrated information from the UKBiobank GWAS for phosphate and calcium (n=366,484), and two GWAS from the CHARGE consortium for PTH (n=29,155) and FGF23 (n=16,624).

**Results:** MTAG increased the effective sample size for all mineral metabolism markers, to n=50,325 for FGF23. After clumping, MTAG identified independent genome-wide significant SNPs for all traits, including 47 loci for FGF23. Many of these loci have not been previously reported in single-trait analyses, including loci involved in inflammation, lipid metabolism, glucose metabolism, and bone health.

**Conclusions:** MTAG boosted the number of genome-wide significant loci FGF23. Our findings highlight the importance of performing multi-trait analysis in GWAS studies of mineral metabolism markers to identify novel genetic associations. These genetic loci may provide insight into the biological mechanisms underlying mineral metabolism and may have implications for the development of therapies for mineral-related disorders.

**Funding:** NIDDK Support

FR-P0299
Activation of Fatty Acid β-Oxidation in Proximal Tubular Epithelial Cells Is an Intrinsic Mechanism for Suppressing Phosphorus-Induced Kidney Injury
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**Background:** Excess phosphorus is known to induce kidney injury. The kidneys are the primary organ that excretes phosphorus and are exposed to a phosphorus burden. Thus, it may be difficult for the kidneys to maintain their function over a lifetime unless they have some countering mechanisms against the phosphorus burden. This study aimed to clarify how the kidneys counteract the phosphorus burden.

**Methods:** Six-week-old male C57BL/6 mice were randomly divided into Ctrl and Pho groups. Mice in the Ctrl and Pho groups were fed with a 0.85% phosphorus diet and a 3.0% phosphorus diet, respectively. Since renal fibrosis was not observed in both groups 3 weeks after the start of dietary intervention, we assumed that the kidney was in

**Funding:** NIDDK Support

FR-P0300
Kidney Proximal Tubule-S1/S2 Cells Showed a 27% Decrease in ETV5
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**Results:** HEK-mKL cell groups treated with FGF23 displayed clear segregation of FOS/JUN target genes by ATACseq. Our results identified ETV5, JUN, and JUNB as ETV5/JUN/JUNB targets. ATACseq showed ETV5 rapidly influenced genomic regions to control MAPK signaling for MAPK targets.

**Conclusions:** Our results identified ETV5, JUN, and JUNB as ETV5/JUN/JUNB targets. ATACseq showed ETV5 rapidly influenced genomic regions to control MAPK signaling for MAPK targets.

**Funding:** NIDDK Support
the stress compensation period and performed single-cell RNA seq (scRNA-seq) analysis at this point. The results obtained from scRNA-seq analysis were validated in vivo and vitro experiments. Results: Kidney component cells were classified into 12 clusters and analyzed differentially expressed genes (DEGs) between the Ctrl and Phos groups in each cluster. Some of the highest number of DEGs were detected in the S1/S2 segments of the proximal tubules (Prox. S1/S2), we focused on the Prox. S1/S2. Kyoto Encyclopedia of Genes and Genomes pathway analyses demonstrated that genes related to fatty acid β-oxidation (FAO) were the top activated pathway in the Prox. S1/S2 cluster of the Phos group. Similarly, cytokine-cytokine receptor interaction (Cytokine-CytokineR), a rate-limiting enzyme in the Phos group. In vitro experiments using cultured proximal tubular epithelial cells (PTECs) revealed that phosphor directly increases CPTIA expression. Etonoxir, a CPT1 inhibitor, significantly reduced cell viability of PTECs only under high phosphos conditions. Conclusions: The activation of FAO is an intrinsic defensive reaction against phosphorus-induced cytotoxicity in PTECs.

FR-PO300 Calemicine Treatment Reduces Progression of High Phosphate-Induced Tubular Injury in Mice

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Background: High phosphate stimulates fibroblast growth factor 23 (FGF23) and both factors are discussed to promote chronic kidney disease progression. Recently, we demonstrated that a high phosphate diet (HPD) in mice leads to increased serum phosphate and calcium levels and a significant decrease in the IKK2 mediated proximal tubule injury and tubulointerstitial fibrosis. In parallel, inflammatory processes in the renal parenchyma with induction of MCP-1 (monocyte chemotactant protein-1; Ccl2) and accumulation of macrophages as well as the development of perivascular lymphoid structures (TLS) in the medulla and cortical junction could be demonstrated in HPD mice. Calemicines are observed both in vitro and in vivo not only in the renal cortex, but also in the medulla and the interstitial tissues. The present study was performed to investigate the calemicine treatment of HPD-induced renal damage and the maturation of TLS in mice.

Methods: To investigate whether calemicine treatment positively affects kidney health, we induced kidney disease in male C57BL/6 mice by the use of a 2% HPD in comparison to a 0.8% phosphate control diet (Ctrl). After four months of dietary intervention, one HPD-fed group was concomitantly treated with 1 mg/kg body weight/day etelcalcetide (Etl) for further two months. At the end, blood and urine were taken and kidneys were harvested for histological and transcriptional analysis.

Results: Therapy with Etl reduced HPD-induced Fgf23 levels but had no effect on elevated serum phosphate levels. Etl reduced activation of the renal Stat3/Kim-1 signaling cascade and decreased HPD-mediated tubule damage. Furthermore, EtI significantly suppressed mRNA expression of Ccl2 and the macrophage-specific marker Adgr1 compatible with the HPD group without therapy. Etl had no effect on the development and maturation of renal TLS in the HPD group, which were characterized by CD3+ T cells, CD45R+ B cell clusters, IgD-secreting cells, CD138+ plasma cells, and podoplanin+ cell networks.

Conclusions: Etl therapy reduces Fgf23 levels and slows progression of tubule injury in mice on HPD. Maturation of renal TLS remained unaffected by Etl, which may be attributed to persistent hyperphosphatemia.

Funding: Commercial Support - Amgen

FR-PO301 Activation of the IKK2-NFκB Pathway in Vascular Smooth Muscle Cells (VSMCs) Inhibits Vascular Calcification and Stiffness in CKD by Reducing the Secretion of Apoptosis-Mediating Calcifying Extracellular Vesicles

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Background: Medial calcification is a major risk factor of cardiovascular mortality, particularly for patients with chronic kidney disease (CKD). The IKK2-NFκB pathway mediated-inflammation in vascular smooth muscle cells (VSMCs) has been proposed to be an etiologic factor in vascular calcification. However, the VSMC-specific role of the IKK2-NFκB pathway in vascular calcification remains to be elucidated.

Methods: To study the role of the IKK2-NFκB pathway in vascular calcification, we used Cas9-CRISPR and Cre-loxP techniques to delete some key genes in the IKK2-NFκB pathway from cultured VSMCs and mice, respectively.

Results: CKD significantly induced inflammatory factors in VSMCs through activation of the IKK2-NFκB pathway. However, CRISPR-mediated knockouts of IKK2, RelA and NFκB1 in VSMCs all exacerbated osteogenic differentiation and mineralization of cultured VSMCs. In vivo studies showed thatCre-mediated IKK2-NFκB pathway deficiency attenuated CKD-dependent medial calcification and vascular stiffness. Inhibition of the IKK2-NFκB pathway induced apoptosis of VSMCs in vitro and in vivo by reducing anti-apoptotic gene expression. In addition, increased calcification extracellular vesicles through the inhibition of the IKK2-NFκB pathway induced mineralization of VSMCs.

Conclusions: Taken together, this study unexpectedly reveals that activation of the IKK2-NFκB pathway in VSMCs plays a protective role in CKD-dependent vascular calcification by reducing the release of apoptotic calcifying extracellular vesicles.

Funding: NIDDK Support, Other NIH Support - R01HL157604, R01DK32181, R01DK124901

FR-PO302 Hypo-Osmotic Condition Accelerates Calcification of Extracellular Matrix in Cultured Vascular Smooth Muscle Cells

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Background: Hypotension, one of the most frequently observed electrolyte disorders in patients with chronic kidney disease (CKD), is associated with increased risk of death. Basic studies have shown that lower sodium levels or osmolar conditions in the culture media induce cell damages, oxidative stress, and apoptosis: the latter two are also shown to accelerate vascular calcification (VC), a critical complication in CKD patients. It is unknown whether hyponatremia or low osmolar condition plays roles in the pathogenesis of VC.

Methods: Human vascular smooth muscle cells (VSMCs) and dissected mouse aortic rings were cultured with calcifying medium, which was supplemented high calcium and phosphate. Sodium and other osmotic substances were further added to confirm their impacts on VC and phenotypic changes of VSMC. To determine the main signalling pathway of VC in relation to osmotic stress, we performed microarray analyses. Rac1-Akt pathway and sodium-calcium co-transporter (NCX1) were investigated. The effect of osmolarity on calciprotein particles formation (CPP) was also confirmed.

Results: The lower NaCl levels in the culture medium accelerated calcification of the extracellular matrix in cultured VSMCs as well as cultured mouse aortic rings. Conversely, the higher osmotic condition induced less calcification. Activation of Rac1-Akt signalling pathway, oxidative stress, CPP generation, and osteochondrogenic differentiation of VSMCs were identified as mechanisms of VC mediated by lower osmotic medium. Furthermore, sodium-depending transcellular calcium influx through NCX1 induced by high osmotic condition was proposed as mechanisms to prevent VC.

Conclusions: Our data suggest that a lower osmolarity including hyponatremic condition accelerates high-phosphate-induced VC by activating multiple cell-mediated processes. Targeted approach to avoid hypoosmotic condition would be important to prevent VC in CKD.

FR-PO303 Role and Mechanism of Interaction Between Autophagy and Ferroptosis in Regulating Osteogenic Transformation of Vascular Smooth Muscle Cells in Vascular Calcification

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Background: Vascular calcification could cause death in chronic kidney diseases (CKD) patients, however, its pathogenesis is not clear. Osteogenic transformation of VSMCs is key to vascular calcification in CKD, but its mechanism has not been fully elucidated. Our previous study has found an interaction between autophagy and ferroptosis involving osteogenic transformation of VSMCs in vascular calcification. This study aimed to elucidate the role of interaction between autophagy and ferroptosis in regulating osteogenic transformation of VSMCs.

Methods: We used the 5/6 nephrectomy rat model with a diet of 1.2 % phosphate at 16 weeks. Rat VSMCs were treated with supplemented medium β-glycerophosphate and CaCl2 for 7 days. All experiments were approved by the ethics committee of Sichuan Provincial People’s Hospital (No. 2017. 36). And we measured autophagy and ferroptosis in CKD vascular calcification. Full-length transcriptome sequencing was performed upon rats abdominal aortic tissues. After bioinformatics analysis with the results of sequencing, we verified the role of interaction between autophagy and ferroptosis in regulating osteogenic transformation of VSMCs.

Results: The oxidative stress effect was enhanced with vascular calcification in CKD, accompanied by ferroptosis and autophagy in VSMCs. Full-length transcriptome sequencing results indicated differential expression that were related to ferroptosis and autophagy pathways significantly enriched, including significantly upregulated expression of Ruxn2, Aeg7 and ATG5, RAB7A, ARNTL, HSP90, LAMP2A and Beclin-1 in VSMC. Protein-protein interaction analysis showed there were interactions between differentially expressed genes that were related to autophagy and ferroptosis. Multispectral fluorescence imaging showed that the expressions of GPX4 and Sm22α decreased and the expressions of NCOA4, Smarca4 and Runx2 increased in calcified vessels of CKD.

Conclusions: These findings shed light on the role of interaction between autophagy and ferroptosis in regulating CKD-associated vascular calcification. Further studies are needed to explore the precise mechanism of interaction between autophagy and ferroptosis in CKD vascular calcification.
FR-PO304
Reversibility of Vascular Calcifications
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Background: Mechanisms of vascular calcification have been extensively studied but little is known about resorption of existing calcifications, which has important therapeutic implications. Current data suggest that vascular calcification is largely irreversible but potential mechanisms for resorption that could be exploited have not been explored. To this end, resorption of calcifications was examined in human arteries implanted subcutaneously in mice or cultured with macrophages, and compared to bone particles and hydroxyapatite (HA).

Methods: Calcified human arteries were obtained from amputation specimens and calcification was quantified by µCT before and after implantation. Devitalized bone particles were obtained by pulverizing mouse femurs in liquid N\textsubscript{2} after removal of marrow, and HA was obtained commercially. Calcified arteries cultured with macrophages for 9 days showed a 34 ± 4% increase in medium calcium (p=0.01) consistent with resorption, without enhancement by RANKL. Findings were similar with bone particles.

Results: There was no decrease in arterial calcifications up to 6 weeks after implantation (+2.8 ± 0.6%) and only slight, insignificant resorption of bone particles after 7 weeks (+10 ± 8%). By contrast, only 24 ± 7% of hydroxyapatite remained after 7 weeks. Osteoclasts were not observed in any implant although TRAP-negative multinucleated giant cells were observed in HA implants. Calcified arteries cultured with macrophages in vitro can occur in vitro with added macrophages, suggesting that vascular calcification is not reversible in vivo due to the failure to form functional osteoclasts or recruit macrophages. Similar findings in bone particles suggest that this extends to other forms of biomaterialization. Further studies are needed to determine the properties of vascular calcifications that prevent recruitment of resorptive cells and identify strategies to overcome this.

Funding: Private Foundation Support

FR-PO305
In the CKD-MBD Absent Vascular Disease, CKD Decreases Cardiac Mitochondrial Function and Activin A Is an Activator of Skeletal Activin Receptor Signaling
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Background: The CKD-MBD is an important factor in the cardiovascular mortality associated with CKD. The cardiac component of the CKD-MBD has not been studied in the absence of vascular disease.

Methods: We developed an animal model of the CKD-MBD without associated vascular disease. We randomized CKD Alport mice into two groups – treatment with a monoclonal Ab to activin A and a control group. Cardiac function was assessed at sacrifice, and tissues were collected for histology, immunohistochemistry and RNAseq. Results: The Alport-Ab and IgG mice had CKD equivalent to human stage 4-5 CKD. PTH and FGF23 levels were one log order elevated, and circulating sclerostin additionally decreased levels of cardiac mitochondrial oxidative phosphorylation genes.

In the skeleton, the Activin A antibody decreased the effect of CKD to stimulate osteoclast formation with an antioxidant methylthio phenylthiol group on its side chain.

Methods: An adenine-containing chew was fed to 9-week-old Sprague-Dawley male rats for 7 weeks, and the treatment groups were administered 0.6 or 1.2 mg/kgBW of MIPMBP consecutively once per week.

Results: The serum creatine levels were elevated by 2-3 folds in the adenine-fed rat groups more than those in the non-adenine-fed groups. Subsequently, the bone turnover rate was significantly elevated in the adenine-fed rat groups, while the mineral densities of femoral bone decreased regardless of MIPMBP administration. Furthermore, the amount of malondialdehyde increased in the tibia increased by 3-fold more in the adenine-fed rats than that in the non-adenine-fed groups. Additionally, MIPMBP decreased the malondialdehyde content in a dose-dependent manner. In the adenine-fed rats, the osteosclerotic ratio, monitored by Raman spectroscopy, significantly increased; however, MIPMBP administration decreased it in a dose-dependent manner. Finally, the femoral bone storage module that was reduced to approximately half its value in the adenine-fed rats was almost completely recovered by MIPMBP administration.

Conclusions: According to the nature of bisphosphonates, most of the MIPMBP molecules administered were immediately delivered to the calcified tissues. The accumulated MIPMBP molecules could scavenger reactive oxygen species, forming an antioxidant barrier around the bone. The barrier aided in oxidative stress-dependent non-physiological collagen croslink formation and reduced osteocyte apoptosis-dependent apatite disorientation, thus improving the bone elastic material properties. MIPMBP exhibits the potential to serve as a new therapeutic device for uremic bone owing to a novel pharmacological mechanism.

FR-PO307
Parathyroid Hormone (PTH) Promotes the Release of H+ by Osteoclasts via the ATF3/V-ATPase Signaling Pathway
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Background: Persistently high levels of parathyroid hormone (PTH) promote osteolysis in patients with end-stage renal disease (ESRD). It is an important part that release of hydrogen ions (H+) by osteoclast leads to hydroxyapatite crystal dissolution in osteolysis, which is closely related to the proton pump (V-ATPase) on the osteoclast membrane. Activating Transcription Factor 3 (ATF3) initiates the differentiation and activation of osteoclasts. This experiment aimed to investigate that PTH promotes the release of H+ by osteoclasts via the ATF3/V-ATPase a3 signaling pathway.

Methods: Chromatin immunoprecipitation (ChIP) assay was used to examine the binding of ATF3 and V-ATPase a3 in mouse osteoclasts. After the treatment in osteoclasts, we used BCECF-AM probe to detect the pH with silencing and overexpression of ATF3. After PTH treatment in osteoclasts, we used BCEO-AM probe to detect the pH with silencing and overexpression of ATF3, and the stronger the green fluorescence, the lower the pH, which indirectly reflected the release of H+ by osteoclasts.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: ChIP assay proved that ATF3 binds to the V-ATPase a3 (Figure 1 A-B). PTH treatment increased the expression of ATF3 and V-ATPase a3 (Figure 1 C-F), and weakened green fluorescence of the cell, increasing the release of H+ by osteoclasts. After PTH treatment in osteoclasts, silencing ATF3 can decrease the expression of V-ATPase a3 and the release of H+ by cells but enhance green fluorescence in osteoclasts (Figure 2), while overexpression of ATF3 can increase the expression of V-ATPase a3.

Conclusions: ATF3 is a transcription factor of V-ATPase a3. PTH promotes the expression of ATF3 and V-ATPase a3, which then facilitates the release of H+ by osteoclasts.

FR-PO308

The Influence of MUC1 on Mg2+ Handling

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Background: Numerous genomic studies find an association between the common MUC1 polymorphism rs4072037 (minor allele frequency 21-47%) and circulating Mg2+ levels. This polymorphism in exon 1 of MUC1 alters mRNA splicing, elongating the N-terminus of mature MUC1. It is referred to as the long-signal peptide variant (LSP), as compared to the short-signal peptide variant (SSP). Although human genome association studies have found an association between the LSP variant and hypomagnesemia, no studies have demonstrated an effect of MUC1 on Mg2+ balance. MUC1 is known to enhance cell surface localization of Ca2+-selective TRP channels (TRPV5 and TRPV6). MUC1 is co-expressed with the Mg2+-selective channel, TRPM6, in the kidney’s distal convoluted tubule (DCT). TRPM6 is a key mediator of renal Mg2+ reabsorption of Mg2+ by cells but enhance green fluorescence in osteoclasts (Figure 2), while overexpression of ATF3 can increase the expression of V-ATPase a3.

Methods: We examined plasma Mg2+ levels in Mac1−/− mice and studied MUC1 and TRPM6 expression in polarized MDCK cells and in human kidney tissue samples.

Results: We found that Mac1−/− mice are hypomagnesemic. In polarized MDCK cells, MUC1 is expressed at the apical surface of polarized epithelial cells, a small fraction is expressed basolaterally, where EGFR is located. Both in MDCK cells and in human kidney tissue, that fraction of MUC1 is reduced in the LSP variant as compared to the SSP variant. EGFR is more heavily phosphorylated in response to basolateral EGFR in MDCK cells expressing SSP-MUC1 compared with LSP-MUC1, suggesting that SSP-MUC1 enhances activation of the EGFR receptor, promoting activation of TRPM6.

Conclusions: These studies provide a mechanistic explanation for the influence of MUC1 upon Mg2+ homeostasis. Ongoing studies are exploring the specific importance of kidney tubule MUC1 for TRPM6 activity and Mg2+ balance and EGFR-dependence of differences in TRPM6 cell surface expression associated with the LSP vs SSP MUC1 variants.

Funding: NIDDK Support, Private Foundation Support

FR-PO309

Lactating Kidneys Uregulate Expression of Cell Proliferation Genes and TRPM6 in the Distal Convoluted Tubule (DCT), Suggesting DCT Hyperplasia

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Background: Lactating females provide large quantities of minerals to nursing offspring, including Ca2+ but also Mg2+. Lactation-associated Ca2+ conservation is stimulated when parathyroid hormone (PTH)-related peptide from the mammary gland activates renal tubular PTHR receptors, promoting Ca2+ channel expression. However, mechanisms responsible for Mg2+ conservation are not described.

Methods: Female C57Bl/6 mice were mated and monitored for parturition. To normalize milk-demand, litters were culled to 4 pups at post-partum day 2 (P2). Urine was collected from P2 or nulliparous females. Mice were euthanized, and blood and kidneys harvested. Bulk RNA-Seq was performed in whole kidneys.

Results: Lactation reduced urinary Ca2+ and Mg2+, even though circulating Ca2+ and Mg2+ were similar or higher, consistent with increased tubular reabsorption. We asked whether acute PTHR receptor (PTHR) stimulation reduced urinary Mg2+ excretion. Acute treatment of animals with 1-34 PTHR accelerated phosphorus excretion and delayed Ca2+ excretion, as expected, but had no net effect on Mg2+ excretion. Transcriptomic analysis in kidneys from lactating dams revealed increased mRNA encoding the Mg2+-selective ion channel, TRPM6, exclusively expressed in the distal convoluted tubule (DCT). Transcript levels of proteins involved in paracellular transport (claudins 10, 16, and 19) were not significantly different. Kidneys from lactating dams were heavier, suggesting tissue hypertrophy. Segment-specific transcripts from the proximal convoluted tubule (PCT) and DCT were up-regulated, consistent with an increase in cell number in these tubule segments. Transcripts encoding numerous cell cycle-associated proteins also increased, including CDC20, cyclin-dependent kinase 1, cyclin D1, and cyclin D3. Cyclin D1 protein abundance also increased. In the early DCT, where TRPM6 is expressed, more cells from lactating than nulliparous females stained positive for cyclin D1.

Conclusions: These suggest that DCT hyperplasia may contribute to lactation-associated conservation of essential minerals.

Funding: NIDDK Support, Private Foundation Support

FR-PO310

Magnesium Decreases Urine Supernaturation but Not Calcium Oxalate Stone Formation in Genetic Hypercalcemic Stone-Forming Rats

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Background: This study assessed the effect of oral magnesium on urine parameters and stone formation in a genetic hypercalcemic stone-forming (GHS) rat model of human idiopathic hypercalciuria.

Methods: When fed the oxalate precursor, hydroxyproline, every GHS rat develops calcium oxalate stones. These rats, fed a normal calcium (Ca) and phosphorus (P) diet with hydroxyproline, were divided into three groups of ten rats per group: control diet with 4.0 g/kg MgO, low MgO diet (0.5 g/kg), and high MgO diet (8.0 g/kg). At baseline and at 6 weeks, twenty-four-hour urines were collected, and urine chemistry and supersaturation were determined. Stone formation was quantified.

Results: After six weeks those fed the low Mg diet had a significant reduction in urinary Mg and those fed the high Mg diet had a significant increase in urinary Mg compared to those fed the control diet. Dietary Mg did not alter urine Ca excretion while the low Mg diet led to a significant fall in urinary Ox. The low Mg diet increased urinary NH3 and decreased urinary citrate while the high Mg diet reduced urinary NH3 and increased urinary citrate. Urine supersaturation with respect to calcium oxalate was significantly increased with low Mg, whereas urine supersaturation was significantly decreased with high Mg. Neither a low nor high Mg diet altered kidney stone formation.

Conclusions: In genetic hypercalcemic stone-forming rats, dietary Mg significantly altered urinary CaOx supersaturation; a low Mg diet increased and a high Mg diet decreased CaOx supersaturation. There was no effect of dietary Mg on stone formation within 6 weeks of treatment.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Urine supersaturation (SS) of CaOx was differentially regulated by Mg. Results are mean ± SEM. *P < 0.05 vs. control; **P < 0.05 vs. low Mg.

FR-PO311

Subdued Limits E. coli Infection and Ca-Oxalate Crystallization in Drosophila Renal Tubules

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Background: Anoctamin (ANO) are Ca2+-activated phospholipid scramblases, Ca2+-activated Cl channels or both. Pathogenic ANO4 changes have been identified in dogs with calcium oxalate (CaOx) stones, and ANO4 protein expression is decreased in urinary extracellular vesicles of human CaOx stone formers. In Drosophila Malpighian tubules (MTs), subdued (ANO4-homolog) has these functions and participates in host defense against gram-negative bacteria. Urinary inoculation of mice with uropathogenic E. coli (UPEC) increases intrarenal CaOx crystallization. Thus, we investigated the interaction of subdued and UPEC for promoting Drosophila MT CaOx crystallization.

Methods: C724-Gal4, Uro-Gal4, and CG10116:Gal4 flies were crossed with UAS:subdued-RNAi flies to knockdown (KD) MT MnSOD alone despite prolonged NaOx feeding crystal formation during short-term in vivo crystallization. PC MnSOD slightly increased UPEC infection but did not change expression levels in PH1 mice. Compared to males, females have significantly reduced kidney A6 and/or A1 expression contribute to the observed differences in urine and plasma oxalate levels in PH1 mice. Compared to males, females have significantly reduced kidney A6 and kidney A1 protein expression exists (with no change in mRNA), where higher A1 expression is observed in male compared to female rats and is associated with significantly higher plasma (~1.8-fold) and urine (~2-fold) oxalate levels in males (including high renal oxalate secretion). Male rats also have higher liver sulfate-oxalate exchange, which could lead to elevated plasma oxalate. We therefore examined whether gender differences in A1 and/or A6 expression contribute to the observed differences in urine and plasma oxalate levels in PH1 mice. Compared to males, females have significantly reduced kidney A6 mRNA (44.6%, using qPCR) and total glycosylated A6 protein (>40%) expression. There were no significant differences in liver and kidney (~19%) A1 mRNA expression levels. We could not assess A1 protein expression due to lack of working antibodies, with reduced expression expected based on data from rats.

Conclusions: Our findings indicated that soluble oxalate is released from macrophages following internalization of calcium oxalate crystals. Slc26a6-/- macrophages demonstrated greatly reduced soluble oxalate release compared to WT macrophages. We therefore concluded that Slc26a6 plays a major role in the release of soluble oxalate from macrophages following internalization of calcium oxalate crystals.

Funding: Government Support - Non-U.S.

FR-PO312

SLC26A6 Plays a Major Role in Release of Soluble Oxalate from Macrophages Following Internalization of Calcium Oxalate Crystals

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Background: Accumulating evidence indicates that macrophages play an important role in recovery from oxalate-induced nephropathy. In in vitro studies showed that macrophages can engulf and dissolve calcium oxalate crystals. In vivo models demonstrated that decreased renal macrophage infiltration is accompanied by increased crystal deposition, suggesting involvement of macrophages in removing oxalate crystals. Despite these findings, the mechanisms mediating crystal clearance by macrophages remain unknown. We previously showed that macrophages express transporter SLC26A6. SLC26A6 functions as a Cl-oxalate exchanger in macrophages. Our studies indicated that under steady-state conditions, SLC26A6 mediates net oxalate efflux and prevents intracellular oxalate accumulation in macrophages. In the present work, we analyzed the role of SLC26A6 in mediating the release of soluble oxalate from macrophages following internalization of calcium oxalate crystals.

Methods: Primary murine wild-type (WT) and SLC26A6-deficient (Slc26a6-/-) macrophages were exposed to calcium oxalate crystals for up to 48 hours. Internalization of oxalate crystals by macrophages was analyzed by transmission electron microscopy (TEM). After crystal uptake, macrophages were washed and reincubated in an oxalate-free medium. Release of soluble oxalate after crystal internalization was measured as appearance of oxalate in the supernatant by use of an enzymatic assay.

Results: We found that WT and Slc26a6-/- macrophages are equally capable of oxalate uptake and internalization. The presence of soluble oxalate increases with time in the supernatant of both WT and Slc26a6-/- macrophages after preloading with oxalate crystals. When compared with WT macrophages, macrophages from Slc26a6-/- mice showed greatly reduced release of soluble oxalate after 48 hours.

Conclusions: Our findings indicated that soluble oxalate is released from macrophages following internalization of calcium oxalate crystals. SLC26A6-/- macrophages demonstrated greatly reduced soluble oxalate release compared to WT macrophages. We therefore concluded that Slc26a6 plays a major role in the release of soluble oxalate from macrophages following internalization of calcium oxalate crystals.

Funding: Government Support - Non-U.S.

FR-PO313

Gender Difference in Plasma and Urinary Oxalate Levels in a Mouse Model for Primary Hyperoxaluria Type 1

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Background: Mutations in the alanine–glyoxylate amino transferase gene (Agxt) cause primary hyperoxaluria type 1 (PH1). A mouse model for PH1 was previously reported, with males having ~17.6% higher urine oxalate compared to females. Methods: mRNA and protein expression levels were assessed by qPCR and immunoblotting.

Results: We now observed that males have significantly higher (~1.7-fold) urine oxalate compared to females (t24-h urine oxalate in mg/g body weight: wild-type = 1.60±0.18; males = 6.69±0.32; females = 3.89±0.14). Males also have significantly higher (2.1-fold) plasma oxalate (µM: males = 4.86±0.86; females = 2.35±0.39). We first confirmed that the observed gender difference in oxalate levels is not due to differences in genotyping by showing that both males and females are homozygous for Agxt-. Anon transporters SLC26A1 (A1) and SLC26A6 (A6) play important roles in oxalate homeostasis. Proximal tubular oxalate secretion involves oxalate entry into the cell from blood via A1, and then its secretion into the urine via A6. A gender difference in liver and kidney A1 protein expression exists (with no change in mRNA), where higher A1 expression is observed in male compared to female rats and is associated with significantly higher plasma (~1.8-fold) and urine (~2-fold) oxalate levels in males (including high renal oxalate secretion). Male rats also have higher liver sulfate-oxalate exchange, which could lead to elevated plasma oxalate. We therefore examined whether gender differences in A1 and/or A6 expression contribute to the observed differences in urine and plasma oxalate levels in PH1 mice. Compared to males, females have significantly reduced kidney A6 mRNA (44.6%, using qPCR) and total glycosylated A6 protein (~40%) expression. There were no significant differences in liver and kidney (~19%) A1 mRNA expression levels. We could not assess A1 protein expression due to lack of working antibodies, with reduced expression expected based on data from rats.

Conclusions: We conclude that male PH1 mice have significantly higher urine and plasma oxalate levels compared to females, and that differences in kidney A6 and/or A1 (liver and/or kidney) expression potentially contribute to the observed gender difference.
Uremic Tonic Indoxyl Sulfate (IS) and Parathyroid Hormone (PTH) Interact and Affect Osteocyte Signaling and Function

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**Background:** Osteocytes are the master regulator of bone remodeling, and studies in CKD patients and animals show defects in osteocyte function and maturation regardless of the PTH level suggesting other CKD specific factors may affect osteocytes. Indoxyl sulfate (IS) has been shown to have an effect on osteoclasts and osteoblasts, but the IS effect on osteocytes has not been evaluated. IS is a potent endogenous ligand for aryl hydrocarbon receptor (AhR) which is critical in the removal of toxins and can lead to inflammation, changes in steroid hormones and altered MAP kinase signaling.

**Methods:** We therefore evaluated the effect of IS with and without PTH on differentiation, signaling, and mineralization in mature osteocytes (day 35) and in early osteocytes when mineralization is occurring (day 14) using IDG-SW3 cell line.

**Results:** The results demonstrated that in mature osteocytes, the addition of IS for 24 hrs dose dependently increased the expression of bone forming genes SOST and Dkk1, bone resorbing genes RANKL/OPG ratio and oxidative stress genes NOX1 & NOX4 (all P<0.01) but no effect on FGF23. In contrast, PTH treatment for 24 hrs decreased SOST by 135 fold, Dkk1 by 155 fold (p<0.01) and increased RANKL/OPG ratio by 1080 fold (p<0.001) with no effect on NOX, IS, but not PTH, inhibited MAP kinase activity (ERK1/2; p < 0.002) and induced AhR activity assessed by downstream CYP1A1 (increased by 10 fold) & CYP1B1 (increased by 4.5-fold). Thus, in mature osteocytes, PTH and IS have opposing effects on osteocyte genes, oxidative stress, mediated by different mechanisms. To assess the impact of IS and PTH on mineralization, osteocytes were treated with IS or PTH alone or together for 14 days. IS and PTH both decreased alkaline phosphatase activity and together reduced further. IS also reduced mineralization but PTH had no effect. PTH increased cAMP secretion by 90%, whereas IS decreased cAMP secretion by 60% alone and significantly reduced IS induced cAMP secretion in osteocytes (p<0.002).

**Conclusions:** In conclusion, IS and PTH have additive effects to inhibit early osteocyte mineralization, and opposing effects on mature osteocyte signaling and the gene expression involved in regulation of bone remodeling and differentiation. These results indicate IS is a major uremic toxin affecting osteocytes.

**Funding:** Private Foundation Support

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**FR-PO313**

Mineral and Bone Biomarkers Associate with Adverse Cardiovascular Outcomes and Mortality Within the German Chronic Kidney Disease (GCKD) Cohort

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**Background:** Mineral and bone disorders (MBD) in chronic kidney disease (CKD) are tightly linked to cardiovascular disease. This study aimed to compare prognostic information of nine MBD biomarkers to determine those associating best with adverse cardiovascular (CV) outcomes and mortality in pre-dialysis CKD. **Methods:** In 5217 participants of the German CKD (GCKD) study, enrolled for glomerular filtration rate (GFR) between 30-60 mL/min/1.73 m2, serum osteoprotegerin (OPG), fibroblast growth factor 23 (FGF23), intact parathyroid hormone (iPTH), bone alkaline phosphatase (BAP), cross-linked C-telopeptide of type 1 collagen (CTX1), procollagen I intact N-terminal propeptide (PINP), phosphate, calcium, and 25-OH vitamin D were measured at baseline. Participants with missing values among these parameters (N ~ 971) were excluded. Hazard ratios (HRs) for associations of OPG, FGF23, iPTH, BAP, CTX1, PINP, phosphate, calcium, and 25-OH vitamin D each alone and in combination, with 1) CV death, 2) non-CV death, 3) combined major adverse CV events (non-fatal MACE), and 4) hospitalization for congestive heart failure (CHF) were estimated using Cox regression analyses adjusted for major clinical risk factors for CKD. **Results:** During a median follow-up of 6.5 years, 385 non-CV deaths, 173 CV deaths, 643 non-fatal major adverse CV events (MACE) and 367 hospitalizations for congestive heart failure (CHF) were observed among 4246 participants. OPG and FGF23 were associated with all outcomes, with the highest hazard ratios (HRs) for OPG. In the final Cox regression model, adjusted for CV risk factors and all other investigated biomarkers, every standard deviation increase of OPG was associated with non-CV death (HR 1.84, 95%CI 1.41-2.40), CV death (HR 2.33, 95%CI 1.61-3.38), MACE overt proteinuria, serum osteoprotegerin (OPG), fibroblast growth factor 23 (FGF23), intact parathyroid hormone (iPTH), bone alkaline phosphatase (BAP), cross-linked C-telopeptide of type 1 collagen (CTX1), procollagen I intact N-terminal propeptide (PINP), phosphate, calcium, and 25-OH vitamin D each alone and in combination, with 1) CV death, 2) non-CV death, 3) combined major adverse CV events (non-fatal MACE), and 4) hospitalization for congestive heart failure (CHF) were estimated using Cox regression analyses adjusted for major clinical risk factors for CKD. **Conclusions:** Out of the nine biomarkers examined, stratification based on serum OPG identified CKD patients best who were at highest risk for any adverse CV outcome and mortality.
Since increased paracellular intestinal phosphate absorption is considered a main factor for hyperparathyroidism, we designed a probiotic cocktail to promote gut barrier, which could subsequently reduce phosphate absorption.

Methods: B. longum TCU1 and L. salivarius TCUA were tested in HK2 cell model to be able to promote zonula occluding-1 (ZO-1) expression and had anti-inflammatory effects. The Cocktail A including 10^8 CFU of B. longum TCU1 and L. salivarius TCUA; inulin and chitosan oligosaccharide (COS), and Cocktail B which was Cocktail 1 added with maltodextrin were used. Cisplatin-induced CKD rats were divided into (a) Control, (b) CKD, (c) CKD with L. casei (commercial probiotic) (d) CKD with Cocktail A and (e) CKD with Cocktail B (n=8 each) were experimented for 12 weeks. Blood was collected to measure calcium (Ca), phosphate (P) and parathyroid hormone (PTH). Immunohistochemistry of intestinal ZO-1 was measured.

Results: All rats with CKD had higher serum creatinine than Control throughout the experiment. At Week 4 & 8, CKD rats treated with probiotics had lower serum P than CKD rats, while week 12, only CKD rats with Cocktail A had significantly lower serum P than CKD, without serum Ca change. In addition, CLD rats with Cocktail A had lower serum PTH level than CKD rats at week 12. Intestinal ZO-1 expression in Cocktail A rats had non-significantly increased compared to the CKD rats as well.

Conclusions: Our study demonstrated the potential therapeutic effects of targeting probiotic cocktail A, which included B. longum, L. salivarius, inulin and COS, to ameliorate hyperparathyroidism and hyperparathyroidism in rats with CKD. Further study in clinical trial of targeting probiotic should be funded.

Funding: Government Support - Non-U.S.

FR-PO319

Extended-Release Calcifediol Overcomes Impact of Low eGFR on Vitamin D Metabolism

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Background: Serum 25-hydroxyvitamin D (25D) falls below 30 ng/mL and serum 1,25-dihydroxyvitamin D (1,25D) becomes undetectable as chronic kidney disease (CKD) progresses. Cholecalciferol or ergocalciferol are widely prescribed but cannot reliably raise 25D and lower elevated parathyroid hormone (PTH). They are replaced/combined with calcitriol (or 1α-OH analog) when PTH inevitably rises, contrary to the current KDIGO guideline, with justification that too much renal CYP27B1 has been lost, limiting hormone production. Randomized clinical trials (RCTs) prove that extended-release calcifediol (ERC) safely and sufficiently raises serum 25D and 1,25D, and effectively treats elevated PTH despite declining eGFR, but the mechanism is not fully elucidated and requires further investigation.

Methods: Changes in serum 25D, 24D, and 1,25D during ERC treatment in four RCTs were compared as a function of eGFR. In one study, 80 non-CKD patients were treated for 4 weeks (wks) with 300 mcg/day (d) for three ds and 60 mcg/d thereafter. In two studies (pooled), 285 non-dialysis patients with eGFR of 30.6±6.0 (mean±SD) mL/min/1.73m^2 were treated for 26 wks with 210 mcg/wk increasing, as needed, to 420. In another, 33 hemodialysis (HD) patients were treated for 26 wks with 900 mcg/wk.

Results: In these RCTs, baseline 25D was 37.7±12.1, 19.9±0.3 and 23.6±2.2 ng/mL, respectively. Mean 1,25D at baseline was inversely proportional to eGFR, ranging from 72.3±3.3 pg/mL in non-CKD patients to 9.4±1.0 pg/mL in HD patients. During treatment, mean 25D, rose to >70 ng/mL with peak levels proportional to dose. Mean 1,25D, rose linearly with 25D, at similar rates in all eGFR groups but mean 24,25D (6-29 ng/mL at baseline) increased at rates proportional to eGFR.

Conclusions: ERC reliably raised both serum 25D, and 1,25D, irrespective of eGFR, making it an attractive alternative to hormones for treating persistently rising PTH in CKD stages 3-4. Declining eGFR did not affect ERC’s ability to increase the rate of 1,25D production, indicating that hormone generation occurred in extra-renal tissue. Increases in serum 24,25D, were dependent on 25D elevation and limited by declining eGFR, suggesting that this metabolite derives solely from the kidney and is not disproportionately increased by eGFR.

Funding: Commercial Support - OPKO Health, CSL Vifor

FR-PO320

Comparative Effectiveness of Cinacalcet Delivered Daily at Home vs. Three Times Weekly In-Center

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Background: Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a common syndrome found in end stage kidney disease (ESKD) patients and marked by dysregulation of three chemicals in the blood: calcium, phosphorus and parathyroid hormone (PTH). A recent review of the evidence showcases that treatment of CKD-MBD should be based on better control of all 3 elements. Cinacalcet, an oral calcimimetic (a PTH-lowering therapy), is one of many daily treatments that ESKD patients are often prescribed, contributing to a high total pill burden. Recent clinical trials have provided evidence that in-center administration of cinacalcet might be a safe and effective treatment option. In this study we sought to evaluate the comparative effectiveness of cinacalcet delivered daily at home versus three times weekly in-center.

Methods: This was a retrospective matched cohort study of 2,894 matched adult in-center hemodialysis patients at a dialysis provider between January 01, 2008 and September 30, 2022 who initiated their first ever calcimimetic therapy (non-exposed group: at home use or exposed group: in-center administration at the end of dialysis). Patients were matched (1:1) on: age at index date, body mass index, cinacalcet dose, and baseline phosphorous, calcium, and PTH. Patients were followed until censoring (i.e., lost to follow up) or 12 months after baseline, whichever occurred first. The primary outcome was achieving triple control of PTH, phosphorous and calcium.

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

Underline represents presenting author.
**Results:** Fitted proportion model results show no statistical difference in achieving triple control between in-center or at home cinacalcet administration groups (Figure 1). In addition, there was no meaningful difference in control of any component.

**Conclusions:** In an observational, well-matched cohort administering cinacalcet in-center at the end of dialysis is non-inferior as prescribing cinacalcet for use at home.

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**FR-PO321**

Denosumab and Fracture Events in Patients on Hemodialysis

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**Background:** It is known that the risk of fracture is much higher in patients with dialysis than in general population. In recent years, osteoporosis treatment has become more widespread including hemodialysis patients. However, there are few studies that analyzed the efficacy of denosumab for fracture events in hemodialysis patients.

**Methods:** We conducted a retrospective observational study of inpatients and outpatients at a maintenance hemodialysis facility to clarify the association between denosumab use and fracture events. The study was from December 2013 to December 2022 and compared the incidence of fractures in the denosumab-treated and non-treated groups. The analysis was performed using the Cox proportional hazards model with the presence or absence of fracture occurrence as the objective variables and the presence or absence of denosumab use, various patient background, and laboratory values as explanatory variables.

**Results:** A total of 263 patients were enrolled in the study, with a mean age of 71.7 ± 12.1 years. Among them, 35.4% were female, and the median duration of hemodialysis was 48 [IQR 4-114] months. The number of patients who developed fractures was 52 in the non-treated group and 8 in the denosumab-treated group. After adjustment for factors such as age, gender, prior fracture, serum intact parathyroid hormone, serum TRACP5b and bone specific alkaline phosphatase, analysis using the Cox proportional hazards model showed that patients treated with denosumab were significantly less likely to develop fractures (HR 0.42 [95% CI: 0.18-0.98]). There were no significant differences in the incidence of hypocalcemia (OR 2.05 [95%CI:0.79-5.29]).

**Conclusions:** Our results suggest that denosumab may be effective in preventing fractures in hemodialysis patients. Further studies with larger sample sizes are warranted to validate and enhance the outcomes of this study.

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**FR-PO322**

Histone Acetyltransferase p300 Inhibition Attenuates Kidney Fibrosis Under Diabetic Conditions

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**Background:** Diabetic nephropathy, the major cause of chronic kidney disease, is associated with progressive renal fibrosis. Transforming growth factor (TGF)-β1 plays important roles in extracellular matrix accumulation in diabetic nephropathy. Recently, acetyltransferase p300 has been shown to mediate intracellular TGF-β1 activity through facilitating Smad function. Therefore, in this study, the effect of p300 inhibition on kidney fibrosis under diabetic conditions was investigated to assess the therapeutic potential of p300 modulation.

**Methods:** Primary tubular epithelial cells (TECs) from C57BL/6 mice were treated with TGF-β1 with or without histone acetyltransferase p300 siRNA transfection of A485, a selective inhibitor for p300. For in vivo experiments, kidney samples were obtained with or without histone acetyltransferase p300 siRNA transfection of A485, constitutive tissue growth factor (CTGF), fibronectin, and type I collagen mRNA and protein expressions in TECs. These increases were attenuated significantly when TECs were transfected with p300 siRNA. Similar findings were found when the cells were treated with p300 specific inhibitor A485 (100nM). In vivo, the mRNA and protein expression of p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen were significantly increased in kidney samples form DM mice compared to non-diabetic control mice. Oral A485 administration abrogated these increases significantly. In addition, the increased blood urea nitrogen and albuminuria levels were significantly attenuated with oral A485 treatment in the diabetic mice. Immunohistochemistry and Sirius Red staining also revealed that fibronectin expression was significantly higher and tubulointerstitial fibrosis was significantly worse in diabetic mice kidneys compared with control mice. These changes were ameliorated by A485 treatment.

**Conclusions:** These findings suggest that inhibition of histone acetyltransferase p300 could improve diabetic-induced tubular fibrosis and may be a potential therapeutic strategy for diabetic nephropathy.

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**FR-PO323**

Pharmacologic Pyruvate Kinase M2 Activation Maintains Mitochondrial Metabolism by Regulating the Interaction Between HIF-1α and PGC-1α in Diabetic Kidney Disease

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**Background:** Previous findings have indicated that pyruvate kinase isomerase M2 (PKM2) activation may protect kidney injury by improving mitochondrial dysfunction and decreasing glycolysis. However, the underlying molecular mechanisms are incompletely understood. Here, we aimed to clarify mechanistic link between PKM2 and HIF-1α-mediated PGC-1α suppression in animal model of diabetic kidney disease (DKD).

**Methods:** In an animal DKD study, db/db mice were intraperitoneally injected with vehicle or a PKM2 activator. In vitro, primary cultured renal tubular epithelial cells (RTECs) from C57BL/6 mice were treated with high glucose (HG) alone and HG+TEPP-46. The interactions between HIF-1α and PGC1α were further investigated using HIF-1α overexpression and HIF-1α knockdown. PKM2 activity, energy metabolism, mitochondrial mass, dynamics, and morphology, and cell injury markers were examined.

**Results:** In the kidney of db/db mice, diabetes resulted in decreased PKM2 activation, aberrant glycolysis, impaired fatty acid oxidation, and decreased mitochondrial mass, integrity, and function. These changes were accompanied by increased HIF-1α and decreased PGC-1α levels. Increased fibrosis and apoptosis markers were observed in diabetic mice. In addition, period acid-Schiff (PAS) staining revealed significant tubular injury in db/db mice. The direct PKM2 activation by TEPP-46 treatment attenuated the dysregulated energy metabolism, mitochondrial dysfunction, and cell death. Similar alterations were also observed in HG-treated RTECs, which were restored by TEPP-46. Notably, a chromatin immunoprecipitation assay revealed that HIF-1α directly binds to the regulatory region of the Ppargc1a promoter and that this interaction is inversely dependent on PKM2 activation. A luciferase reporter assay showed that HIF-1α regulates the transcriptional activity of PGC-1α in a PKM2-dependent manner. Moreover, Hif1a overexpression suppressed PGC-1α and induced aberrant energy metabolism, mitochondrial dysfunction, and apoptosis. Conversely, these changes were reversed by HIF-1α knockdown.

**Conclusions:** PKM2 activation improves impaired mitochondrial metabolism and function by modulating HIF-1α and PGC-1α interactions in DKD.

**Funding:** Government Support - Non-U.S.
renal decline. This study provides compelling evidence that the LOF of FRAS1 leads to the downregulation of NPR1, ultimately resulting in rapid renal decline. Given the crucial role of NPR1 in maintaining normal renal function, it represents a promising therapeutic target for individuals affected by FRAS1 LOF, diabetic kidney disease (DKD), or chronic kidney disease (CKD). Further investigations are warranted to explore the therapeutic implications of targeting NPR1 in these conditions.

Funding: NIDDK Support

FR-PO325

Cell Surface GRP78 and α2M* Are Important Mediators of Tubulointerstitial Fibrosis in CKD

Jackie Trink, Melissa Macdonald, Bo Gao, Joan C. Krepsinsky. McMaster University Faculty of Health Sciences, Hamilton, ON, Canada.

Background: Diabetic kidney disease (DKD) is characterized by glomerular accumulation of extracellular matrix (ECM) proteins followed by the development of tubulointerstitial fibrosis. We recently showed the endoplasmic reticulum resident GRP78 translocates to the cell surface (csGRP78) in response to HG, promoting profibrotic responses in mesangial cells. We hypothesize that both csGRP78 and α2M* act as a regulator of fibrosis progression and protect the glomerulus from hypertrophy. At the same time, it is known to be increased by both HG and TGF-β1-induced ECM production (fibronectin and collagen IV). By HG treatment, downstream TGFβ1 signaling (measured by activation of Smad3) was attenuated by csGRP78 or α2M* inhibition. Interestingly, we observed no effect on Smad3 activation with csGRP78 or α2M* inhibition with TGFβ1 treatment. We hypothesized a potential role for non-canonical TGFβ1 signaling being mediated by csGRP78 or α2M*. We next assessed the known non-canonical TGFβ1 signaling molecules yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). Here we observed that inhibition of either csGRP78 and α2M* attenuated YAP and TAZ expression under both HG and TGFβ1 treatment. This implicates Smad-dependent and independent signaling being mediated by csGRP78 and α2M*.

Conclusions: These data support a role for csGRP78 and α2M* in mediating HG or TGFβ1-induced profibrotic signaling in PTEC and RF. Inhibition of this signaling pathway may be a novel target for preventing DKD or CKD-associated fibrosis which we are currently evaluating in vivo.

Funding: Government Support - Non-U.S.

FR-PO326

Functional Coupling of ANXA1 and KCa3.1 Attenuated Renal Tubulointerstitial Fibrosis in Diabetic Kidney Disease

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Background: Tubulointerstitial fibrosis (TIF) is the common pathway and major pathological basis for almost all kinds of renal disease including diabetic kidney disease (DKD) progress into chronic kidney disease, thus it is essential to reveal its pathogenesis. Previous research showed that up-regulation of intermediate-conductance Ca2+–activated K+ channel (KCa3.1) contribute to TIF. However, targeting the channel directly have unfortunately side-effect in clinical trials.

Methods: Molecular docking and co-immunoprecipitation were used to detect the binding capability between ANXA1 and KCa3.1. HEK293T and HK-2 cell line were cultured and transfected to confirm whether ANXA1 can be modified by SUMOylation. SUMOylation enzymes were predicted by SUMOsp2.0, and ANXA1 lysine residues K113, K161, K185, K257 and K12 were mutated to test the related site change. Biotinylation assay were used to evaluate the ANXA1 activation to KCa3.1 surface expression. Western blot was used for evaluate KCa3.1-mediated TGF-β1/Smad signaling activation to detect the expressions of α-SMA, fibronectin collagen matrix and Smads.

Results: We found that ANXA1, an endogenously generated molecules that promote the physiological resolution of inflammation, could interact with KCa3.1. Mechanistic studies demonstrated that intracellular ANXA1 could be modified by SUMOylation and that SUMOylation primarily occurs at three lysine residues K113, K161, and K257 in hyperglycemia/high glucose stimulation, thereby SUMOylated ANXA1 regulating the membrane transport and lysosomal degradation of KCa3.1 channel protein, and ultimately delaying KCa3.1-mediated TGF-β1/Smad activation and TIF progression in DKD state.

Conclusions: Our study suggests that ANXA1-KCa3.1 functional coupling may be a promising therapeutic strategy to mitigate DKD-induced TIF.

FR-PO328

Diet Modification to Drive Fibrotic Response in Diabetic Kidney Disease (DKD) Model

Cassandre Cavanaugh, Simon A. Hinke, Matthew M. Rankin, Rong Meng, Neetu Shukla, Andrea R. Narwrocki. CVMR & PH Discovery In Vivo Pharmacology, Janssen Research and Development LLC, Spring House, PA.

Background: Diabetes is a major cause of chronic kidney disease, affecting approximately 25% of diabetic patients. Several rodent models of Diabetic Kidney Disease (DKD) have been developed; however, drug discovery is hampered by the lack of preclinical rodent models with clinically relevant urinary albuminuria creatinine ratio (UACR). Here, two rodent models of DKD were developed in humans. Here we sought to develop a new translational mouse DKD model incorporating streptozotocin (STZ)-induced hyperglycemia, mild hypertension from nitric oxide synthase inhibition, and dietary modification to drive the fibrotic response, on top of a uninephrectomized (UNx) hyperfiltration phenotype.

Methods: UNx Male 129S1 mice (Jackson Labs) were uninephrectomized at 7 weeks old and given STZ injections (5-40mg/kg IP) to induce diabetes. Trimethylamine-n-oxide (TMAO) and Choline formulated in D12450 low fat diet (LFD) and D12492 high fat diet (HFD) for rodents (Research Diets). 100mg/L-nitroarginine (L-NNa) provided in drinking water. Body weight, food intake and blood glucose collected weekly and urine collected biweekly for 8 weeks. At the end of treatment, animals euthanized, kidneys collected for collagen and histological analysis. Terminal plasma analyzed for blood chemistry, TMAO and circulating dietary precursors of TMAO.

Results: TMAO-induced hyperglycemia confirmed in the mice (396.3±3.6mg/dL). Daily TMAO and choline intake, both LFD and HFD diet admixtures were similar (Choline: LFD 166.9±7.6g/kg; HFD 178.4±4.6g/kg; TMAO: LFD 54.1±1.8g/kg; HFD 65.2±2.0g/kg). Betaine, Carnitine and Choline dietary TMAO precursors increased in both LFD and HFD choline admixtures. TMAO did not significantly change any dietary precursor levels compared to control. UACR significantly increased after 8 weeks in both Choline supplemented, LFD (p=0.0024, 72.4±13.6) and HFD (p=0.0472; 59.7±8.2). The primary histological lesion observed was tubulointerstitial collagen thickening, seen in both LFD TMAO & Choline, and HFD Choline groups.

Conclusions: Refinement of a hypertensive, diabetic, hyperfiltering mouse kidney disease model using dietary supplements to increase renal fibrosis observed to achieve clinically relevant kidney functional impairment to that of human DKD patients, with some evidence of histological damage. This animal model may be used to assess preclinical efficacy of investigational therapies for DKD.

Funding: Commercial Support - Janssen R&D Pharmaceutical Companies of J&J
Loss of LRG1 Effectively Curbs Diabetes-Induced TGF-β Signaling in Glomerular Endothelial and Mesangial Cells to Attenuate Diabetic Kidney Disease (DKD)

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Background: Despite the immense burden of DKD, optimal therapies remain limited. Although TGF-β is a well-established central mediator of DKD pathogenesis, because of its pleiotropic actions in multiple organ systems, its indiscriminate blockade is not desirable. Moreover, evidence of diverse kidney cell-specific effects of TGF-β, both deleterious and protective, continues to emerge. TGF-β signaling is strongly influenced by cell type- and context-dependent regulators and determinants, and we previously showed that cell surface modulators, such as LRG1 and BAMBI, can significantly influence TGF-β signaling in kidney disease. Since LRG1 is increased in glomerular ECs in DKD, we postulated that LRG1 loss may shift the balance away from excessive pathological endothelial TGF-β signaling to attenuate DKD, without a full systemic blockade of TGF-β signaling associated with unwanted side effects.

Methods: Type 1 diabetic OVE26 mice were crossed with Lrg1−/− mice to generate OVE26:Lrg1−/− mice, and DKD progression was assessed by renal function and histopathological parameters. scRNA-seq was employed for kidney single-cell gene expression analysis of control and diabetic mice.

Results: scRNA-seq confirmed that increased LRG1 is limited to GECs in early diabetic kidneys. As anticipated, LRG1 loss significantly attenuated diabetic glomerulopathy including podocyte loss, and improved renal function. scRNA-seq analysis showed that LRG1 loss was sufficient to reverse all significant molecular pathway changes in GECs in early DKD, which were associated with the dampening of TGF-β-induced gene expression. Notably, LRG1 loss also led to a significant attenuation of TGF-β-mediated gene expression in mesangial cells of diabetic mice. These results indicate that LRG1 promotes DKD by enhancing TGF-β signaling in GECs and mesangial cells in an autocrine and paracrine manner, and indirectly via glomerular cross-talk.

Conclusions: Our study indicates that increased LRG1 directly enhances TGF-β signaling not only in GECs but also in mesangial cells in DKD, thereby exacerbating subclinical kidney damage. Knockdown of LRG1 in diabetic mice resulted in protection of glomeruli and mesangium, while having no gross defects in mice, significantly attenuated diabetic glomerulopathy in OVE26 mice. Therefore, specific antagonists of LRG1 may be an effective approach to curb TGF-β signaling in glomerular cells and attenuate DKD.

Funding: NIDDK Support

FR-PO330

Nogo-B Suppresses Endoplasmic Reticulum Stress in Glomerular Endothelial Cells of Diabetic Nephropathy

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Background: Diabetic vascular injuries contribute to the disease progression and glomerular endothelial cells are the critical targets of injury under hyperglycemia. Nogo-B is an endoplasmic reticulum (ER)-resident protein, which plays an important role in vascular remodeling after injury. Given the location of Nogo-B in the endoplasmic reticulum in glomerular endothelial cells, we set out to investigate whether Nogo-B is involved in the ER stress of endothelial cells in diabetic nephropathy.

Methods: The level of serum and urinary Nogo-B was measured in patients with diabetic nephropathy using ELISA. The expression of Nogo-B in the ER of endothelial cells was detected by immunofluorescence co-staining with the ER marker, PDI. The expression level of ER stress related markers GRP78 was examined using WB analysis.

Results: Compared with healthy control subjects, the level of serum (fig.A) and urinary(fig.B) Nogo-B was significantly increased in DN patients. In vitro, Nogo-B was co-localized with PDI by immunofluorescent co-labeling (fig.C). The RNA-seq results demonstrated that AGE-RAGE signaling pathway was among the top 10 activated pathways by KEGG analysis (fig.D). In high glucose cultured endothelial cells, knocking down Nogo-B caused an increase in the protein level of GRP78 (fig.E). In db/db diabetic mice, knocking down Nogo-B induced glomerular endothelial cell injuries (fig.F) as demonstrated by swollen changes and karyorrhexis of the cells.

Conclusions: Nogo-B, an ER-resident protein, plays a beneficial role in glomerular endothelial cells by inactivating the ER stress. Protecting the vasculature by targeting Nogo-B may serve as a potential therapeutic strategy in the treatment of DN.

Funding: Government Support - Non-U.S.

FR-PO331

Short-Chain Fatty Acids Restore Glomerular Endothelial Cell Stabilization in Diabetic Mice, Circumventing the Reduced CPT1A Transporter

Maria Novella Nieces, Lushun Yuan, Gangqi Wang, Tor J. Rabelink, Joris I. Rotmans, Bernard van den Berg. Leids Universitair Medisch Centrum, Leiden, Netherlands.

Background: Renal injury is one of the major consequences for patients with type 2 diabetes mellitus (T2DM). Previously, we observed that diabetic nephropathy (DN) resulted in loss of the endothelial glyocalyx, but the molecular and metabolic mechanisms underlying this loss and in general endothelial dysfunction in T2DM remain largely unexplained. In the present study we tested the mechanistic and metabolic changes in human primary glomerular endothelial cells (hGECs) exposed to serum from patients with T2DM.

Methods: hGECs have been exposed for 4 days to T2DM serum in either static or laminar flow conditions. Cells were then used for Seahorse and ECIS assays, to measure mitochondrial function and monolayer integrity, respectively. In order to visualize the monolayer, cells were stained for VE-cadherin and β-catenin. We also ran qPCR analysis to measure the expression levels of endothelial and metabolic genes.

Results: qPCR data showed that hGECs cultured with T2DM serum have an increased IL-8 mRNA expression while HAS2, HAS3, NO3 and the fatty acid transporter CPT1A mRNA were reduced. For this reason, we performed a CPT1A knockdown to investigate the effect of the lack of this transporter in hGECs. Monolayer resistance, either in the presence of T2DM serum or after CPT1A knockdown, was decreased. In each case, administration of the short chain fatty acids (SCFAs) butyrate and acetate restored barrier function. The beneficial effects of SCFAs on the endothelial monolayer were also confirmed when visualizing cell-cell contacts with immunofluorescence staining for VE-cadherin and β-catenin. Using Seahorse assay, we observed that SCFAs also improved fatty acid oxidation which was reduced after T2DM serum exposure.

Conclusions: SCFAs supplementation can rescue endothelial cell integrity after treatment with T2DM serum. Mechanistically, reduction of CPT1A in ECs exposed to T2DM serum revealed the importance of fatty acids for ECs homeostasis, which was confirmed by the knockdown of CPT1A. With butyrate and acetate supplementation we can circumvent this pathway and restore cellular homeostasis by improving fatty acids metabolism.

FR-PO332

L-NNAME Accelerates the Onset of Diabetic Nephropathy in Genetically Diabetic Mice

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Background: Diabetic nephropathy (DN) represents one of the major causes of end stage kidney disease worldwide. Despite DN having such a high incidence, mouse models of DN rarely mimic all aspects of the human disease and usually show very slow development of DN phenotype. For this reason, in this project we aimed to develop an accelerated and reproducible rodent model of DN.

Methods: For our experiments we chose 9-week old female and male of the leptin receptor knock-out (BKS.Cg-Dock7m +/- /LeprdB/J) mice as type 2 diabetes model. As these mice are still prone to develop severe kidney injury despite their diabetic condition, we administered the eNOS inhibitor L-NNAME for 6 weeks, in order to aggravate kidney damage. Mice were divided in three groups: one vehicle control group, one receiving 40 mg/kg/day of L-NNAME and one receiving 80 mg/kg/day of L-NNAME dissolved in drinking water. Blood pressure and glomerular filtration rate (GFR) were measured, besides glycosia and albuminuria. At the end of the experiment, animals were killed and blood and organs collected.

Results: Mice treated with 80mg/kg/day of L-NNAME showed an average increase of 10 mmHg in systolic blood pressure, with a peak of 30 mmHg increase at week 4 of treatment. Despite the increased blood pressure, three weeks of L-NNAME administration...
caused a significant reduction in GFR for both doses of L-NAME, with 5% reduction for the 40mg-group and 23% for the 80mg-group. No change in GFR was observed in the controls. This decrease in GFR was accompanied by a 10-fold increase in urinary albumin for both the experimental groups already after 3 weeks of treatment. PAS staining of kidney sections revealed that in particular mice treated with 80mg of L-NAME have enlarged glomeruli and a reduced glomerular capillary density, coinciding with mesangial expansion. Electron microscopy analysis showed that glomerular basement membrane (GBM) thickening was also occurring.

Conclusions: Our results show that L-NAME considerably accelerates the onset of DN in db/db mice, with signs of kidney dysfunction already after 3 weeks. This model could be used to assess the therapeutic potential of novel interventions aimed to slow down the progression of DN.

FR-PO335
Protease-Activated Receptor-1 Deficiency Protects Against Glomerular and Endothelial Injury in Type 2 Diabetic Nephropathy
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Background: We recently showed that depletion of protease-activated receptor-1 (PAR-1) confers kidney protection in rodent models of CKD. Whether the same phenomenon may be observed in the diabetic kidney remains unknown.

Methods: We generated a novel double transgenic PAR-1 KO db/db mouse and observed its pathophysiology weeks in comparison to the respective wild-type and non-diabetic control animals. Fasting, non-fasting serum and urine were collected for up to week 24 of age. Vascular permeability assay of Evan’s blue extravasation was performed to assess endothelial injury in the kidneys. Kidney function and histological changes were determined post-mortem. Six animals were included in each experimental group for analysis.

Results: PAR-1 deficiency significantly reduced fasting blood glucose level and basal glucose tolerance by OGTT associated with higher serum insulin levels in db/db mice. Morphologically, db/db control mice developed glomerular hypertrophy and tubulointerstitial damage compared to db/+ non-diabetic mice, whereas db/db;Par1-/- mice displayed less mesangial expansion and tubular dilatation. db/db;Par1-/- mice had lower albuminuria with restoration of nephrin and WT-1 levels in the glomerulus compared to db/db controls. PAR-1 deficiency also preserved endothelial integrity and capillary permeability, along with an increase of VEGFA levels in db/db kidneys.

Conclusions: PAR-1 deficiency confers kidney protection by reducing vascular dysfunction and glomerular injury in experimental type 2 diabetic nephropathy. These novel findings suggest the potential of a PAR-1 targeted therapeutic strategy in diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO334
Effects of a Vascular Endothelial Protein Tyrosine Phosphatase (VE-PTP) Blocking Antibody in a Mouse Model of Severe Diabetic Kidney Disease

Background: Diabetic Kidney Disease (DKD) is a disease with complex pathophysiology wherein endothelial dysfunction plays a central role in disease formation and progression. Emerging evidence emphasizes the critical role of the Tie-2 receptor and Angiopoietin 1 and 2 ligands in DKD. Tie-2 signaling is negatively regulated by the endothelial specific transmembrane Vascular Endothelial Protein Tyrosine Phosphatase (VE-PTP). Recently, it has been reported that the genetic deletion of VE-PTP provided protection from hypertension and diabetes induced renal injury in a mouse model of DKD. In the current study we investigated the efficacy of VE-PTP inhibition in a mouse model of severe DKD with an extracellular domain (ECD) targeting VE-PTP blocking antibody.

Methods: VE-PTP blocking antibody was characterized in vitro, in vivo in dermal vascular permeability assays, and in pharmacological experiments. The in vivo proof-of-concept experiment with the VE-PTP blocking antibody and standard of care lisinopril were performed in hypertensive diabetic mice. Renin overexpression (AAV) was used to induce hypertension in db/db mice following uninephrectomy (Unx). Treatment was initiated 4 weeks after renin AAV administration and continued for another 4 weeks.

Results: Our results showed that VE-PTP inhibition with an ECD targeting VE-PTP antibody induced Tie2-phosphorylation and provided protection against VEGF-A induced vascular permeability both in vitro and in vivo. Furthermore, treatment with the VE-PTP antibody resulted in decreased kidney gene expression of endothelial activation markers (Angpt2, Edn1, Icam1 and Vcam1). However, the VE-PTP blocking antibody treatment did not alter urinary albumin-to-creatinine ratio (uACR) in a severe mouse model of DKD.

Conclusions: VE-PTP inhibition with an ECD targeting antibody did not ameliorate hypertension and diabetes-induced albuminuria in a preclinical mouse model of DKD.

Funding: Commercial Support - Janssen Pharmaceuticals, Johnson & Johnson
**FR-PO336**

**Piezo1 Mediates Vasodilation Induced by Acute Hyperglycemia in Mouse Renal Arteries and Microvessels**

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**Background:** Acute hyperglycemia (HG) is a risk factor for developing acute kidney injury and poor renal outcome in critically ill patients. The role of renal vasculature in this context is not clear. We hypothesize that HG-associated hyperosmolality facilitates vasodilation through Piezo1-mediated eNOS activation.

**Methods:** Vasoreactivity of isolated mouse mesenteric (MA) and renal interlobar (ILA) arteries was analyzed using wire myography and that of renal afferent (AA) and efferent (EA) arterioles, and vasa recta (VR) using microvascular perfusion. Immunofluorescence and western blot were used for molecular analyses of isolated mouse blood vessels as well HUVECs.

**Results:** Pre-treatment with HG (44 mmol L−1 glucose; 4 h) increased acetylcholine (ACh)-induced relaxation in ILA and MA, which was prevented by eNOS inhibition using L-NAME. Hyperosmotic mannitol solution had a similar effect. HG induced an immediate, L-NAME-inhibitable dilation in AA, EA, and VR, whereby stronger dilation in AA compared to EA. HG also increased glomerular filtration rate in mice. In HUVECs, HG and the Piezo1 activator Yoda1 increased levels of Piezo1 protein, phosphorylated CaMKII (p-CaMKII), Akt, and p-eNOS. The HG-effect could be prevented by inhibiting Piezo1 using GsMTx4 and CaMKII using KN93. Furthermore, in arteries and microvessels, inhibition of Piezo1 using GsMTx4 prevented the HG-effect, while Yoda1 caused relaxation and dilation, respectively.

**Conclusions:** Results reveal that Piezo1 mediates renal vasodilation induced by hyperosmolality in acute HG. This mechanism may contribute to the pathogenesis of renal damage by acute HG.

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

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**FR-PO337**

**Podocyte-Specific Regulation of PP2A Worsens Diabetic Kidney Disease (DKD) Progression**

Zhengying Fang, Kyung Lee, Ruijie Liu, John C. He. Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** We previously showed a critical role of protein phosphatase 2A (PP2A) in regulation of podocyte function and progression of DKD. However, PP2A is ubiquitously expressed with pleiotropic functions, limiting its role of being a DKD therapeutic target. Here, we investigated the role of a podocyte-specific regulatory subunit of PP2A, PPP2R2B in vitro and in vivo in the context of DKD.

**Methods:** By using PHEWAS approach, we screened the variants of genes coding for all PP2A subunits to determine their association with renal outcome in DKD patients. Knock-in (KI) mice with one of the clinical worse outcome-related ppp2r2b missense variants (T202M) was generated, and diabetes was induced with streptozotocin (STZ). Renal function was assessed every two weeks, and all mice were euthanized at the age of 24 weeks for examination.

**Results:** By PHEWAS study, several variants of ppp2r2b gene were found to be associated with a better or worse renal outcome in DKD patients. Interestingly, single cell transcriptomic data showed that ppp2r2b gene expresses mostly in human podocytes. In vitro study confirmed that ppp2r2b variants correlated with a better or worse clinical outcome led to an increased or decreased PP2A activity, respectively. We generated KI mice with one of the clinical worse outcome-related ppp2r2b missense variants (T202M). In vivo study revealed that diabetic KI mice developed significantly higher level of albuminuria in comparison to diabetic WT mice. Besides, diabetic KI mice also showed worst podocyte injury and loss, and mesangial matrix expansion. As PP2A dephosphorylates p65 NF-κB, we evaluated the phosphorylation level of p65 NF-κB in the glomeruli of these mice. Compared to wildtype mice, KI mice had a higher level of glomerular phosphorylation of p65.

**Conclusions:** The missense ppp2r2b variants were significantly associated with renal outcome in humans with DKD. KI of one of ppp2r2b missense variants (T202M) resulted in worsened glomerulopathy in diabetic mice. Thus, PPP2R2B, a podocyte-specific PP2A regulatory subunit, could be a better therapeutic target for DKD.

**Funding:** NIDDK Support, Veterans Affairs Support

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

Underline represents presenting author.
Stimulator of Interferon Genes (STING) Deletion Alleviates Podocyte Injury and Mitochondria Dysfunction by Promoting hnRNP A1 and SIRT1 in Diabetic Nephropathy

Jinxiu Hu, Yue Liu, Huimin Chen, Zhiemei Lv, Rong Wang. Shandong Provincial Hospital, Jinan, China.

Background: Dysfunction of podocytes has been identified as a crucial pathologic characteristic of diabetic nephropathy (DN), while the regulatory effect of long non-coding RNAs (IncRNAs) in this process has not been fully elucidated.

Methods: We conducted RNA-seq on renal tissues and identified a significantly upregulated IncRNA ENST00000585189.1 (IncRNA 585189) in patients with DN. Subsequently, we assessed its correlation with clinical indicators and demonstrated its localization with RNA-FISH. In high-glucose-induced human podocytes, the expression of IncRNA 585189 was assessed via real-time PCR and RNA-FISH. Subsequently, gain- and loss-of-function experiments detected the effect of IncRNA 585189. The expression of Desmin, ZO-1, hnRNPA1 and SIRT1 were evaluated using real-time PCR, western blot and immunofluorescence assays. Mitochondrial morphologies were evaluated using Mitotracker, while mitochondrial ROS and membrane potential were assessed using MitoSOX Red and TMRE staining. Mechanistically, bioinformatics analysis predicted the interaction between IncRNA 585189 and hnRNPA1, which was confirmed by RIP, pull-down, and EMSA assays. Moreover, the binding of hnRNPA1 to SIRT1 mRNA was validated through RIP and pull-down assays. Additionally, the stability of hnRNPA1 and SIRT1 was assessed by treatment with Cloheximide, MG-132, and Actinomycin D.

Results: IncRNA 585189 displayed a positive correlation with renal insufficiency and was found to be upregulated in both DN patients and high-glucose-induced human podocytes. Silence of IncRNA 585189 decreased the production of ROS, rescued the aberrant mitochondrial morphology and membrane potential, restored the podocyte damage caused by high glucose. Mechanistically, IncRNA 585189 binds to hnRNPA1, inducing destabilization of hnRNPA1 protein and downregulating its expression. Conversely, hnRNPA1 promotes the expression of IncRNA 585189. Furthermore, the interaction between hnRNPA1 and SIRT1 mRNA promotes the stability of SIRT1 mRNA and enhances its expression. Finally, our findings suggested that IncRNA 585189 inhibited SIRT1 expression through hnRNPA1, hindering the recovery of mitochondrial abnormalities and podocyte damage.

Conclusions: In summary, targeting IncRNA 585189 may represent a promising strategy for reversing mitochondrial dysfunction and treating DN.

Funding: Government Support - Non-U.S.

Inhibition of the IncRNA 585189 Prevents Podocyte Injury and Mitochondria Dysfunction by Promoting hnRNP A1 and SIRT1 in Diabetic Nephropathy

Jinxiu Hu, Yue Liu, Huimin Chen, Zhiemei Lv, Rong Wang. Shandong Provincial Hospital, Jinan, China.

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Conclusions: In summary, targeting IncRNA 585189 may represent a promising strategy for reversing mitochondrial dysfunction and treating DN.

Funding: Government Support - Non-U.S.

Podocyte-Specific Clusterin Triggers the Activation of Proximal Tubule-Specific CAMKID Signaling to Attenuate Kidney Injury in Diabetic Kidney Disease

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Background: The role of podocyte-proximal tubule (PT) crosstalk in the progression of Diabetic Kidney Disease (DKD) remains understudied. Podocyte-specific overexpression of Krüppel-like factor 6 (KLF6), a zinc finger transcription factor, attenuated proximal tubule (PT) injury in murine DKD model. Initial snRNA-seq studies demonstrated a potential interaction between podocyte Clusterin (CLU), a secretory ligand, and proximal tubule CAMKID. The aim of this study is to investigate the mechanism by which the podocyte primes the PT to attenuate kidney injury in DKD.

Methods: Conditioned media (CM) was collected from GFP-labeled podocytes obtained from podocyte-specific induction of KLF6 (KLF6POUT) and control mice to carry out proteomic analysis and in vitro assays in primary (1°) PT. 1° PT cells were treated with control CM as well as CM blocked with CLU antibody. CAMKID signaling was pharmacologically inhibited using STO-609, an inhibitor of the upstream kinase CAMKII. Oxygen consumption rate (OCR) was measured with seahorse analyzer. Immunofluorescence staining, western blot analysis, and pulldown assay for calmodulin were performed. Single nuclei ATAC (SnATAC) and snRNAseq were sequenced on the kidney cortex of all mice.

Results: Immunostaining of experimental mice as well as proteomic analysis of the podocyte CM and urine, led to identification of CLU as a potential ligand for PT signaling. KLF6POUT CM-treated 1° PT cells demonstrated an increase in calmodulin binding affinity as well as an increase in OCR compared to control CM-treated cells in high glucose (HG) conditions, and this OCR change was abated by the addition of CLU blocking antibody. CAMKID expression was unique to the first segment of PT in mice as well as human tissue. 1° PT cells treated with STO-609 had a decrease in cell viability and OCR in HG conditions, a decrease in p-DRP1, and an increase in fragmented mitochondria. SnATACseq in combination with snRNAseq also validated pathways related to calcium signaling and podocyte-PT communication.

Conclusions: These data suggest that CLU secreted from podocytes attenuates mitochondrial fission in the PT by inducing CAMKID signaling, thereby priming the PT against injury under diabetic conditions.

Funding: NIDDK Support, Veterans Affairs Support
High Glucose-Induced Pyruvate Kinase M2 (PKM2) Tyrosine Phosphorylation Drives a Feedback Loop by PDGFRβ to Force mTORC1 Activation for Mesangial Cell (MC) Injury in Diabetic Nephropathy (DN)

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Background: Besides its role in the last step of glycolysis to produce pyruvate, increased expression and tyrosine phosphorylation of PKM2 regulate mitotic checkpoint in many cancers. We investigated the role of PKM2 tyrosine phosphorylation in DN.

Methods: MCs, OVE26 and db/db mice were employed. Results: Incubation of MCs with 25 mm glucose (HG) increased the expression of PKM2 in a sustained manner. HG induced translocation of PKM2 into the nucleus and increased its phosphorylation at tyrosine-105 residue in both cytosol and nucleus. We have recently shown a role of PDGFRβ in DN. We hypothesized that PDGFRβ may regulate PKM2. JNJ, a PDGFRβ inhibitor, abrogated HG-stimulated PKM2 expression and tyrosine phosphorylation. Interestingly, expression of kinase dead PKM2 K267M and tyrosine phosphorylation deficient PKM2 Y105F mutants inhibited HG-induced MC hypertrophy. In contrast, overexpression of wild type PKM2 induced MC hypertrophy similar to HG treatment. Mesangial matrix expansion is an aspect of DN. Both PKM2 K267KM and PKM2Y105F mutants mitigated HG-stimulated expression of fibronectin, collagen I (α2) and PAI-1 whereas, overexpression of PKM2 had the opposite effects similar to HG. Previously, we reported that Akt/mTORC1 signaling regulates MC pathways. We found that PKM2 K267KM and PKM2 Y105F mutants suppressed HG-stimulated Akt and mTORC1 activity while overexpression of PKM2 increased their activities. Intriguingly, Akt and mTORC1 inhibitors MK2206 and rapamycin, respectively, suppressed expression and tyrosine phosphorylation of PKM2. While addressing the in vivo relevance, we found increased PKM2 expression and tyrosine phosphorylation concomitant with fibronectin, PAI-1 and collagen I (α2) expression in the renal cortex of OVE26 and db/db mice, models of type I and type 2 diabetes, respectively.

Conclusions: Our results identify a previously unrecognized HG-stimulated novel positive feedback loop involving PDGFRβ, activated Akt/mTORC1 and tyrosine phosphorylated PKM2 in the pathogenesis of DN.

Funding: Veterans Affairs Support

Hic-5 Overexpression Drives Tubular Cell Senescence and Degeneration in Diabetic Kidney Disease

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Background: Emerging data suggest that tubular cell senescence plays a crucial role in the onset and development of diabetic kidney disease (DKD). However, the underlying mechanism responsible for the tubular cell senescence of DKD remains elusive. Hydrogen peroxide induced clone 5 (Hic-5) has been shown to be associated with senescence-related genes and cell-senescent phenotypes. Ergo, this study investigated the role of Hic-5 in DKD tubular cell senescence.

Funding: Underline represents presenting author.
Methods: The expression of Hic-5 was examined in kidney tissues of DKD patients. The effect of Hic-5 overexpression in vitro on cultured tubular epithelial cells by knockdown or by forced expression of Hic-5 in diabetic mice, or in vivo in mouse models of DKD with knockdown of Hic-5. The cell senescent phenotype, tubular degeneration or kidney injury as well as function were tested.

Results: The tubulointerstitial expression of Hic-5 was markedly increased in kidney tissues of DKD patients, as compared with healthy living donors, which was positively associated with the curated kidney-aging-related gene set “RODWELL_AGING_KIDNEY_UP”, as analyzed by gene set enrichment analysis. In vitro in cultured tubular epithelial cells exposed to diabetic milieu, Hic-5 was significantly increased accompanying by increased expression of p16ink4a, fibronectin, and increased cell senescence-associated beta-galactosidase activity as well as reduced expression of the epithelial marker E-cadherin. All these senescent phenotypes and degenerative changes were largely abrogated by knockdown of Hic-5 but reinforced by forced expression of Hic-5. In vivo in mouse models of DKD, knockdown of tubular Hic-5 expression mitigated tubular cell senescence and secretion of senescence-associated secretory phenotype including IL6, monocyte chemotractant protein 1 and plasminogen activator inhibitor 1, concomitant with attenuated kidney function as well as decreased fibronectin and collagen I expression of the kidney.

Conclusions: Hic-5 plays an instrumental role in DKD progression by mediating cellular senescence, and thus is likely a druggable target for halting DKD progression.

FR-PO348
Inhibition of Fatty Acid-Binding Protein 4 Protects Renal Tubulal Epithelial Cells and Rescues Diabetic Kidney Disease
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Background: Previous clinical observations have shown that increased circulating fatty acid-binding protein 4 (FABP4) is associated with the progression of diabetic kidney disease (DKD) in patients with type 2 diabetes. This study aimed to investigate the potential mechanistic role of FABP4 and the direct effects of FABP4 inhibition in experimental DKD.

Methods: To mimic the presence of hyperglycemia in DKD, human renal proximal tubular epithelial cells were cultured with high glucose (25 mM) for 3 days and in vivo study. In addition, Leprdb/+/Narl type 2 DM mice were used for a mouse model of DKD. Mice were randomly assigned to receive an oral FABP4 inhibitor, BMS-309403, for 2 weeks.

Results: Administration of FABP4 inhibitor reduced the high glucose-induced apoptosis of renal proximal tubular epithelial cells. Furthermore, FABP4 inhibitor attenuated high glucose-induced inflammatory protein (tumor necrosis factor-α, interleukin-1β, interleukin-6) and fibrotic protein (transforming growth factor-β1, collagen-I) expressions in vitro. In vivo study, treatment of FABP4 inhibitor reduced the increase of serum blood urea nitrogen and creatinine levels in DKD mice. Moreover, the urinary albumin-to-creatinine ratio and kidney-to-body weight ratio were attenuated by FABP4 inhibitor treatments.

Conclusions: Taken together, inhibition of FABP4 could protect renal proximal tubular epithelial cells against the high glucose-induced damage in vitro and improve renal function, renal hypertrophy, and urinary albumin-to-creatinine ratios in DKD mice in vivo. Further molecular mechanistic insights may be explored to provide a novel theoretical basis for the potential therapeutic target of FABP4 in DKD.

FR-PO349
Oxidised IL-33 Mediates Proximal Tubular Injury Through the RAGE/EGFR Pathway
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Background: We previously described IL-33 role in DKD mediating glomerular endothelial inflammation through ST2 signalling and a P2b2 signal in DKD using tozorakimab (NOTAL 33) as a model for organ crosstalk. Recently, IL-33 was shown to get oxidised extracellularly (IL-33ox) and exert distinct activity through a novel RAGE/EGFR complex to modulate lung epithelial remodelling. As ST2 and RAGE/EGFR act as putative receptors, we explored IL-33ox and RAGE/EGFR signalling role in kidney.

Methods: While RAGE is a predominant receptor for RAGE signaling with a neutralising antibody prevented progression of albuminuria in the db/db uninephrectomy model. Mechanistic studies were further developed using primary human glomerular endothelial (GEC) and proximal tubular epithelial cells (PTEC) to address IL-33ox and RAGE/EGFR contribution to human DKD.

Results: GEC but not PTEC expressed ST2 and hence reduced IL-33ox (IL-33ox) did not display an inflammatory response in PTEC contrary to the effects seen in GEC. However, IL-33ox stimulation of PTEC promoted EGFR receptor activation which was inhibited by antibodies against EGFR and RAGE. IL-33ox led to phosphorylation of EGFR downstream targets, like ERK1/2 but no other MAP kinases. Data also showed IL-33ox upregulated epithelial injury markers (KIM-1) and inflammatory cytokine release in PTEC. Preliminary results indicated that IL-33ox modulated epithelial cell proliferation and reparative mechanisms in the context of DKD. Under normal culture conditions IL-33ox but not IL-33ox stimulated PTEC proliferation, while under stress (serum starvation) IL-33ox prevented this effect. In a PTEC wound closure assay, tozorakimab facilitated wound healing suggesting oxidation induced apoptosis of the injured epithelium. GEC biology was also assessed too. In contrast to the endothelial inflammation caused through the IL-33ox/ST2 pathway, minimal effects were observed upon IL-33ox stimulation.

Conclusions: Although mechanism of action of the IL-33ox/RAGE/EGFR pathway still needs further elucidation, we suggest that IL-33ox can contribute to tubular epithelial repair and remodelling. Tozorakimab may therefore be beneficial in DKD by preventing IL-33ox mediated glomerular inflammation and IL-33ox mediated tubular injury.

Funding: Commercial Support - AstraZeneca
Conclusions: Here, we demonstrate for the first time that loss of function of the proton-sodium glucose co-transporter SGLT2 reveals significant upregulation of cardioprotective pathways, indicating that the cardiac benefit of SGLT2is secondary to primary effects on the kidney and not a result of off-target pharmacologic effects.

Funding: NIDDK Support

FR-P0352
SGLT2 Inhibition Causes Methionine Metabolic Modulation in Diabetic Kidney Disease
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Background: Therapeutic inhibition of the sodium glucose cotransporter 2 (SGLT2) protects the kidney although underlying mechanisms are incompletely known. We tested the hypothesis that cellular metabolic pathways activated by SGLT2 inhibition in diabetic kidney disease (DKD) underlie benefits.

Methods: Kidneys harvested from 10-week-old male Sglt2 mutant (MT) and wildtype (WT) mice, fed with normal or high fat diet (HFD, 60% calories from fat) for 8 or 18 weeks, were analyzed. Single cell RNA sequence (scRNA-seq) analysis was performed on libraries prepared from whole kidneys. Metabolomic analysis of renal cortex was conducted by Metabolon, Inc. Two dosages (10 or 50 mg/kg BW) of Methionine Adenosyltransferase 2A inhibitor (MAT2Aii), an inhibitor of the methionine cycle, was injected into intraperitoneal cavity of WT/MT mice with prior exposure to HFD for 8 weeks. Human proximal tubular cells (HK-2), were exposed to 50 mM of D-glucose with/without 1 uM of MAT2Aii or S-Adenosyl methionine (SAM) for 48h.

Results: HFD-induced obesity was similar in both MT and WT while compensatory hyperplasia was observed in MT. Glucose intolerance occurred in mice fed HFD (WT-MT). Molecular and functional markers of kidney injury including serum creatinine, KIM-1, number of apoptotic cells and albuminuria were higher in WT-MT. Analysis of scRNA seq showed a new class of proximal tubular cells (New-PTC), predominantly found in HFD-fed WT. New-PTC showed increased expression of genes related to epithelial-mesenchymal transition (EMT), apoptosis and inflammation. Pathway enrichment analysis of metabolomic data uncovered differences in WT vs MT renal cortex; metabolites of methionine cycle including SAM were preferentially increased in WT-MT. HFD-fed MT. MAT2Aii abrogated renal protection with anti-inflammatory (reduced IL-6, IL-8, IL-1β and TNF) and fibrotic (reduced collagen 1α1 and SM22α) responses in MT. High glucose treatment of HFK-2 recapitulated molecular changes observed in New-PTC, including markers of EMT (elevated fibronectin) and inflammation (increased IL-6, IL-8, IL-1β, TNF) which could be inhibited by MAT2Aii and suppressed using carnitine and metabolites related to methionine metabolism. Conversely MAT2Aii exacerbated EMT and inflammation.

Conclusions: SGLT2 inhibition prevents the emergence of New-PTC with inflammatory and fibrotic phenotypes via methionine metabolic modulation in DKD.

FR-P0353
SGLT2 Inhibition Reveals Kidney Reconfiguration and Metabolic Interorgan Communication
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Background: SGLT2 inhibitors, originally employed for hyperglycemia management, exhibit protective effects against renal and cardiovascular complications irrespective of diabetes presence. The precise molecular mechanisms underlying these effects remain largely unknown and cannot be solely attributed to their primary function of inhibiting renal glucose re-absorption.

Methods: To gain insights into these mechanisms, we employed LC-MS/MS to investigate various aspects, including the proteome, phosphoproteome, gut metaproteome, metabolome, and SGLT2 interaction. For proteomics/phosphoproteomics analyses, we used TMT16-plex labeling or label-free approaches with an Exploris 480 mass spectrometer (Thermo Fisher Scientific) connected to an UltiMate3000 RSLC (Thermo Fisher Scientific) system. For targeted metabolomics, we utilized a quadrupole time-of-flight Impact II instrument (Bruker) connected to either a Bruker Elute HPLC or an Agilent 1290 infinity HPLC device. Targeted metabolomics was conducted using a 6495 triple quadrupole mass spectrometer (5911a/6460b; Agilent) or a 1290 infinity HPLC.

Results: We performed an extensive analysis of the proteome, phosphoproteome, and metabolome following one week of SGLT2 inhibitor treatment in non-diabetic and early diabetic mice. We integrated data from multiple metabolic organs and body fluids, including the kidney, liver, heart, white adipose tissue, skeletal muscle, plasma, urine, and gut microbiota. The kidney exhibited the strongest and most significant response to SGLT2 inhibitors in terms of metabolic signaling and transporter reconfiguration. Additionally, the gut microbiome displayed a reduction in bacteria taxa capable of fermenting aromatic phenylalanine and tryptophan, resulting in lower plasma levels of aromatic toxins. Among the most prominently affected metabolites was p-cresol sulfate, a finding confirmed in cohort studies involving diabetic and heart failure patients with reduced ejection fraction.

Conclusions: The metabolic communication facilitated by SGLT2 inhibitors reduced the presence of circulating waste products such as p-cresol sulfate, consequently reducing the need for renal detoxification. This, combined with decreased glucotoxicity in the proximal tubules and a broad downregulation of apical transport activity, provides a metabolic explanation for the cardiac benefit observed.

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

FR-P0354
Canagliflozin Greatly Improves Mitochondrial Stress Response in Proximal Tubular Cells (PTCs) of Mice with Combined Hypertension and Type 1 Diabetes
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Background: Canagliflozin (CAN) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor with blood glucose lowering effects. CANA promotes kidney protection in patients with type 2 diabetes (T2D), as well as cardiovascular complications. Both diabetes and hypertension induce mitochondrial dysfunction and oxidative stress. However, it is still unclear whether CANA modulates mitochondrial function in diabetic kidney diseases.

Methods: In vivo: Male and female 8 weeks old genetic hypertensive mice (Lin) were subjected to daily intraperitoneal injections of streptozotocin (STZ) for 5 days. 4 weeks after the STZ injections, mice were fed either regular or CANA-infused diet for 1 week. Urinary albumin levels were determined by ELISA and urinary creatinine by colorimetric assay. Proximal tubular epithelial cells (PTCs) isolated from experimental mice were subjected to Seahorse MitoStress test. Kidney OXPHOS complexes were analyzed by Western blotting. In vitro: PTCs were isolated from Fvb mice, treated with 100nM Ang II + 30nM glucose for 24h, followed by treatment with 10μM CANA or vehicle for 24h.

Results: Male and females LinSTZ mice had elevated albumin to creatinine ratio (ACR), while CANA reverted the ACR increase in males (23,578 ± 7,937 vs 4,014 ± 492,5, P<0.05) and females (6,758 ± 906.8 vs 623.4 ± 103.8, n=3, P<0.05). Overexpression of PTCs from LinSTZ + CANA greatly improved oxygen consumption rate (OCR) throughout the mitochondrial stress test (P<0.0001), with significant increase in OCR after inhibition of complexes I, II, and V in males (n=4, P<0.05) and females (n=3, P<0.05). A trend to decrease protein levels of OXPHOS complexes were also observed in the kidney of LinSTZ + CANA mice (n=2-3, P<0.08).

Conclusions: Canagliflozin promoted kidney protection, shown by improvement of albuminuria in diabetic-hypertensive mice. Moreover, we show evidence of improved mitochondria function induced by CANA in vivo and in vitro. Besides the benefits related to restoration of glucose homeostasis, CANA could play a role on proximal tubular mitochondrial function and remodeling.

Funding: Private Foundation Support

FR-P0355
Combination of SGLT2 Inhibition and ARB Additively Ameliorate High Glucose-Induced Epithelial-Mesenchymal Transition in HK-2 Cells
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Background: Both angiotensin receptor blocker (ARB) and sodium-glucose co-transporter 2 (SGLT2) inhibitors have renal protective effects in diabetic kidney disease; however, their synergistic effects when used in combination are not well understood.

Methods: Human kidney-2 (HK-2) cells were divided into five groups: 1) normal glucose (NG, 5.5 mM), 2) high glucose (HG, 25 mM), 3) HG + candesartan (1uM), 4) HG + dapagliflozin (10 uM), and 5) HG + candesartan + dapagliflozin combination treatment groups. The levels of epithelial-mesenchymal transition (EMT) and inflammation markers were evaluated using real time polymerase chain reaction and western blotting. In vitro, the high-molecular weight (HMW) albumin and protein expressions and the effect was the greatest in combination therapy. These changes in mRNA and protein expressions and the effect was the greatest in combination therapy. These findings suggest that combining SGLT2 inhibitor to ARB therapy holds great promise in suppressing the progression of renal fibrosis through the inhibition of EMT. In addition, we exhibited increased expressions of HMGB1, RAGE, and NF-kB, and treatment with either ARB or SGLT2 inhibitor effectively reversed the upregulation of these molecules. However, combination therapy did not significantly improve HMGBl, RAGE, and NF-kB expression compared to monotherapy.

Conclusions: Our results suggest combining SGLT2 inhibitor to ARB is more effective than the monotherapy for preventing EMT in HG stimulated HK-2 cells.
FR-PO356

Empagliflozin Rescues the Loss of Mitochondrial Mass via ERα in Proximal Tubular Epithelial Cells from db/db Mice

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Background: It is known that mitochondrial dysfunction of proximal tubular epithelial cells (PTECs) contributes to the pathogenesis of diabetic nephropathy. However, the ultrastructural changes of PTEC mitochondria in diabetic kidneys remain unclear. Empagliflozin (EMPA) protects the diabetic kidney via SGLT2 located only on PTECs. ERα is highly expressed in PTECs and associated with mitochondrial biogenesis. The present study aimed to investigate the role of ERα in mitochondrial mass in diabetic tubular injury and the mechanism of the protective effects of EMPA.

Methods: Transmission electron microscopy (TEM) was used to identify ultrastructural changes in the mitochondria of PTECs from diabetic mice and RNA sequences of isolated renal tubules were performed to identify the DEGs related to mitochondria and ERα. The expression of ERα was also evaluated by immunohistochemistry (IHC) and Western blot (WB). EMPA was then administered to db/db mice for 16 weeks and the mitochondria was assessed by TEM and the expression of ERα was evaluated by WB, RT-qPCR and IHC. WB was also used to assess the expression of Fis1 and PGC1α. In HK-2 cells, High glucose (HG) or ERα siRNA or pcDNA-ERRα or EMPA were used to modify the expression of ERα. The mass and function of mitochondria were evaluated by Mitotracker Red and JC-1 in corresponding culture conditions.

Results: PTECs presented less mitochondrial mass and swelling mitochondria with more mitochondrial cristae fracture in 16-week-old db/db mice. RNA-sequences of isolated renal tubules from db/db mice revealed that 110 downregulated genes were related to mitochondrial function or mitochondrial energy metabolism. ERα is among the genes with prominent changes. The downregulation of ERRα in diabetic kidney was further evaluated by WB and IHC. In HG-exposed HK-2 cells, the expression of ERα was decreased and the mitochondrial mass and membrane potential (MMP) were inhibited. ERRα gene silencing decreased mitochondrial mass and MMP while ERα overexpression or EMPA rescued HG-induced loss of mitochondrial mass in HK-2 cells.

Conclusions: EMPA alleviated ultrastructural changes of PTECs and the downregulation of ERα from db/db mice.

Funding: Government Support - Non-U.S.

FR-PO357

Kidney Disease Progression in Obese ZSF1 Rats Treated with the SGLT2 Inhibitor Empagliflozin

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Background: The obese ZSF1 rat is a model of spontaneous diabetic kidney disease. These rats are bred from a Zucker diabetic fatty female and a spontaneous hypertensive heart failure male and carry two mutations in the leptin receptor gene: Lepr-Lepr/Δr. Thus, these rodents closely resemble the lean ZSF1 (Lepr-Lepr/Δr). In contrast to many other animal models of kidney disease, the obese ZSF1 rat model is a slow progressing kidney disease model. In this study, we evaluated kidney disease progression in obese ZSF1 rats and for the first time investigated renal outcomes upon treatment with the SGLT2 inhibitor empagliflozin.

Methods: Lean and obese ZSF1 rats were fed with Purina #5008 diet. In the first sub-study, lean and obese animals were left untreated and regular plasma and urine samples were collected for 36 weeks. In the second sub-study, obese animals were treated with empagliflozin (in feed, estimated intake: 30 mg/kg/day) or vehicle at 14 weeks of age until 15 weeks.

Plasma and urine samples were collected bimonthly or monthly, respectively. Glomerular filtration rate (GFR) was measured at baseline and upon 14 weeks of treatment. Plasma and urine samples were analyzed for lipid and kidney injury markers using COBAS analysis as well as various ELISAs. Histological analyses were performed on liver and kidney tissue.

Results: Plasma cholesterol, triglycerides, glucose as well as proteinuria increased with age in obese ZSF1 rats. Urinary excretion of the kidney injury markers KIM-1 and NGAL were also elevated, reaching up to 20 folds at age 34 weeks. Histological analyses revealed severe glomerular damage at 46 weeks of age compared to lean controls. SGLT2 inhibition with empagliflozin indeed reduced plasma glucose and triglyceride levels whereas urine volume and urinary glucose excretion were elevated.

Conclusions: Obese ZSF1 rats were hyperglycemic and hypercholesterolemic. Proteinuria increased with age in these rats, and severe glomerular damage was observed at 46 weeks of age. Empagliflozin reduced blood glucose and increased urine volume as well as glucose excretion. Future analyses investigating proteinuria, GFR as well as morphological characteristics of kidney tissue are ongoing and warranted to evaluate renal outcomes upon treatment with empagliflozin in obese ZSF1 rats.

Funding: Commercial Support - Novo Nordisk A/S, Private Foundation Support

FR-PO358

Expression Profiles of Glucose Transporters Along the Nephrin in Non-Diabetic and Diabetic Kidneys

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Background: In non-diabetic kidneys, over 99% of filtered glucose is reabsorbed in the proximal tubule (PT), resulting in limited delivery to the distal nephron. However, in diabetic kidneys, the excessive filtration of glucose surpasses the reabsorption capacity of the PT, allowing glucose delivery to the distal nephron. This may trigger adaptations in the distal nephron to compensate for glucose reabsorption and minimize its excretion in urine. Despite extensive research, the comprehensive expression profiles of glucose transporters along the nephron remains incompletely understood. This study aims to identify the specific glucose transporters expressed in each tubule segment and investigate alterations in their expression in diabetes.

Methods: We identified glucose transporters expressed in distinct segments of the nephron and compared their gene expression between db/db and db/db mice by analyzing the siRNA-seq data (GEO: GSE184602). Additionally, we conducted microdissection of individual nephron segments from db/db and db/db mice and measured the gene expression of glucose transporters in these isolated tubular segments using RT-qPCR and qPCR. To further validate the protein expression of these glucose transporters, we performed immunofluorescence (IF) staining and Western blot (WB) assays on whole kidneys.

Results: We unveiled the expression profiles of glucose transporters in specific segments of the nephron. Specifically, Slc2a4 (GLUT4) is expressed in thick ascending limb (TAL), distal convoluted tubule (DCT), connecting tubule (CNT), and intercalated cells (IC), and Slc2a1 (GLUT1) is expressed in TAL, macula densa, DCT, CNT, principal cells, and IC. Furthermore, our analysis revealed an upregulation of Slc2a4 expression in the TAL (27.96%), DCT (6.10%), CNT (53.95%), and IC (66.03%) and a downregulation of Slc2a1 expression in the DCT (-40.98%), CNT (-49.05%), and IC (-103.6%) in db/db mice compared to db/m mice. Additionally, we confirmed these findings through RT-qPCR and qPCR in isolated tubular segments, as well as IF staining and WB assays in whole kidneys.

Conclusions: In this study, we identified glucose transporters expressed along the nephron and compared their expression levels in db/m and db/db mice. Notably, the glucose transporter GLUT4 in the distal nephron segments appears to play a significant role in compensating for glucose reabsorption in diabetes.

Funding: NIDDK Support, Private Foundation Support

FR-PO359

Direct Effects of SGLT2 Inhibitors on Proximal Tubule Function

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT2i) have been shown to have cardiorenal protection in patients with and without T2DM. Inhibition of proximal tubule (PT) sodium/hydrogen exchanger type 3 (NHE3), which is known to regulate endocytosis and fluid transport in the PT, has been suggested to contribute to the SGLT2i renoprotective effects. Also, some SGLT2i have been demonstrated to activate AMPK. However, the underlying mechanisms behind the beneficial effects of SGLT2i are unknown. To circumvent the challenges of untangling the direct effects of SGLT2i on PT function in vivo, we examined the effects of gliflozins in a well-characterized and highly differentiated opossum kidney (OK) cell culture model of the PT S1 segment.

Methods: The effect of gliflozins vs NHE3 inhibitor S3226 on albumin uptake and fluid transport was quantified in OK cells. Endosomal pH was measured by fluorescence ratio imaging in OK cells treated with cana vs S3226. Effects of gliflozins, S3226, and AMPK pathway perturbants were determined by immunoblotting. 10-week-old male C57BL/6 mice were given cana or empa by oral gavage daily following vehicle gavage. Urine was collected via metabolic cages at baseline and after 24h and 48h. Creatinine and albumin were measured by ELISA.

Results: A subset of SGLT2i (cana and tofo, but not empa) impaired endocytosis and fluid transport in a dose-dependent and glucose-independent manner. Surprisingly, SGLT2i did not recapitulate the effect of S3226 on NHE3 phosphorylation or endosomal pH. Treatment with cana but not empa caused a rapid increase in AMPK phosphorylation and subsequent decrease in phosphorylated AMPK (pAMPK). A downstream target of NTR. These effects were observed at concentrations comparable to plasma levels in humans on standard doses of cana. In our mouse study, both treatment conditions led to increased urine volume compared to baseline, cana treated mice urinated significantly more than empa treated mice.

Conclusions: Differential effects of SGLT2i on fluid transport and albumin uptake in OK cell monolayers may be mediated by off-target effects on AMPK/mTOR activity. These off-target effects could contribute to the differences we observed in mice treated for short periods with cana vs empa, and could impact the renal protective mechanisms of SGLT2i in humans.
FR-PO360

A Human Single-Cell Transcriptomic Atlas Charakterizes the Kidney in Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD), a common and devastating microvascular complication of diabetes, is the leading cause of end-stage renal disease (ESRD). However, the mechanisms of kidney injury in DKD are largely unknown.

Methods: To elucidate the heterogeneity and the underlying mechanisms for DKD progression, we performed single-cell RNA sequencing (scRNA-seq) on human kidneys collected from 3 DKD and 3 normal samples using 10x Genomics.

Results: A total of 51315 cells were enrolled for analyses, and nine kidney cell types and seven immune cell types were identified. The cell-type-specific changes in gene expression and signaling pathways of podocytes, fibroblasts, endothelial cells, proximal tubules and macrophages indicate abnormal regulation associated with inflammation, apoptosis, oxidative stress, extracellular matrix accumulation, fibrosis and immune activation. In particular, we show that podocytes and proximal tubules have a tremendous capacity to regenerate, which is involved in the repair of injury. Extracellular vesicles, important mediators of intercellular communication, might play vital roles in this process. In addition, we identified new candidate transcription factors responsible for the progression of DKD. We also revealed an M1-M2 hybrid pattern, in which M1 and M2 are coupled for activation in macrophages in DKD. Furthermore, we observed an increased intercellular interaction among podocytes, fibroblasts, endothelial cells, proximal tubules, and macrophages in DKD.

Conclusions: Our study advances the understanding of DKD pathogenesis and provides novel therapeutic targets for its treatment in the future.

FR-PO362

Identification of Novel Noninvasive Biomarkers for Caudium-Induced Renal Injury Through Transcriptome Profiling and Machine Learning
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Background: Kidney is the major toxic organ for cadmium. Once entering the body, cadmium accumulates in proximal tubule cells, resulting in the death of renal epithelial cells through necrotic or apoptotic mechanisms. Of particular interest, cadmium is closely associated with diabetes and the diabetic population is more sensitive to cadmium induced cell damage. The molecular mechanisms underlying the chronic cadmium induced toxicity and the increased susceptibility under diabetic conditions are not fully understood.

Methods: In the present study, we optimized an animal model to study chronic cadmium exposure-induced renal injury by using low dose and repetitive CdCl2 treatment. In conjunction with clinical biochemistry and histopathology, we performed whole transcriptome profiling analyses on kidney. Machine learning with cloud computing was applied to identify novel biomarkers indicative of increased susceptibility in diabetic populations with particular focus on secreted molecules.

Results: Repetitive CdCl2 exposure resulted in cadmium accumulation and remarkable renal injuries with the ob/ob mice manifesting increased severity of renal injury. RNA-Seq data showed that cadmium treatment induced dramatic gene expression changes correlated with the level of cadmium-induced nephrotoxicity. In order to better understand the increases susceptibility under diabetic conditions, we focused our analyses on the low dose ob/ob group. Canonical pathway enrichment analysis revealed key pathways such as Integrin, Ap1, IL23, Fra, A53 and TAP63 pathways. Furthermore, a subset of 14 secreted molecules was found to be enriched including Il1b, Cdl2, Iilrn, Gdf15 and Il17f.

Conclusions: A subset of potential sensitive biomarkers which can be measured in peripheral early for diagnosis of cadmium-induced renal injury has been identified. Applicability of these biomarkers in clinical will be tested in human samples.

Funding: Government Support - Non-U.S.

FR-PO361

Integrative Transcriptome and Proteome Profiling of Insulin-Resistant Kidney Cell Models and Patient Biopsies Reveals Common and Cell Type-Specific Mechanisms Underpinning Diabetic Kidney Disease
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Background: Diabetic kidney disease (DKD) is the leading cause of end stage kidney failure worldwide. It is now clear that cellular insulin resistance is a major driver of this disease.

Methods: Using established human conditionally immortalized podocytes (Pods), glomerular endothelial cells (GECs), mesangial cells (MCs), and proximal tubular cells (PTCs), we modelled both insulin sensitivity and insulin resistance and performed simultaneous transcriptomics and proteomics for integrated analysis. Our data was further compared with bulk- and single-cell transcriptomic kidney biopsy data from early- and advanced-stage DKD patient cohorts.

Results: We identified several consistent changes (individual genes, proteins, and molecular pathways) occurring across all insulin-resistant kidney cell types, which were replicated in human early- and/or advanced-stage DKD biopsies. These included the genes CTSS, NBR2F2, C3, CXCL1, TPP12, and PFKFB3, and pathways related to the inflammatory response, ER stress and glycoprotein metabolism. We further identified several cell-line-specific molecular changes occurring in response to insulin resistance, which were replicated in single-cell sequencing data from DKD, together with a selective reduction in mitochondrial function in Pods, MCs and PTC, but not GECs.

Conclusions: Our study provides new data resource to direct future studies in elucidating underlying kidney signalling pathways and potential therapeutic targets in DKD.

Funding: Government Support - Non-U.S.

FR-PO363

Cytochrome P450: The Metabolic Pathways and the Genetic Epigenetic Regulation Involved in Shaping the Story of Diabetic Kidney Disease (DKD).
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Background: Cytochrome P450 (CYPs) epoxygenases metabolize arachidonic acid (AA) into 20-HETE and EETs. Our group has described the implication of CYPs and their metabolites in the pathogenesis of DKD, in experimental animal model of diabetes. Yet the correlation of these finding in human setting is under investigation. More importantly, CYPs-encoding genes possess polymorphisms that can alter the expression of these key enzymes, affecting the prognosis of patients with DKD. Herein, we hypothesize that alteration in 20-HETE and EETs levels in diabetes leads to kidney injury, and that genetic variants/epigenetic regulation of AA-metabolizing CYPs may potentiate the development of DKD.

Methods: Healthy volunteers, individuals diagnosed with type 2 diabetes (T2DM) with a without clinical manifestation of DKD were enrolled in this study. Levels of 20-HETE and EETs were assessed in the urine and plasma samples of the recruited individuals and correlated with the extent of renal injury. To detect single nucleotide polymorphisms (SNPs) in CYPA11, CYPA49 and CYP2B6, TaqMan PCR assay was performed on the DNA extracted from the collected blood samples.

Results: Circulating levels of 20-HETE were increased in patients with DKD when compared to T2DM patients with no clinical signs of DKD, which in turn had higher levels of 20-HETE in comparison to the healthy volunteers. This was associated with an increased expression of CYPA11 and CYPA49 in the human kidney biopsies of patients with DKD. In parallel, EETs levels were decreased in patients with T2DM and DKD as compared to patients with T2DM only and this was positively correlated with the decreased CYP2B6 expression in kidney biopsies of patients with DKD. Furthermore, a difference in 2 SNPs for CYP2B6 and ISNP for CYPA411 was observed across patients with different conditions, suggesting an increased risk with the mutant allele for diabetes and DKD.
Conclusions: This study may yield important findings about novel regulatory pathways involved in diabetes-induced renal injury and may identify novel prognostic diagnostic biomarkers associated to CYPs pathways in DDK.

FR-PO364
Deciphering Renal Restoration: Single-Cell Transcriptional Insights from Pre- and Post-Vertical Sleeve Gastrectomy Kidney Biopsies
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Background: Vertical sleeve gastrectomy (VSG) attenuates the metabolic dysfunction characteristic of obesity and type 2 diabetes. The molecular mechanisms diminishing risk of kidney disease by VSG remain unclear.

Methods: Cell-type-specific differentially expressed genes (DEGs) before and 12 months after VSG (n=5 pairs) were determined from single-cell RNA sequencing (scRNAseq) of kidney biopsies. Top up- and downregulated pathways associated with VSG based on pathway enrichment of DEGs were compared with similarly curated Sodium-Glucose Cotransporter-2 inhibitor (SGLT2i) effects (https://doi.org/10.1172/JCI164486) to identify shared and unique pathways in cell types experiencing significant transcriptional changes.

Results: VSG improved UACR for all, and 75% with initial high albuminuria saw a category stepdown. Glomerular and mesangial volume decreased in the subset with kidney biopsy data. Proximal tubular cells had the most genes suppressed, while thick ascending limb cells the most enhanced, after VSG based on scRNAseq. Metabolic pathways like glycolysis, the TCA cycle, and gluconeogenesis were downregulated, while others like notoferin, the kidney injury molecule, and heart failure were upregulated. Noteworthy transcriptional variations were seen between SGLT2i treatment and VSG (Figure).

Conclusions: scRNAseq provided insights into cell-specific effects of VSG on kidneys. Despite commonalities, VSG and SGLT2i modified distinct cell-specific signaling pathways, offering potential avenues for innovative therapeutic interventions.

Funding: NIDDK Support, Private Foundation Support

FR-PO365
GDF-15 and NETosis Cross-Talk in Diabetes-Induced Renal and Cardiovascular Complications: Unraveling the Molecular Interactions
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Background: Diabetic kidney disease (DKD) and diabetic cardiomyopathy (DCM) are severe complications of diabetes, posing significant risks of renal failure and cardiovascular events. One potential biomarker with promising implications in this context is growth differentiation factor 15 (GDF-15), a cytokine belonging to the transforming growth factor-β (TGF-β) family. Elevated levels of GDF-15 are observed in the presence of tissue injury, inflammation, and stress. Moreover, our research group has focused on exploring the relationship between neutrophil extracellular trap formation (NETosis) and the progression of injury in DKD and DCM. This article aims to elucidate the relationship and interplay between GDF-15 and NETosis in the development of renal and cardiac injury induced by type 2 diabetes.

Methods: T2DM was induced in C57BL/6 male mice using the high fat diet/STZ model in two sets of experiments. In the first set, mice were divided into control, PMA-induced NETosis, T2D, and T2D treated with CLA (NETosis inhibitor) groups. In the second set, control mice, GDF-15 antibody AV-380-treated control mice (at 7.5mg/kg or 20mg/kg), T2D mice, and AV-380-treated T2D mice (at 7.5mg/kg or 20mg/kg) were utilized. Functional, histopathological, and molecular studies were performed on kidney and heart tissues from all groups.

Results: Our data demonstrate that inhibiting GDF-15 with AV-380 or NETosis with CLA can restore renal and cardiac homeostasis in T2D mice. This is evident through reduced proteinuria, glomerulosclerosis, collagen deposition in the kidneys and heart, as well as improved cardiac ejection fraction and decreased inflammatory markers in the serum of diabetic mice. Importantly, NETosis inhibition attenuated the diabetes-induced overexpression of GDF-15 in kidney and heart tissues, suggesting a crosstalk between these 2 signaling molecules. Intriguingly, inducing NETosis in control mice using PMA resulted in similar renal and heart injuries observed in diabetes.

Conclusions: Our study findings provide valuable insights into the role and interplay between GDF-15 and NETosis in diabetes-related cardiac and kidney injury. Targeting the GDF-15/NETosis signaling cascade through pharmacological interventions offers a basis for future clinical studies that aim to manage diabetes-associated complications.

FR-PO366
Stress Response Protein REDD1 Sustains the Chronic Inflammatory Response in Diabetic Nephropathy
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Background: Diabetic nephropathy (DN) is one of the most common and severe complications of diabetes. We recently demonstrated a role for the stress response protein REDD1 in development of renal complications in DN. However, there remains a significant gap in our understanding of the molecular events whereby REDD1 contributes to the development of renal dysfunction. Herein, we investigated the hypothesis that diabetes-induced REDD1 expression acts to exacerbate pro-inflammatory NF-κB signaling and consequently development of renal inflammation.

Methods: REDD1−/− and REDD1−/+ mice were administered low dose streptozotocin to induce diabetes. Kidneys were isolated after 16 weeks of diabetes, weighed, and analyzed for protein and mRNA expression. Spot urine albumin and creatinine levels were assayed. Kidney sections were fixed and renal sections were visualized by immunofluorescence microscopy. Complementary analyses were performed with conditionally immortalized human podocyte cultures exposed to hyperglycemic conditions. Inhibition of SGT2 or GSK3 was achieved by dapagliflozin or VPS-15 administration, respectively. Nuclear NF-κB activity was estimated by luciferase assay.

Results: Diabetes increased REDD1 expression in the kidney and promoted albuminuria and renal immune cell infiltration. In diabetic mice treated with dapagliflozin, blood glucose concentrations were reduced and both REDD1 expression and immune cell infiltration were attenuated. In contrast with REDD1−/− mice, REDD1−/+ mice did not exhibit an increase in pro-inflammatory marker expression or renal macrophage infiltration with diabetes. In cultured human podocytes, exposure to hyperglycemic conditions promoted REDD1 expression, which was required for activation of both NF-κB and the NLRP3 inflammasome. Upregulation of NF-κB target genes and IL1β production by podocytes exposed to hyperglycemic conditions was prevented by REDD1 deletion. REDD1 acted via an Akt-GSK3β signaling axis, as GSK3β inhibition prevented diabetes-induced NF-κB activation and reduced immune cell infiltration in kidneys of diabetic mice.

Conclusions: These findings demonstrate a role for REDD1-dependent GSK3 signaling in diabetes-induced renal pathophysiology and support the possibility that therapeutics targeting REDD1 or GSK3 could be beneficial in the context of DN.

Funding: Other NIH Support - R01 EY029702, R01 EY02379, Private Foundation Support

FR-PO367
SerpinA3K Deficiency Ameliorates Diabetic Kidney Disease (DKD)
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Background: We showed that SerpinA3K is an early urinary biomarker of Acute Kidney Injury (AKI) to Chronic Kidney Disease (CKD) transition. SerpinA3K or anti-chymotrypsin is a serine protease inhibitor with non-canonical functions such as anti-neutrophil, anti-inflammatory, and anti-fibrotic in rodent diabetic retinopathy. Nevertheless, we recently showed that AKI is attenuated in SerpinA3K deficient mice by inducing higher expression of antioxidant defense, however, its involvement in CKD remains elusive. This study was designed to evaluate the impact of SerpinA3K absence in DDK.

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

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Methods: Thirty wildtype (WT) [SerpinA3K+/+] and thirty knock-out (KO) [SerpinA3K/-/+] male mice after breastfeeding were randomized in the following six groups: Standard Diet (WT+SD and KO+SD), High Fat Diet (WT+HFD and KO+HFD), and Streptozotocin (STZ) [100 mg/kg] + HFD (WT+DKD and KO+DKD). Glucose monitoring was done every 15 days. A cut-off point was established above 500 mg/dL to receive insulin 2 days per week to increase animal survival. Urine collection was done monthly. After 7 months of follow-up, each group was euthanized for kidney functional, histological, and molecular analyses. Differences between groups were analyzed through ANOVA and post-hoc testing with a significance level of p<0.05.

Results: GFR measured by fluorescein sinistrin was significantly increased in the WT+HFD but not in the KO+HFD group. Furthermore, the WT+DKD group exhibited an increase in Hif1a, Hif6, and Tgh1 which was not seen in the KO+DKD group.

Conclusions: The absence of SerpinA3K was associated with DKD attenuation. This protective effect seems to be mediated by improving metabolic health against hyperglycemia. Nevertheless, the mechanisms and causes of this protection required further studies to deepen into the role of SerpinA3K in DKD induced by STZ.

Funding: Government Support - Non-U.S.

FR-PO368 Specialised Proresolving Mediators Protect the Diabetic Kidney Against Podocyte Loss
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Background: Kidney macropores are a heterogeneous population of cells that contribute to the chronic unresolved inflammation that underlies diabetic kidney disease (DKD). The macrophage subpopulations initiating and promoting inflammation in DKD, particularly in the glomerulus, have not been characterized. There has also been growing interest in specialised pro-resolving mediators (SPMs) such as Lipoxin A4 (LXA4) as potential renoprotective agents. The focus of this study was to investigate the effect of LXA4 on kidney macropores in a model of DKD.

Methods: Six-week-old male ApoE KO mice were rendered diabetic by five daily IP injections of streptozotocin (55mg/kg). Controls received citrate buffer alone. After 10wks of diabetes, mice were randomized to receive twice weekly administration of either vehicle (0.02% ethanol) or LXA4 (518µg) via IP (n=30/gp) for a further 6 weeks. At endpoint, mice were culled, and kidneys collected for gene expression analysis, single cell RNA sequencing (scRNA-Seq) of glomerular cells, immunohistochemistry and histology.

Results: Diabetic mice had elevated blood glucose, glycated haemoglobin and albuminuria, as well as increased expression of fibrotic (fibronectin, Col 4a3), inflammatory markers (IL1β, TNFα, MCP1, VCAM-1, ICAM-1) compared to control. Interestingly, LXA4 reduced in reduced albuminuria, Collagen IV and inflammatory and fibrotic markers (IL1β, MCP1, ICAM1 and VCAM1) independent of any changes in metabolic parameters. scRNA-Seq of the glomerular cell populations demonstrated an increase in macrophages in kidneys of diabetic mice. These changes were associated with renal injury, including the increased expression of apoptotic markers and depletion of podocytes (reduced by 42% in diabetic versus control). LXA4 reduced macrophage numbers and prevented podocyte loss in the diabetic kidney.

Conclusions: SPMs protect against DKD by reducing fibrotic and inflammatory signalling, as well as reducing monocyte recruitment and increased macrophage numbers in the diabetic kidney. These effects are accompanied with improved kidney function. These further support the use of SPMs as typified by LXA4, as a novel treatment for DKD by targeting macrophores in the kidney.

Funding: Government Support - Non-U.S.

FR-PO369 Mitochondrial Dysfunction-Related Glycogen Synthase Kinase 3β (GSK3β) Overexpression Drives Early Diabetic Tubulopathy
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Background: Over these years, the traditional “glomerulocentric” paradigm of DKD has partly shifted to diabetic tubulopathy (DT) because of renal insufficiency and prognosis of patients is closely related to tubular atrophy and interstitial fibrosis. New insights indicate that mitochondrial dysfunction represents an early event in DT, but the precise mechanism for such pathological process is not clear.

Methods: The present study was designed by using high-fat diet (HFD)-fed combined with STZ mice as an insulin resistance model of tubular injury in TDM. We also reported the expression of GSK3β in human proximal renal tubular (HK-2) cells.

Results: As a potential novel biomarker for predicting a variety of renal diseases, glycogen synthase kinase 3β (GSK3β) is overexpressed and hyperactive with mitochondrial dysfunction in proximal tubular epithelium, correlating with functional and histological signs of renal tubular injury in diabetic mellitus (DM). Moreover, tubule-specific ablation of GSK3β substantially attenuated mitochondrial damage and early tubular lesions in mice. Multiple regulatory mechanisms of mitochondrial damage, such as mitochondrial biology, mitochondrial dynamics, mitophagy and oxidative stress, are closely related to the hyperactivation of GSK3β. In addition, therapeutic targeting of GSK3β by T2Dz-D8 ameliorated mitochondrial dysfunction and delayed early stage of DT in mice.

Conclusions: Thus, GSK3β appears to play a key role in early DT by modulating mitochondrial dysfunction and may be an actionable target for intervention to delay DKD in advance.

Funding: Government Support - Non-U.S.
FR-PO371
Promoting Mitochondrial Dynamics by Inhibiting the PINK1/PRKN Pathway to Relieve Diabetic Nephropathy
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Background: Diabetes is a metabolic disorder characterized by high blood glucose levels and a leading cause of kidney disease. Dysfunctional mitochondria have been associated with diabetic nephropathy. However, many questions remain about the exact mechanisms and understanding is important to develop effective therapeutics.

Methods: Structure, function, and molecular pathways are highly conserved between mammalian podocytes and Drosophila nephrocytes. Thus we used flies on a high sucrose diet to model type 2 diabetic nephropathy. We then investigated the structural and functional effects of the fly nephrocytes and their mitochondria.

Results: The nephrocytes of flies on a high sucrose diet showed remarkable levels of functional decline and decreased cell size; the flies had a shortened lifespan. Structurally, the slit diaphragm—nephrocyte filtration structure—was disorganized. At the cellular level, we found altered mitochondrial dynamics and dysfunction. Regulating mitochondrial dynamics by either genetic modification of the PINK1/Parkin (mammalian PINK1/PRKN) pathway or treatment with BGP-15, mitigated the mitochondrial defects and nephrocyte functional decline.

Conclusions: These findings support a role for PINK1/Parkin-mediated mitophagy and associated control of mitochondrial dynamics and health in diabetic nephropathy; and demonstrate that targeting this pathway might provide therapeutic benefit in type 2 diabetic nephropathy.

Funding: Private Foundation Support

FR-PO372
Obesity Augments Urinary Tract Infection Susceptibility by Activating Focal Adhesion Kinase in Kidney Intercalated Cells
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Background: Obesity affects at least 30% of the global population. Among the comorbidities, obesity is linked to increased urinary tract infection (UTI) and pyelonephritis risk. The obesity mediated factors that increase UTI risk are unknown. In this study, we assess the impact of diet-induced obesity on UTI susceptibility using male and female mice. Because recent data show intercalated cells (IC) in the kidney have a key role in protecting against pyelonephritis and pyelonephritis, we also assess how diet-induced obesity effects murine IC gene expression and antibacterial defenses.

Methods: C57.BL6 male and female mice were fed a high fat diet (HFD; 60 kcal% fat) or standard diet (SD; 10 kcal% fat) for 8-12 weeks. Mice were subjected to experimental UTI and infected with E. coli (PEC). PEC burden was quantified 24 hours after infection. ICs from SD and HFD fed mouse kidneys were infected using FACTS and subjected to RNAseq. Differentially expressed genes were used to generate lists of enriched pathways and ontologies. Western blot confirmed pathway suppression or activation. To test how these pathways impact UTI outcomes, ICs were cultured to confluence, treated with targeted inhibitors, and challenged with UPEC.

Results: Male and female mice fed a HFD showed a 30% increase in body weight, reduced insulin sensitivity measured by glucose tolerance testing, and 100-fold greater UPEC burden following UTI. Changes in gene expression in ICs from HFD and SD mice diverged depending on sex. Activation of focal adhesion kinase (FAK) was consistent between sexes when comparing HFD and SD ICs. Western blot confirmed increased FAK signaling in HFD kidneys, as well as increased NFkB, a downstream FAK target. When cultured ICs were treated with the FAK inhibitor PF-573228 and challenged with UPEC, bacterial invasion was abolished.

Conclusions: These results suggest that diet-induced obesity leads to increased UTI susceptibility by activating FAK signaling in ICs. Future studies will investigate the factors regulating FAK as targets for reducing UTI risk.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program

FR-PO373
Overexpression of Adiponectin, via an Adipocyte Specific Promoter, Confers Metabolic Benefits and Transient Improvements in Urine Albumin-Creatinine Ratio (UACR)

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Background: Adiponectin is an endocrine factor synthesized and released from adipose tissue. Clinical and pre-clinical data have linked low adiponectin levels with increased risk of type 2 diabetes. Although adiponectin has protective effects on the fly nephrocytes and their mitochondria. We hypothesized that in-vivo overexpression of adiponectin using adipocyte-specific promoter would lead to extended increased systemic exposure of functional adiponectin forms.

Methods: We engineered an adipocyte-specific promoter and achieved AAV8 uptake and overexpression of adiponectin in vivo with exposure for up to 12 weeks in plasma. We evaluated the effects of adiponectin overexpression on metabolism and kidney function in the BTBR ob/ob mouse model of dyslipidaemia and diabetic kidney disease.

Results: In human glomerular endothelial cells and iPS differentiated podocytes, protective effects of adiponectin signaling were observed in in vitro disease models. Mice treated with AAV-adiponectin displayed a decrease in body weight change from the first week after treatment up to 9 weeks in BTBR ob/ob mice. In addition, adiponectin overexpression also decreased the urinary albumin to creatinine ratio by an average of 70% with no significant difference in weight and body composition. However, this effect was lost at late time points. At termination, AAV-adiponectin-treated obese animals had significantly decreased plasma cholesterol, liver triglyceride levels, and a decreased liver weight as a proportion of body weight. The effect of AAV-adiponectin overexpression on body weight gain was reproduced in a second cohort of mice in which WT mice were treated with AAV8 for 12 weeks.

Conclusions: Adiponectin overexpression can reduce body weight gain and improve metabolic parameters in the liver. Overexpression of adiponectin can transiently decrease kidney damage, as assessed by UACR, but further work is required to determine how to maintain the kidney protective effects of adiponectin.

Funding: Commercial Support - AstraZeneca

FR-PO374
Insulin and Glucose Tolerance Assessment in Guanylyl Cyclase/Natriuretic Peptide Receptor-A Gene-Targeted Mutant Mice
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Background: Atrial natriuretic peptide (ANP), acting through the guanylyl cyclase/natriuretic peptide receptor-A (GC-ANPRA), is pivotal in regulating blood pressure and cardiac homeostasis. Ablation of Npr1 (encoding NPARA) in mice exhibits hypertension and provokes congestive heart failure; however, the underlying mechanisms are not yet precisely determined. The objective of this study was to investigate whether Npr1 plays a critical role in regulating glucose homeostasis.

Methods: The adult male (14-18 wk) Npr1 gene-knockout haplotype (Npr1+/−, 1-copy), wild-type (Npr1+/+, 2-copy), and gene-duplicated (Npr1+/+++, 4-copy) mice were fasted overnight (16 h) and then received an ip-injection of 1.0 Ukg of insulin. Blood glucose levels were determined by performing tail bleeds at 0, 15, 30, 60, 90, and 120 min using Alphatrak. The non-invasive tail-cuff method determined systolic blood pressure (SBP).

Results: The results showed that administration of glucose resulted in a greater increase in blood glucose levels at 120 mins in 1-copy male mice (OGTT: 237 ± 5 mg/dL; IPGT: 246 ± 6 mg/dL, ITT: 239 ± 7 mg/dL) than 2-copy male mice (OGTT: 131 ± 3 mg/dL; IPGT: 126 ± 6 mg/dL, ITT: 127 ± 6 mg/dL), respectively. The blood glucose was also significantly lower in 4-copy mice (OGTT: 113 ± 5 mg/dL; ITT: 107 ± 4 mg/dL; ITT: 107 ± 3 mg/dL) than in 2-copy mice. SBP was significantly greater in 1-copy mouse (130 ± 4 mmHg) than in 2-copy mouse (100 ± 3 mmHg) and significantly lower in 4-copy mice (90 ± 2) in 2-copy mice. The increase in plasma glucose levels were significantly lower in OGTT than in IPGT.

Conclusions: NPARA markedly prevented a steep rise in blood glucose levels after glucose injection and ameliorated glucose intolerance, as reflected in 2-copy and 4-copy mice than 1-copy mice. The results suggest that NPARA signaling predisposes to arterial pressure, hyperglycemia, and insulin resistance, thus Npr1 gene might regulate glucose homeostasis. Supported by NIH grant DK133833.

Funding: NIDDK Support

FR-PO375
Inhibition of Endogenous Adenine Synthesis Ameliorates Kidney Injury in db/db Mice with Type 2 Diabetes
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Background: Elevation of kidney and urine adenine is associated with chronic kidney disease (CKD) including diabetes. Although adenine administration induces CKD in animal models, the effect of endogenous adenine on diabetic kidney disease (DKD) has not been studied. We hypothesize that inhibition of adenine synthesis ameliorates DKD by inhibiting mTORC in mice with type 2 diabetes.

Methods: C57BL6 WT male mice received adenine containing water or control water for 4 weeks. dd/db male mice with type 2 diabetes received methylthioadenosine phosphoribosyltransferase (MTAP) inhibitor in drinking water for 4 weeks. Kidney metabolites were measured by ZipChip mass spectrometry. Mouse proximal tubule (MCT) cells were employed for in vitro experiments.

Results: Adenine increased albuminuria, blood urea nitrogen (BUN), kidney hypertrophy, and kidney KiM-1 mRNA. Kidney mTORC1 activity in WT mice. Adenine stimulated senescence-associated secretory phenotype along with reduction in Klotho expression in the kidney. Rapamycin (a selective inhibitor of mTORC1) inhibited adenine-induced mTORC1 activation and matrix protein accumulation, and kidney mTORC1 activity in WT mice. Adenine inhibited stimulated senescence-associated secretory phenotype along with reduction in Klotho expression in the kidney. Rapamycin (a selective inhibitor of mTORC1) inhibited adenine-induced mTORC1 activation and matrix protein accumulation, and kidney mTORC1 activity in WT mice. Adenine inhibited stimulated senescence-associated secretory phenotype along with reduction in Klotho expression in the kidney.

Conclusions: Adenine increased albuminuria, blood urea nitrogen (BUN), kidney hypertrophy, and kidney KiM-1 mRNA. Kidney mTORC1 activity in WT mice. Adenine inhibited stimulated senescence-associated secretory phenotype along with reduction in Klotho expression in the kidney.

Funding: NIDDK Support
J Am Soc Nephrol 34: 2023

Diabetic Kidney Disease: Basic - I

MTAP inhibitor decreased diabetic kidney hypertrophy, KIM-1 expression, fibrosis, and
mTORC1 activation in the kidney of db/db mice without changes in BUN, body weight,
blood glucose level, and intake of food or water. Klotho expression was increased by
MTAP inhibitor in the kidney of db/db mice. MTAP inhibitor did not affect other diabetesrelated metabolites.
Conclusions: Our data suggest that elevation of adenine drives DKD which is
ameliorated by inhibiting adenine synthesis in the kidney. Therefore, adenine metabolism
could be used for a biomarker and therapeutic target of DKD.
Funding: NIDDK Support, Veterans Affairs Support, Other U.S. Government
Support

FR-PO376

Poster Friday
Diabetic Kidney Disease: Basic - I

Elucidating NOX5 as a Potential Therapeutic Target and a Biomarker of
Kidney Disease in Diabetes
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Geneve, Geneve, Switzerland.
Background: Diabetes related chronic kidney disease (CKD) is the leading cause of
end stage renal failure. Oxidative stress due to excessive production of reactive oxygen
species plays a critical role in diabetic kidney disease (DKD). Pro-oxidant enzyme
NADPH oxidase-NOX5 is considered as a major contributor of reactive oxygen species
(ROS) mediated kidney damage in diabetes. We aim to identify the renoprotective effect
of NOX5 inhibition in the in vitro setting of human derived renal cells and organoids
exposed to diabetic milieu. We also aim to validate NOX5 as a biomarker for the early
prediction of human DKD.
Methods: We examined the effect of NOX5 silencing or inhibition by NOX5specific inhibitors on ROS formation along with markers of fibrosis, inflammation and
ROS-sensitive factors in human renal cells and iPSC derived renal organoids. We assessed
the expression of NOX5 in human kidney biopsies as well as in urine and serum obtained
from non-diabetic and diabetic individuals by ELISA and FACS. Correlation between
NOX5 level and clinical data sets including albuminuria was performed.
Results: Renal NOX5 expression was increased in diabetic patients in comparision
to non-diabetic subjects. Increased expression of NOX5 was associated with upregulation
of a transcription factor, EGR-1 and down regulation of an endosulfatase, SULF-1
(an enzyme which maintains the integrity of glomerular filtration barrier) in diabetes.
Both genetic silencing of NOX5 in renal cells and pharmacological inhibition of NOX5
in renal cells as well as in renal organoids attenuated high glucose induced upregulation of
CTGF, MCP-1, TLR-4 and EGR-1 and restored the expression of SULF-1 via reduction
in ROS formation. These novel findings suggest the role for NOX5 in renal fibrosis
and inflammation as well as in the regulation of EGR-1 and SULF-1 in diabetes like
conditions. Moreover, increased level of NOX5 in human urine and serum was observed
in diabetic individuals even in the absence of albuminuria.
Conclusions: These findings suggest that NOX5 plays a key role in human DKD by
promoting inflammation and fibrosis, thereby providing the fast track validation of NOX5
specific inhibitors to combat DKD in humans. In addition, NOX5 appears to be a potential
biomarker for the early detection of DKD.

FR-PO377

Poster Friday
Diabetic Kidney Disease: Basic - I

Novel Molecular Therapy of Diabetic Nephropathy by Repurposing
Niclosamide to Modulate Renal RNA-Binding Protein HuR
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Background: Hu antigen R (HuR) influences the expression of genes involved in
pathways critical to the pathogenesis of diabetic nephropathy (DN). We identified a FADapproved anthelmintic drug, niclosamide (NCS), as a novel inhibitor of HuR. This study
sought to determine whether HuR- targeted therapeutics with NCS are therapeutic for DN.
Methods: Four groups of uninephrectomized mice with normal control and diabetic
db/db mice without treatment but being terminated at 14 and 22 wks respectively, or
treated with NCS (20mg/kg daily via i.p.) from wks 18 to 22 were included.
Results: A significantly increased HuR expression was observed in diabetic kidneys
from both patients and db/db mice, while the latter was inhibited by NCS treatment.
Immunofluorescent staining for HuR confirmed the Western blot measurement. Untreated
db/db mice developed progressive albuminuria and glomerular mesangial matrix
expansion between age of weeks 14 and 22, associated with increased renal production
of fibronectin and a-smooth muscle actin but decreased glomerular WT-1+-podocytes and
nephrin expression. NCS treatment did not affect mouse body weight but reduced blood
HbA1c levels (10.8±1.0 in treated db/db vs. 13.4±0.93% in db/db, P<0.05), arrested the
increases in albuminuria, markers of glomerulosclerosis and podocyte injury seen in db/
db mice. Renal expressions of NF-κBp65, TNF-a, MCP-1, Nox2, and urine TBARS
levels, the markers of inflammation and oxidative stress, were increased during disease
progression in db/db mice, which were halted by NCS treatment (P<0.05). In addition,
a downstream factor of the Wnt signaling pathway, known as WNT1-inducible signaling
pathway protein 1 (WISP1), has been identified as one of key downstream mediators of
HuR-dependent action and found to be markedly increased by 3.2 fold in db/db mouse
kidneys at 22 wks, compared with non-diabetic controls, which was abrogated by NCS
treatment, approaching to normal levels.

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Conclusions: These results indicate that inhibition of HuR with NCS is therapeutic
for DN through improving hyperglycemia and renal inflammation and oxidative stress.
The efficacy of NCS in reducing renal WISP1 expression and action may also contribute
to its reno-protective effect. Our study provides a proof-of-concept for re-purposing HuR
inhibitor as a novel intervention therapy for progressive DN.
Funding: NIDDK Support

FR-PO378

Poster Friday
Diabetic Kidney Disease: Basic - I

Increased Oxidative Stress with Reduced Renal PON2 in Type 2 Diabetic
Nephropathy Mice
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Background: Enhanced oxidative stress with excess accumulation of reactive oxygen
species (ROS) triggers progression of type2 diabetic nephropathy (T2DN). However, the
effects of antioxidant enzymes including paraoxonase (PON) enzyme family in T2DN are
not been studied fully. Therefore, our study was conducted to investigate the alterations in
renal oxidative stress, especially antioxidant enzyme expression, in T2DN mice.
Methods: 1. Mouse model: Male 6-week-old C57BL/6J mice were fed a 60%
high-fat diet (HFD) for 6 weeks, and then was injected with STZ intraperitoneally at 60
mg/kg/day (T2DN, n=7) or vehicle (controls, n=5) for 3 days. Mice fed a 10% normal-fat
diet (NFD) served as the background group (n=5). The mice were sacrificed at 16 weeks
of HFD or NFD. 2. Cultured mouse renal proximal tubular cells (mRPTCs): the cells in
low-glucose DMEM and 1%FBS were treated with 300μM sodium palmitate (PA) plus
24.5mM D-glucose or mannitol for 24h (n=4). 3. P<0.05 was considered significant for 2
group-comparison by t-test.
Results: Compared with HFD-fed mice, T2DN mice exhibited an elevated
blood glucose (26.2±1.0 vs 8.7±0.6,mmol/L) together with polydipsia (13.4±1.6 vs
2.5±0.3,mL), polyphagia (4.9±0.4 vs 3.8±0.2,g), polyuria (10.6±1.5 vs 1.3±0.1,mL) and
weight loss (28.2±0.7 vs 38.4±2.5,g). HOMA-IR (239.2±23.3 vs 109.5±7.8,mmol/L) and
insulin tolerance test (AUC: 249±23% of control) were increased in T2DN mice with
raised urine albumin-to-creatinine ratio (48.5±3.0 vs 20.8±30.7,mg/g), serum creatinine
(90.7±26.6 vs 21.9±6.1,mmol/L) and urinary 8-isomeric prostaglandin (1482±86 vs
207±85,pg/mg of Cr). The staining of PAS and Masson’s trichrome presented glomerular
hypertrophy and collagen deposition while transmission electron microscopy revealed
glomerular basement membrane thickening and podocyte fusion. Renal PON2 (66±0.03%
of control) by immunoblotting was decreased while NOX1,2,4, PON1, HO1, HO2, and
SODs1-3 were not affected. Except a slightly blunted response to insulin, blood glucose
and renal ROS enzymes in HFD mice were not altered relative to NFD mice. PON2 was
located mainly in NHE3-positive proximal tubules. Similar decrease in PON2 (73±5% of
control) was also seen in cultured mRPTCs exposed to high glucose combined with PA.
Conclusions: Decreased renal PON2 may be involved in the pathogenesis of T2DN.
Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO379

Poster Friday
Hypertension and CVD: Basic

A Novel Method for the Analysis of Renal Sympathetic Nerve Activity
(RSNA) from Multi-Fiber Nerve Recordings
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Background: Measurement of RSNA via bipolar electrodes from multi-fiber
preparations in various species has been used for decades in the context of autonomic
regulation research. Traditionally, raw neurograms are usually integrated over short time
intervals and this approach works perfectly for the analysis of dynamic RSNA changes
due to acute intervention. However, comparability of baseline activities between groups
is limited. We present a novel analysis method, based on the raw neurogram sampled at
rate of 25 kHz.
Methods: For RSNA-burst analysis a software based programmable algorithm was
used. Continuous activities longer than three single spikes (i.e., >8ms) were defined as
bursts, followed by silent periods with some single spikes. Approximately 10.000 bursts/
rat were analyzed and burst amplitude, burst duration, burst area (i.e., duration integral),
as well as the burst frequencies were analyzed.
Results: In rats with myocardial infarction (n=11) we found no difference in
integrated baseline RSNA as compared to controls ((n=10). However, the new method
revealed higher higher burst rate per cardiac cycle [CC] (2.65 ± 0.39 vs. 1.61 ± 0.38
bursts/CC; P<0.001) and burst frequency (15.09 ± 2.42 vs. 8.52 ±1.54 Hz; P<0.001)
compared to healthy controls, indicating increased RSNA.
Conclusions: Our new method of RSNA baseline analysis was able to detect subtle
differences between groups of animals that could not be detected by the traditional
method of integrated RSNA analysis. Furthermore, this method has the potential to give
further insights into RNSA patterns and synchronization to afferent regulatory input form
the kidney itself or other organs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Background: Previous work of ours suggests that pathologically increased sensitivity of renal afferent neurons (reduced number of highly active tonic neurons) due to high salt diet is normalized 1 wk after renal denervation (DNX). Now we tested the hypothesis that normalized sensitivity of renal neurons persists after DNX even through regrowth of afferent axons after 12 wk. This morphological regrowth of afferent nerves 12 wk after renal DNX (post-DNX) was shown in a previous publication (DOI: 10.1152/ajpnd.00227.2014).

Methods: 6 male Sprague Dawley (SD) rats were put on high salt diet (HS; 8% NaCl) for 10 days. In another group of 12 rats on high salt diet (HS) left kidneys were denervated (post-DNX) 12 weeks prior to examination. Rats on standard diet were used as controls. Harvested dorsal root ganglion neurons (DRG Th1-T12) with renal afferents were investigated in primary neuronal cell culture using current clamp mode to assess action potential generation during current injection and to characterize neurons as tonic highly active and phasic less active neurons.

Results: In renal neurons from rats on HS the relation of tonic to phasic neurons shifted towards less active phasic units (62% tonic neurons in control vs. 42% on HS, p<0.05, z-test) Denervation of the left kidney in rats on high salt diet (HS-DNX) led to a decrease of afferent renal DRG neurons after 1 wk (42% tonic neurons on HS vs. 72% tonic neurons on HS-DNX). Even 12 weeks after renal denervation this regained electrophysiological property of tonic firing persisting (42% tonic neurons on HS vs. 69% tonic neurons on HS-post-DNX, p<0.05, z-test).

Conclusions: The reduced proportion of highly active tonic neurons increased 1 wk after renal denervation to control levels. Even 12 weeks after renal denervation, this effect of renal denervation persisted, and the sensitivity of renal neurons to electrical stimuli did not change despite high-salt diet. Hence, the positive effects of renal denervation persisted even through the regrowth of renal afferent axons to the kidney.

FR-PO381
Mechanosensitive Potassium Channels in the Afferent Limb of the Cardio-Renal Baroreflex
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Background: We have recently shown that the cardiorenal baroreflex (CRB) is impaired already in congestive heart failure with preserved ejection fraction. There might be a number of possibly involved mechano-sensitive channels and receptors in the afferent limb of the CRB. Since cardiac function is dependent on tight control of serum potassium levels, we put forward the hypothesis that mechano-sensitive potassium channels are expressed in the afferent limb of the CRB.

Methods: We used inside-out-patches from cultured cardiac nodose ganglion neurons of rats that comprise the first neuron of the afferent limb of the CRB. The channels were activated by applying suction patch in the stepwise protocol.

Results: Using the pipette perfusion technique two MS channels could be distinguished: One could be blocked extracellularly with 10 mM gadolinium, a known blocker of MS ion channels. It exhibited a slope conductance of 116.4 ± 5.3 pS in symmetrical potassium concentrations. The other was not affected by gadolinium and had a slope conductance of 76.1 ± 6.5 pS. The channels exhibited also sodium- besides potassium-conductivity. The relative conductivity from potassium to sodium was 3.4 in both groups of channels, which allows membrane depolarization to levels where voltage-activated sodium-channels open.

Conclusions: Hence, through mechano-sensitive cation channels putatively also influenced by extracellular potassium concentrations, the CRB might indirectly influence serum potassium levels via altered salt and water excretion.

FR-PO382
Significance of the Nav 1.8 Voltage-Gated, Tetrodotoxin-Resistant Sodium Channel for Renal Sensory Innervation in Mice and Rats
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Background: Our previous work repeatedly showed that the sensory innervation of the kidney in rats has a peculiarity containing predominantly (more than 50%) highly active tonic neurons to electrical stimulation. In a previous publication (DOI: 10.1112/jn.00011.2012) we demonstrated an increased mRNA expression of the TTX-resistant sodium channel Nav1.8 in renal sensory ganglia. Moreover, we tested the hypothesis that tonic firing pattern is related to the specific expression of Na.1.8 on the cell surface of neurons with renal sensory axons in the dorsal root ganglia (DRG Th12-L2).

Methods: Harvested dorsal root ganglion neurons (DRG Th1-L2) from male Sprague Dawley (SD) with renal afferent neurons were investigated in primary neuronal cell culture using current clamp mode to assess action potential generation during current injection and to characterize neurons as tonic highly active and phasic less active neurons using a Nav1.8 blocker (A-803467) before and after stimulation. Further, renal DRG neurons from a Nav1.8 knock out mouse (C57BL6/J-Scn10a-1Jwo) were investigated in a current clamp mode. C57BL6 mice were used as controls.

Results: At a concentration of 0.3µM the maximum AP firing frequency was blocked from 131±1.1 APs/60ms to 7.6±1.4 APs/60ms under superfusion with a Nav1.8 blocker. The blocker effects were even more pronounced after 12 min. In addition, with the solvent melathalone alone. The firing pattern of renal neurons in the C57BL6 mouse was similar to that in the SD rat with a dominance of the tonic highly active neurons. In a Nav1.8 knock out mouse (C57BL6J-Scn10a1Jwo) in the population of neurons we found no differences from the kidney only a single cell out of 70 showed tonic firing behavior (control vs Nav1.8 KO mouse, z-test, p=0.05).

Conclusions: Under physiological conditions, renal sensory neurons exhibit predominantly a firing pattern associated with higher excitability. Our findings in this study support the significance of the TTX-resistant sodium channel Nav1.8 for the specific tonic firing pattern of renal neurons. That might be of importance for pharmacological interventions to influence renal nerve activity likely involved in the control of blood pressure and cardiovascular function.
trended towards being mildly but non-significantly higher in RC/RC vs WT. Carotid artery EDD was also impaired (peak EDD 74.6 ± 46 vs 92.7 ± 3%, p<0.01) but not 4mo (93.5 ± 92.4%) of age in RC/RC mice vs WT.

**Conclusions:** Our data suggest that the RC/RC mouse model of ADPKD presents with vascular dysfunction like that observed in patients with ADPKD. Our vascular data is in line with a recent described cardiac phenotype showing cardiac hypertrophy, and echocardiographic changes in the heart in RC/RC mice (FR-PO279 ASN 2022). Thus, this model can be used to study mechanisms and test novel interventions aimed to reduce CVD risk in ADPKD.

**FR-PO385**

The IRE1α/XBP1s Pathway Promotes Vascular Calcification in CKD by Enhancing Oxidative Phosphorylation

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**Background:** Endoplasmic reticulum stress has been reported to be linked to several vascular diseases. However, whether Inositol-requiring enzyme 1α (IRE1α) participates in vascular calcification in chronic kidney disease remains poorly understood.

**Methods:** The expression level of IRE1α were measured in the artery tissues of CKD patients and mice. The Ern1flox/flox mice were intercrossed with SMMHC-CreERT2 to obtain VSMC-specific IRE1α knockout mice (Ern1flox/cre, SMMHC-Cre). The mice were treated with vitamin D3 to induce vascular calcification. Besides, VSMC were stimulated with high phosphate or human uremic serum to induce calcification. The calcium content and Alizarin red staining were used for analysis of calcification, and the mRNA expression level of regulated IRE1-dependent decay-related genes were measured. After transfected with Ad-XBP1s, transcriptome analysis was performed.

**Results:** The expression level of IRE1α were upregulated in the artery tissues of CKD patients and mice, while the expression level of regulated IRE1-dependent decay-related genes were measured. After transfected with Ad-XBP1s, transcriptome analysis was performed.

**Conclusions:** The IRE1α/XBP1s Pathway Promotes Vascular Calcification in Chronic Kidney Disease by Enhancing Oxidative Phosphorylation.

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

**FR-PO386**

THOC5-Dependent Posttranscriptional Control Maintains Vascular Smooth Muscle Cells Homeostasis Against CKD-Related Vascular Calcification

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**Background:** Modulation of the vascular smooth muscle cell (VSMC) osteogenic transition plays a fundamental role in CKD-associated VC. Despite transcriptional control mechanisms of VSMC osteogenic transition having been extensively studied, posttranscriptional regulation is still awaiting elucidation. In the present study, we explore the mechanism of THOC5-dependent VSMCs osteochondrogenic switching.

**Methods:** Vonsossa staining and immunohistochemistry staining were used to detect calcification and expression of THOC5 respectively. Thoc5 shRNA and Thoc5 overexpression lentivirus were used to modulate the expression of THOC5. RNA-Seq combined with RIP-Seq was used to explore the target mRNAs that directly bind to THOC5, and FISH was used to confirm its subcellular localization.

**Results:** Immunohistochemical staining showed significantly increased THOC5 expression in the calcified artery of CKD patients. Besides, calcification-induced increase of THOC5 expression was found in both in vivo and in vitro calcification models. The overexpression of THOC5 represses the calcification and osteogenic differentiation of VSMCs significantly in vitro, which is mainly manifested by the reduction of calcium ion deposition and the decreased expression of osteogenic markers. Furthermore, RIP-Seq revealed that THOC5 overexpression in osteogenic-induced VSMCs closely resembled the gene expression changes induced on TGF-β treatments in cultured VSMCs. RIP-Seq was selected to detect target genes of THOC5. It was found that THOC5 directly interacts with the growth arrest-specific gene 6 (GAS6) mRNA, and required for its expression.

**Conclusions:** Our data indicate the binding of THOC5 to GAS6 as a novel mechanism contributing to maintaining VSMCs homeostasis and imply THOC5 as a potential intervention node for vascular calcification diseases.

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

**FR-PO387**

The Role and Mechanism of Ubiquitin-Specific Protease 25 in Cardiorenal Syndrome Type 4

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**Background:** The development of chronic kidney disease will lead to cardiorenal syndrome type 4 (CRS4). At present, there is no research on ubiquitin-specific protease 25 (USP25) in CRS4. The aim of this research was to investigate the function and mechanism of USP25 in CRS4.

**Methods:** C57BL/6 mice received 5/6 nephrectomy and were fed with high phosphate diet to establish the model of CRS4. The express levels of USP25 in the heart of mice in the CRS4 group and the H9C2 rat cardiomyoblast cell line treated with high phosphate (HP) were detected. The changes of hypertrophic markers and cross-sectional area of H9C2 cells in the siUSP25 + HP group were detected by qPCR and phalloidin staining. qPCR and echocardiography were used to compare the degree of cardiac hypertrophy in usp25−/− CRS4 mice and usp25−/−CRS4 mice. To prove that USP25 regulated the cardiac hypertrophy in CRS4 through PTEN/AKT signaling pathway, the effect of knockout of USP25 in vivo or knockdown of USP25 in vitro on the AKT signaling pathway in cardiomyocytes was detected by western blot. The interaction between USP25 and PTEN was verified by immunoprecipitation, and the ubiquitination level and type of ubiquitination of PTEN in cells from the siNC group and USP25 group were detected. The degree of cardiomyocyte hypertrophy in the plasmid-USP25 + HP + PTEN inhibitor group and plasmid-USP25 + HP + DMSO was detected by qPCR and phalloidin staining.

**Results:** The level of USP25 in the heart of mice in the CRS4 group and the cells in the HP group were increased. In H9C2 cells stimulated by HP, knockdown of USP25 in vitro aggravated cardiomyocyte hypertrophy. In CRS4 mice, knockout of USP25 in vivo aggravated cardiac hypertrophy. Knockout of USP25 in vivo or knockdown of USP25 in vitro promoted the activation of the AKT signaling pathway in cardiomyocytes.

**Conclusions:** USP25 stabilized PTEN by removing the K63-linked ubiquitin chains of PTEN, which inhibited the activation of the AKT signaling pathway and relieved cardiac hypertrophy in CRS4.

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

**FR-PO388**

Aristolochic Acid-Induced Aortic Stiffening in Mice Can Replicate Vascular Dysfunction Seen with CKD

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**Background:** Cardiovascular disease (CVD) is highly prevalent in CKD and contributes to the leading cause of death. Stiffening of large arteries precedes overt CVD and contributes to the pathogenesis. It is unclear if commonly used mouse models of CKD develop arterial stiffness.

**Methods:** Male and female C57Bl/6J mice (n=3-8/group) received 4 doses of aristolochic acid (AA) at 2 mg/kg and 8 mg/kg, respectively. Aortic pulse wave velocity (PWV), the gold-standard measure of arterial stiffness, was assessed in anesthetized mice 7-9 weeks after AA injections. Serum, aortas, and kidneys were collected at 9 (males) or 11 (females) weeks. To determine if increases in PWV were due to structural changes in the arteries, elastic modulus (EM) was determined in aorta rings by stress-strain testing. We compared CKD-induced fold increases in aortic PWV in mice and carotid-femoral PWV in patients with stage 3-4 CKD (17M/18F, age 66±7, eGFR 34±12 mL/min/1.73 m²) vs. age-matched controls (17M/18F; 63±7, eGFR 84±12 mL/min/1.73 m²).

**Results:** Male mice developed significant CKD as assessed by renal fibrosis (hydroxyproline content 6.3±1.4 mg/g vs. 3.2±0.8 mg/g protein, p<0.05) and renal dysfunction (blood urea nitrogen [BUN] 100±23 mg/dL vs. 33±9 mg/dL, p<0.05). Both aortic (441±64 vs. 342±15 cm/s, p<0.05) and EM (6,525±392 vs. 5,011±898 kPa, p<0.07) were 1.3-fold higher with AA, and this increase in aortic stiffness was found to be higher in normal male CKD patients vs. controls (1.2-fold; 1,014±229 vs. 835±130 cm/s, p<0.05). Female mice developed renal fibrosis (hydroxyproline 11.8±3.5 mg/g vs. 4.2±0.7 mg/g protein) and renal dysfunction (BUN 41±22 mg/dL vs. 21±4 mg/dL, p<0.05) despite less severe renal dysfunction than males, aortic PWV (408±43 vs. 350±16 cm/sec, p<0.08) and EM (7,905±1635 vs. 5,980±1190 KPa, p=0.09) were increased (1.2- and 1.3-fold higher) comparably to male mice and to female CKD patients (1.2-fold; 907±337 vs. 789±141 cm/s, p<0.08). The range of aortic stiffness in female mice was wider than males, which was also reflected in our cohort of female patients.

**Conclusions:** AA administration produces CKD and aortic stiffening in both male and female mice that is similar to that seen in patients with CKD. This model may be a promising pre-clinical model to test vasculoprotective therapies in patients with CKD.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Histone Deacetylase 9 Contributes to Vascular Calcification in CKD

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Background: Vascular calcification (VC) is a serious chronic kidney disease (CKD) complication. Unfortunately, there is no effective therapy for VC beyond supportive care due to the complex pathogenesis of VC. Histone deacetylase 9 (HDAC9) could regulate bone and soft tissue calcification and cholesterol deposition in atherosclerotic aorta calcification. However, the role of HDAC9 in VC upon CKD is unclear. This study aimed to investigate the role and mechanism of HDAC9 in VC upon CKD.

Methods: Male wild-type and TRF1 KO mice were used to identify potential signalings. The circadian clock, clock, can influence porphyrins and HO-1 generation which play an important part in the protection of vascular diseases.

Conclusions: The clock regulates the expression of key risk factors for cardiovascular disease. These include HO-1 which is significantly increased in Bmal1 KO mice. The expression of HO-1 mRNA in Bmal1 KO mice was reduced by 60%, while in wild-type mice it was increased by 50%.

Funding: Government Support - Non-U.S.

The Effects of Neutrophil Extracellular Traps (NETs) on Endothelial Homeostasis

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Background: Thrombosis and hemorrhage as two opposite pathologies are prevalent within the chronic kidney disease (CKD) population. Platelet homeostasis, which positions centrally in their pathogenesis, varies among the CKD population, while the underlying mechanism is poorly understood.

Methods: We explored the role of platelet homeostasis and its association with renal Klotho deficiency. Renal Klotho deficiency was determined based on a cohort study as well as CKD mice and Klotho-deficient mice with CKD. The effects on thrombopoiesis and platelet lifespan were examined by flow cytometry and platelet transfer. The underlying mechanism was explored by proteomics, flow cytometry, western blot, and immunoprecipitation.

Results: We show that platelet count declines in both patient and mouse model with advanced CKD (Adv-CKD) and is positively associated with circulating Klotho levels. Mechanistically, we identify that ubiquitin ligase UBE2O governs Bcl-xL ubiquitination and degradation. The levels of Bcl-xL were reduced in platelets from Adv-CKD mice. We found that UBE2O knockdown in platelets stimulates p38MAPK to promote Bcl-xL phosphorylation, which facilitates UBE2O-mediated ubiquitination of Bcl-xL. Further, we show that Bcl-xL ubiquitination and degradation are negatively correlated with platelet count in CKD patients.

Conclusions: These findings indicate that platelet count does not only provide a molecular mechanism underlying CKD-associated thrombocytopenia and hemorrhage but also offers a new therapeutic strategy.

Funding: Government Support - Non-U.S.
Schematic diagram of the p38MAPK-UBE2O axis-mediated Bel-xL degradation and apoptosis of platelet.

**FR-PO394**

Characterization of Cardiac Phenotype in Mouse CKD Models
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**Background:** Cardiovascular disease (CVD) constitutes ~40-50% of mortality of chronic kidney disease (CKD) patients. Heart injury was described as left ventricular (LV) diastolic dysfunction, cardiac hypertrophy and fibrosis. While CKD rat models partially develop such cardiac phenotype, this is more challenging in mouse models. In this study, we aim to comprehensively examine various cardiac phenotypes in two CKD mouse models.

**Methods:** The Col4a3-/- (Alport) mice, and wild-type (wt) mice on 6- or 12-weeks of mixed adenine diet (0.2% adenine + Western diet + 1.8% P) were examined for LV contractility using Millar-catheter, plasma Troponin I and BNP, and echocardiography (ECHO, Simpson’s method). Heart histology, CD31 (endothelial cell) and CD45 (immune cell) were assessed.

**Results:** Compared to wt mice, the 8-week-old Alport mice developed CKD with histological kidney injury and fibrosis. Alport mice had decreased stroke volume, cardiac output and ejection fraction in ECHO and reduced LV relaxation in Millar-catheter measurement. The mice also showed higher plasma troponin I and BNP, reduced CD31/myocyte area ratio and increased myocardial CD45+ cells. Compared to the control diet, mice with mixed adenine diet at both time points showed higher serum cholesterol and phosphorus and reduced calcium and histological signs of kidney injury, fibrosis and tubular atrophy. In the heart, mice with mixed adenine diet showed reduced LV contractility (ejection + relaxation phase), increased plasma Troponin I and BNP, and at 12 weeks, LV wall thickening and reduced stroke volume/cardiac output. The mice also showed increased cardiac infiltration of CD45+ cells and reduced CD31 expression. No overt cardiacontirial fibrosis was observed in all models.

**Conclusions:** Alport mice, and mice fed with mixed adenine diet showed signs of CVD with LV dysfunction, elevated plasma cardiac injury marker, myocardial capillary rarefaction and microinflammation, while no overt fibrosis was observed. Alport mice have short lifespans thus limits the therapeutic time frame. The mixed adenine diet model further accelerates the cardiac injury onset compared to other CKD mouse models, with a good survival rate and similar physiology to CKD-CVD patients. Thus, the mixed adenine diet model with both kidney and heart injury has the potential for CKD-related CVD studies.

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

**FR-PO395**

Disregulation of Thrombo-Inflammatory Biomarkers in ESRD and Their Potentiation with Heart Failure
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**Background:** In patients with end-stage renal disease undergoing hemodialysis (ESRD-HD), heart failure with reduced ejection fraction (HFrEF) represents a common comorbidity. Thromboinflammatory processes in both ESRD and HFrEF represent complex pathophysiology, and are demonstrated by dysregulation of thromboinflammatory biomarkers. This study aims to investigate the effects of HFrEF as a comorbidity on these biomarkers in ESRD-HD patients.

**Methods:** Blood samples from 71 ESRD-HD patients and 40 healthy normal controls were analyzed via commercial ELISA and other chromogenic methods for levels of angiotensin-2, endogenous glycosaminoglycans, FABP, IL-6, LPS, free fatty acids, proENP, TNFα, VEGF, Vit D, and WVF. Patient groups were stratified into those with or without HFrEF (EF<50%) in the 6 months prior or following the plasma collection using echocardiography records obtained via chart review.

**Results:** Compared to ESRD-HD alone, a significant increase (p < 0.05) was noted in IL-6 and proBNP, in those with ESRD-HD and HFrEF. Notably, Spearman’s rank correlations were compiled for both groups, and markedly stronger correlations were noted in those with both ESRD-HD and HFrEF. Moreover, PAI-1 and ITP were higher in HFrEF group, suggesting the fibrolytic deficit.

**Conclusions:** The dysregulation of thrombo-inflammatory biomarkers in ESRD-HD is amplified in comorbid HFrEF. Correlation among biomarkers in this cohort indicates the mechanisms of thrombo-inflammatory biomarker generation have an integrative process that is shared between the two conditions. The role of fibrolytic deficit is to be further investigated.

**FR-PO396**

HIF-1α/mTOR/REDD1 Pathway Modulates the Effect of Adipose Tissue-Derived Stem Cells on Kidney Disease Progression in Spontaneously Hypertensive Rats (SHRs) with Induced Visceral Obesity
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**Background:** Cardiovascular disease (CVD) constitutes ~40-50% of mortality of chronic kidney disease (CKD) patients. Heart injury was described as left ventricular (LV) diastolic dysfunction, cardiac hypertrophy and fibrosis. While CKD rat models partially develop such cardiac phenotype, this is more challenging in mouse models. In this study, we aim to comprehensively examine various cardiac phenotypes in two CKD mouse models.

**Methods:** The Col4a3-/- (Alport) mice, and wild-type (wt) mice on 6- or 12-weeks of mixed adenine diet (0.2% adenine + Western diet + 1.8% P) were examined for LV contractility using Millar-catheter, plasma Troponin I and BNP, and echocardiography (ECHO, Simpson’s method). Heart histology, CD31 (endothelial cell) and CD45 (immune cell) were assessed.

**Results:** Compared to wt mice, the 8-week-old Alport mice developed CKD with histological kidney injury and fibrosis. Alport mice had decreased stroke volume, cardiac output and ejection fraction in ECHO and reduced LV relaxation in Millar-catheter measurement. The mice also showed higher plasma troponin I and BNP, reduced CD31/myocyte area ratio and increased myocardial CD45+ cells. Compared to the control diet, mice with mixed adenine diet at both time points showed higher serum cholesterol and phosphorus and reduced calcium and histological signs of kidney injury, fibrosis and tubular atrophy. In the heart, mice with mixed adenine diet showed reduced LV contractility (ejection + relaxation phase), increased plasma Troponin I and BNP, and at 12 weeks, LV wall thickening and reduced stroke volume/cardiac output. The mice also showed increased cardiac infiltration of CD45+ cells and reduced CD31 expression. No overt cardiacontirial fibrosis was observed in all models.

**Conclusions:** Alport mice, and mice fed with mixed adenine diet showed signs of CVD with LV dysfunction, elevated plasma cardiac injury marker, myocardial capillary rarefaction and microinflammation, while no overt fibrosis was observed. Alport mice have short lifespans thus limits the therapeutic time frame. The mixed adenine diet model further accelerates the cardiac injury onset compared to other CKD mouse models, with a good survival rate and similar physiology to CKD-CVD patients. Thus, the mixed adenine diet model with both kidney and heart injury has the potential for CKD-related CVD studies.

**Funding:** Government Support - Non-U.S.
FR-PO397

Role of Ca++ Calmodulin-Dependent Kinase II in Cardiac Pathological Remodeling in Uremia

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Background: Left ventricular hypertrophy is a ubiquitous finding in advanced chronic kidney disease associated (CKD) associated with high risk of heart failure. Our understanding of such pathological hypertrophy in CKD is still evolving. In this study, we set out to test the hypothesis that Ca++ - Calmodulin Dependent Kinase II (CAMKII) pathway, a well-recognized downstream mechanism in the genesis of myocardial pathological remodelling, is activated in uremia using a rodent model of experimental uremia.

Methods: Wistar rats had subtotal nephrectomy (STNx, n=10) or sham surgery (sham, n=8) and were followed up for 10 weeks. In vivo and in vitro cardiac assessments were performed. Cardiac tissue was extracted and protein expression of CAMKII, phosphorylated-CAMKII, and myocyte enhance factor 2 (MEF2), the target transcription factor, were quantified using immunoblotting. Data was analysed using an independent sample t-test with Welch’s correction and expressed as means ± SEM.

Results: Serum creatinine was elevated in the STNx group (55.00±3.66 vs 32.50±1.44 μmol/L, P=0.01). Echocardiographic left ventricular mass (896.37±54.59 vs 629.81±24.27 mg) and heart weight to tibia length ratio (0.035±0.002 vs 0.027±0.001) were higher in the STNx group (both P<0.01). Furthermore, there was more myocardial fibrosis in the STNx group (4.2±4.9 vs 0.9±1.6 %, P<0.05) (Figure 1). CAMKII signalling was activated in the heart following STNx. An increase in both phosphorylated-CaMKII and total CaMKII was observed. The expression of MEF2 was also increased (Figure 1).

Conclusions: The study shows that experimental uremia induces cardiac pathological hypertrophy via activation of CAMKII-MEF2 pathway. This novel finding not only offers a mechanism of pathological hypertrophy in uremia but also a potential treatment target to prevent such hypertrophy and the subsequent myocardial dysfunction in CKD.

FR-PO398

Diabetic Kidney Disease (DKD)-Induced Cardiac Damage Is Characterized and Reduced by Standard-of-Care Treatment in a Translational Diet-Induced Hypertension-Accelerated Mouse Model of DKD

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Background: We recently developed a diet-induced hypertension-accelerated mouse model of diabetic kidney disease characterized by progressive loss of GFR. Since cardiovascular disease is the major cause of death in CKD, we investigated the occurrence of cardiac damage in this model. Additionally, we studied the efficacy of combination therapy with an ACE-inhibitor (Lisinopril) and SGLT2-inhibitor (Dapagliflozin) on cardiac damage.

Methods: Male KK/Ay mice underwent uninephrectomy. After recovery mice received high fat diet (45% LARD) and drinking water with or without 50 mg/L LNNA (wk0). In the intervention study, at week 4, lisinopril (2.5 mg/kg/day; drinking water) and at week 8 dapagliflozin (5 and 20 mg/kg/day; foodadmix) treatment were started. At week 6 mice were terminated and lung and heart weight and cardiac histology were determined.

FR-PO399

Combiné Dapagliflozin and Eplerenone Treatment Improve Cardiorenal Function in Rats with CKD

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Background: Patients with chronic kidney disease (CKD) present higher risk of cardiovascular (CV) complications as well as renal functional decline. The DAPA-CKD trial showed reduced CV events in non-diabetic CKD patients treated with Dapagliflozin (DAPA). Mineralocorticoid Receptor Antagonists (MRAs) have shown similar beneficial effects in diabetic CKD patients (FIDELIO-CKD & FIGARO-CKD trials) but impact in non-diabetic CKD patients is unknown. The aim of this study was to compare DAPA and Eplerenone (EPLE), alone or in combination on renal and CV functions in a non-diabetic rat CKD model.

Methods: CKD was induced in SD rats by 5/6 nephrectomy. Rats were treated with DAPA (10 mg/kg/day PO), EPLE (100 mg/kg/day PO) or the combination during 3 months after CKD induction before cardiorenal function assessment. Renal impact was assessed by histology and creatinine clearance and 24h albuminuria. Cardiac function was evaluated by cardiac echocardiography and left ventricle (LV) hemodynamics (catherization). LV perfusion was assessed by Magnetic resonance imaging (MRI).

Results: After 3 month kidney fibrosis is decreased in the 3 treated groups compared to untreated CKD. No changes of creatinine clearance were observed while albuminuria increased in the DAPA groups with no significant effects of EPLE. The fractional shortening and the cardiac output were not modified by the treatments (not shown). Cardiac hemodynamic was improved with reduced LV end diastolic pressure (LVEDP). The CKD rats treated with EPLE or a combination of EPLE and DAPA while LV end diastolic pressure volume relationship (LVEDPVR) was decrease by both DAPA and EPLE and further decreased by DAPA + EPLE. Decreased cardiac perfusion was prevented with EPLE alone or with the combination. Conclusions: Use of DAPA + EPLE appears to be more effective than DAPA or EPLE alone on diastolic function in non-diabetic CKD rats while cardiac perfusion is improved by EPLE only.

FR-PO400

Tryptophan Metabolite 3-Hydroxy Anthranilic Acid Decreases CKD-Associated Atherosclerosis

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Background: The tryptophan catabolism pathway is upregulated in chronic kidney disease (CKD), and tryptophan metabolite 3-hydroxy anthranilic acid (3-HAA) is an anti-inflammatory metabolite that has been shown to decrease atherosclerosis in preclinical and clinical models. However, the mechanistic link between 3-HAA and CKD accelerated atherosclerosis is unknown.
Methods: Twenty-four male LDLr−/− mice underwent 5/6 nephrectomy (CKD) and were randomly assigned to D-adrenoceptor agonist (D1-3.3 mg/kg/day for 3 days) or was injected intraperitoneally three times a week (3-HAA mice, n = 12), while controls (n = 12) were injected with PBS for 16 weeks. We quantified atherosclerosis with Oil Red-O staining of en face aortic sections at the end of 16 weeks. We used human macrophage cultures following irradiation with 10αM 3-HAA and measured changes in transmembrane profiles and macrophage functions like apoptosis, phagocytosis, and cytokine profiles. Results: 3-HAA treatment increased 3-HAA levels which negatively correlated with aortic atherosclerotic lesions in 3-HAA mice. 3-HAA treatment decreased IL-6 and levels of HIF-1α, a mediator of human macrophages’ nitric oxide, platelet-derived growth factor, and CXCR3 signaling, while 3-HAA treatment had no effect on T cells. Activated human macrophage cultures reveal that 3-HAA treatment decreases macrophage apoptosis and increases phagocytosis.

Conclusions: In summary, 3-HAA treatment decreases CKD-associated atherosclerosis by its action on macrophage apoptosis, phagocytosis, cytokine profiles, and inflammatory signaling.

Funding: Other NIH Support - NHLBI

**FR-PO401**

D4 Dopamine Receptors Regulate Insulin and Salt Sensitivities in Mice

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Background: Insulin resistance associated with dysfunction of dopamine receptors is underlined by multiple metabolic disorders including diabetes and hypertension. Dopamine D4 receptor(D4R) null mice are hypereumatic.

Methods: To explore the effects of D4R on insulin resistance and hypertension, we determined the insulin/salt sensitivities, renal insulin pathway and sodium transporters in D4R null mice.

Results: D4R−/− mice(14mos) had increased fasting blood glucose regardless of sex. Serum insulin levels at fasting were increased in male but not in female Drd4−/− mice. The male and female D4r−/− mice presented a blunted blood glucose lowering effect at 30, 45 min after insulin injection (0.75U/kg,IP). Their body weights, fasting serum total and free cholesterol, triglycerides were similar between the mouse strains. D4r−/− (PDI=168077,1mg/kg) increased but D4r antagonist(754870,1mg/kg) decreased insulin sensitivity of D4+/- mice vs osmotic mini-pumps for a week. Changing the salt intake from low to high increased mean arterial pressure by 25±4% in D4+/- but only by 13±1% in D4−/− mice while switching from high salt to low salt decreased it by 20±1% in D4+/- and by 11±3% in D4−/− mice (tail-cuff, BP=98A, Softon, Tokyo, Japan). The higher salt-sensitivity in KO than WT was also confirmed by telemetry measurements. Less increase in urinary sodium excretion was found in D4−/− than in D4+/- mice.

Conclusions: Therefore, D4R interacts with renal IRβ, NKCC2 and NCC, and may normalize blood pressures via reducing insulin resistance.

Funding: Other NIH Support - NHLBI

**FR-PO402**

Angiotensin II-Induced Cellular and Transcriptional Remodeling of Mouse Kidney Stroma

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Background: The kidney stroma consists of perivascular cells that play multiple crucial roles. Recent data have shown that murine kidney stromal cells abundantly express the type 1a angiotensin receptor, however, how these cells respond to AngII treatment is poorly understood. Moreover, the cellular heterogeneity of the kidney stroma has been poorly characterized at the molecular level because they comprise a small percentage of kidney cells.

Methods: Pdgfrβ-creERT2 mice were crossed with the intact mouse to create Pdgfrβ-intact mice which express GFP connected to the nuclear envelope protein. Pdgfrβ-intact mice were implanted with osmotic minipumps containing either saline (Veh) or AngII (3000ng/kg/min) for 21 days. Nuclei were extracted from BMDM isolated by flushing out bone marrow with AngII (10-8 M). Nuclei sorting (PANS) and microfluidic partitioning (10X Genomics). After sequencing the resulting cDNA libraries and deconvolution (Cell Ranger) the dataset was dimensionally reduced, integrated, and evaluated for differentially expressed genes (DEGs) with Seurat V2. Results: 16499 nuclei were sequenced (9644 from Veh; 6805 from AngII). Nuclei were enriched for expression of Pdgfrβ and divided into 7 populations (Figure A); but at the same proportion. Suggestive of AngII inducing myofibroblast remodeling, there was an increase in cycling cells (5 in Veh vs. 31 in AngII) with a concurrent decrease in contractile cells (1394 in Veh vs. 607 in AngII). While each population had a unique set of DEGs, one gene that was more abundant in AngII treated cells was Myf5. While each population had a unique set of DEGs, one gene that was more abundant in AngII treated cells was Myf5. While each population had a unique set of DEGs, one gene that was more abundant in AngII treated cells was Myf5. While each population had a unique set of DEGs, one gene that was more abundant in AngII treated cells was Myf5. While each population had a unique set of DEGs, one gene that was more abundant in AngII treated cells was Myf5.
Targeted Single-Nucleus RNA-sequencing of Kidney Stromal Cells from Mice Treated with Angiotensin II.

FR-PO407

Increased Epithelial Sodium Channel (ENaC) Activity Mediates Fructose-Induced Salt-Sensitive Hypertension

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Background: Elevated dietary fructose causes sodium retention and salt-sensitive hypertension. In a preliminary bioinformatics study on kidney cortexes from fructose-fed rats, we found an increase in aldosterone-responsive genes, which included subunits of the epithelial sodium channel (ENaC). Regulation of ENaC in the aldosterone sensitive distal tubule involves transcriptional and post-translational mechanisms, and is key to maintain electrolyte homeostasis and blood pressure. An important post-translational regulation of ENaC and γ-ENaC subunits is cleavage activation by luminal and intracellular proteases. We hypothesized that “dietary fructose increases ENaC subunits expression and cleavage, thereby contributing to sodium retention and salt-sensitive hypertension”.

Methods: Sprague-Dawley rats were fed with matched diets containing 4% NaCl and either 20% fructose (FHS) or glucose (GHS) for up to 11 days. Protein expression and mRNA transcripts were measured in the kidney cortex by Western blotting and next generation sequencing, respectively. The expression of cleaved α-ENaC and γ-ENaC subunits was measured as surrogate of ENaC activation. The effect of inhibiting ENaC on blood pressure was assessed by tail-cuff plethysmography on rats given oral amiloride for 24h.

Results: Seven days after starting the diets, FHS presented higher abundance of both α-ENaC transcripts (Scnm1a gene; log2FC = 1.04; p = 0.01, n = 6) and proteins (121±20 vs. 18±4; n=4, analyzed by gel-based immunoblotting (OD); A 90.34%, p<0.03, n = 6) as compared to GHS. No differences in either protein or RNA abundance were found for γ-ENaC or β-ENaC subunits. In addition, the expression of cleaved α-ENaC protein, was higher in FHS than in GHS (85±5 vs. 58±5 OD, A 4.8±16%, p < 0.01, n = 6). Between days 5 and 11 reduced systolic pressure in FHS by 10±3 mmHg (paired t-test: p = 0.05), while caused no significant change in GHS (paired t-test: p = 0.23).

Conclusions: Cleavage of ENaC subunits was increased in fructose and sodium, present increased expression and activity of ENaC than those eating a diet matched with glucose, contributing to the salt-sensitivity of blood pressure seen in this model.

Funding: NIDDK Support

FR-PO408

Deficiency of Peroxiredoxin-4 and Dopamine D5 Receptor Increases NLRP3-Inflammasome Activity

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Background: Dopamine 5 receptor (D5 R) interacts with Peroxiredoxin-4 (PRDX4) to reduce oxidative stress and inflammation. Drd5 knockout (Drd5−/−) mice are hypertensive and in a state of oxidative stress and chronic inflammation. However, the gene’s specific association with the regulation of inflammasosomal activity in the kidney is unknown.

Methods: To investigate inflammasomal activity, the protein expressions of inter leukin (IL)-1β, IL-18, and caspase-1 were quantified by immunoblotting. The PRDX4 gene was silenced in HEK 293 cells overexpressing D.R. Drd5−/− mice were generated as previously reported.

Results: D.R protein expression was decreased in PRDX4 siRNA-transfected D.R. HEK 293 cells (PRDX4 siRNA; 58.8±6.7% vs Mock: 100±9.6%, n=4, and PRDX4 protein was also reduced in the kidney cortices of Drd5−/− mice (Drd5−/−:100±12.8%, n=3; D.R.−/−: 69.2±7.5%, n=4). In D.R. HEK 293 cells -transfected with PRDX4 siRNA, the protein expressions of nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing 3 (NLRP3) were increased compared with mock-transfected cells (siRNA: 142.7±8.9%, Mock: 100±8.1%). The protein expressions of cleaved IL-1β (siRNA: 176.3±37.0%, Mock: 100±12.7%) and cleaved IL-18 (siRNA:710±24.18%, Mock: 100±8.1%) were likewise increased compared with mock- transfected cells, indicating an increase in inflammasomal response (due to NLRP3) activity. The increase in NLRP3 activity with silenced PRDX4 was confirmed by a cell proliferation assay, a superoxide dismutase mimetic, in D.R.-HEK293 cells, indicating that oxidative stress was upstream of the increase in NLRP3-associated inflammasome activity induced by PRDX4 deficiency. Consequently, protein expression of cleaved caspase-1 was increased in renal cortices of Drd5−/− mice (ΔCaspase: 112±15%, n=4, and 19.4±2% in Mock and Drd5−/− mice, n=4). Consistent with this increase, the protein expressions of cleaved IL-1β (Drd5−/−: 100±11.1%, n=3; D.R.−/−: 152±93.13%, n=4), secreted IL-1β (Drd5−/−: 100±31.5%, n=3); Drd5−/−: 137±42.2%, n=4), and cleaved IL-18 (Drd5−/−: 100±8.3%, Drd5−/−:160±10.4%, n=3) were also increased compared with their mock-littermates.

Conclusions: The increase in renal inflammation associated with PRDX4 deficiency in Drd5−/− mice is due to the increase in NLRP3-inflammasome activity.

Funding: NIDDK Support
FR-PO409

Renal ABCA1 Deficiency Induces TLR4 that Regulates Epithelial Sodium Channel (ENaC)

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Background: Na sensitive blood pressure (BP) and restricted cholesterol (cholesterol) efflux (AIsc) are risk factors for cardiovascular mortality. In preliminary studies, renal tubular ablation of ABCA1, a cholesterol efflux protein, leads to greater systolic BP (SBP) vs control (WT) mice, while a low Na diet quenches this difference. Moreover, toll-like receptor 4 (TLR4) is stimulated by cho and associated with Na sensitive models. We hypothesize that TLR4 contributes to chronic transport in an ABCA1 deficient model.

Methods: Transgenic mice, which express a doxycycline inducible CREB in the liver, were bred with mice expressing floxed ABCA1 to produce mice deficient in ABCA1 (FF). Western blotting of kidney and cortical collecting duct (mpkCCD) cells lysate was performed. Immunofluorescence (IF) was performed on kidneys and amlodipine sensitive short-circuit current (Alsc) measured in mpkCCD cells.

Results: Mice were fed a 1% cho diet (X 6 weeks), a low Na and a high Na diet for 1 week each and then euthanized and kidneys extracted. TLR4 expression was enhanced in FF (1.9±0.3; n=3; p<0.05) vs WT (1.0±0.2; n=3) kidneys. Phospho-ERK/ERK was 2.3±1.3 (p<0.05) fold greater in FF (n=5) vs WT (n=5) kidneys. IF of kidneys localized pERK to CDs while TLR4 was seen in CDs and non-CDS. Next, mpkCCD cells were incubated with PSC833 (PSC; 5 µM), an ABCA1 inhibitor, which increased abundance of pERK (1.7±0.3; n=4; p<0.05) vs untreated cells (1.0±0.2; n=4). Dual TLR4 antagonist (TAK242 10µM) and PSC833 suppressed γ-ENaC expression vs. untreated and PSC alone. While TAK242 did not affect AIsce in untreated mpkCCD cells, TAK242 repressed AIsce in PSC treated mpkCCD (11.2±2.2 µA/cm²; n=6; p<0.05) vs PSC alone (17.1±3.1 µA/cm²). Fluid shear stress (FSS) induces pERK, and ERK inhibition suppresses flow-induced in Na absorption (Repetti et al. 2021). The role of TLR4 signaling on FSS mediated Na transport was tested in mpkCCD cells. The AIsce in FSS (0.4 dynes/cm²) exposed cells was greater (40.8±2.1 µA/cm²; n=20; p<0.05) than in static cells (26.7±1.6 µA/cm²; n=20) and the FSS induced AIsce was reduced (31.5±2.6 µA/cm²; n=18; p<0.05 vs FSS exposed cells) by TAK242.

Conclusions: ABCA1 deficiency induces TLR4 and pERK abundance in renal CD, while in mpkCCD cells exposed to FSS or ABCA1 inhibition sensitizes them to TLR4 dependent AIsce. We speculate repression of cho efflux TLR4 enhances renal dependent action of pERK and AIsce.

Funding: Veterans Affairs Support

FR-PO411

Independent Predictors of One-Year Quality of Life Trend in a Large Population of Hemodialysis Patients: Importance of Vascular Access Management

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Background: Health-related quality of life (QoL) is recognized as a relevant patient-centered outcome in hemodialysis (HD). Studies evaluating the trend of QoL with time in large populations are scarce. We aimed to evaluate the changes in QoL over a one-year period in a multinational HD population.

Methods: This was a multicenter prospective observational study using a quality database from a large HD organization. All adult patients that voluntarily responded to KDQOL-36 in 2021 and 2022 were included. Mental (MCS) and Physical Composite Scales (PCS) were analyzed and divided in two groups: Group I, increase in MCS and PCS by more than 5 points; Group II, decrease in both scales. At the time of the first survey, demographic (age, gender) and clinical data (diabetes, comorbidity index - CI, vascular access) were collected. Death was registered until 6 months after the second survey. T-test and z-test were performed for group comparisons. Multivariate logistic regression was performed.

Results: 20 006 HD patients with valid responses to both KDQOL-36 were included. Increase on both scores was observed in 2381 patients (11.9% of surveys) and decrease in 2051 (10.3%). Group I patients were significantly younger, less diabetic, had a lower CI, and higher percentage of fistulas and lower of death on dialysis. A significantly higher number of deaths at 6 months were observed in Group II (6.5% vs. 4.2%, p<0.005). In multivariate analysis, age and the presence of a fistula were independently associated with global QoL improvement, whereas female gender and diabetes were independent predictors of QoL decrease. Six-month mortality was associated with worsening of QoL. Males and diabetic patients in Group I and older and diabetic patients in Group II presented significantly higher hazard ratios of death.

Conclusions: In our HD population, one-year trend of QoL scores were associated with age, sex, demographic and clinical variables, allowing us to define and target specific interventions on a group at risk for rapid QoL decrease. The presence of a fistula was a predictor of QoL improvement, confirming the importance of vascular access management in the global outcomes of HD patients.

FR-PO412

One-Year Quality of Life Trend in a Large Population of Incident Hemodialysis Patients

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Background: Health-related quality of life (QoL) is an important outcome in prevalent hemodialysis (HD) patients, but the evolution in the first months of treatment is still to be explored. We aimed to evaluate the 1-year changes in QoL in incident patients in a large, multinational HD population.

Methods: This was a multicenter prospective observational study. All adult patients treated for at least 3 months on HD that voluntarily responded to KDQOL-36 in 2021 were selected and included after the response to the 2022 survey. Mental (MCS) and Physical Composite Scales (PCS) were analyzed. At the time of the first survey, demographic (age, gender) and clinical data (diabetes, comorbidity index - CI, vascular access) were collected. T-test, z-test and multivariate logistic regression were used for statistical analysis.

Results: 1 401 HD patients with valid responses to both KDQOL-36 were included. QoL reported on HD admission was low: PCS=36.7±9.05 and MCS=44.07±10.29. In multivariate analysis, female gender and CI were independently associated with a poorer QoL at baseline, whereas diabetes was positively correlated with MCS but not with PCS. In the second survey, a significant increase in QoL was documented: PCS=38.75±9.77, p<0.01 and MCS=46.09±10.20, p<0.01. Increase in both scales after 1-year was observed in 234 patients (16.7% of surveys) and a decrease in 112 (8.0%) with the remaining presenting mixed results. The group with improvement in QoL was significantly younger, had a higher percentage of fistulas and lower prevalence of diabetes, when compared to the group with a decrease in both scales. In multivariate analysis, diabetic status was associated with PCS improvement after 1-year, whereas male gender was an independent predictor of PCS decrease.

Conclusions: In our incident HD patients, QoL was poor at baseline, but increased during the first months on dialysis. Diabetes was associated with QoL improvement, despite the low baseline values normally reported by this population, suggesting that HD may positively impact on QoL of diabetic patients with advanced renal disease. Despite the higher scores at baseline, male patients were more prone to QoL decrease during the first year, alerting for the importance of following QoL through time after the beginning of HD.
Hemodialysis: Quality of Life, Symptoms, Palliative Care

**FR-PO415 Trust in Physicians Among Hospitalized Patients Receiving Maintenance Dialysis: Prevalence and Correlates**

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**Background:** Trust between physicians and patients is crucial for a therapeutic patient-physician relationship and effective healthcare delivery. However, there is limited research examining the prevalence and correlates of physician trust in chronic disease populations, especially among acutely ill hospitalized individuals receiving maintenance dialysis.

**Methods:** We surveyed 223 hospitalized individuals undergoing maintenance dialysis (59% response rate) at Strong Memorial Hospital, an academic tertiary care center. Our sample included 120 patients (53%) over 65 years, 105 women (47.1%), and 91 (41%) White, 82 (37%) Black/African American and 36 (16%) patients from other self-identified racial groups. Patients had been on dialysis for an average of 3.16 years (SD ± 2.369, IQR 1–4). Physician trust was assessed using the validated Primary Care Assessment Survey (PCAS) trust scale. Dependent variables included quality of life measured by Kidney Disease Quality of Life Scale (KDQOL-36) and 30-days self-reported hospitalizations. Co-variates, included age, gender, race, education, annual household income and time on dialysis.

**Results:** Out of the 223 respondents, 72 (32%) reported not trusting their doctor, and 91 (41%) reported not trusting their doctor’s judgments about their medical care. Linear regression analysis revealed a statistically significant correlations between trust and symptom burden subscale (estimate 0.1, CI 0.05-0.016, p<0.0002) and number of hospitalizations in the last 30 days (estimate -0.56, CI -1.10, -0.03, p<0.007). Female participants reported lower trust scores than their male counterparts (estimate -1.56, CI -3.07, -0.05, p<0.043).

**Conclusions:** Mistrust of physicians is prevalent among hospitalized patients receiving maintenance dialysis. Hospitalized women receiving maintenance dialysis were more likely to mistrust their physicians than men. Higher trust scores were associated with lower symptom burden while lower scores were associated with greater number of hospitalizations in the last 1 month. Interventions to improve patient-physician communication and patients symptoms may improve trust.

**FR-PO414 Self- and Observer-Rated Computer-Based Cognitive Function and Abilities Tests Are Valid for Dialysis Patients**

Kristen Cronin, 1 Özlem K. Tunçel, 1 Mirja Humpert, 1 Le Hong Ngoc Pham, 1 Tatiana De los Rios, 1 Yusuf Çelik, 2 Ismail Agirbas, 1 Tugce Bedel, 2 Sibel Kalaets, 2 Gulay Asci, 2 Carrie R. Houtz, 2 RJ Wirth, 2 Erkan Ok, 2 Hayriye Elbi. 2DOPRO. 1Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; 2Charite Universitätsmedizin Berlin, Berlin, Germany; 3Ege Universitesi, Izmir, Turkey; 4Marmara Universitesi, Istanbul, Turkey; 5Ankara Universitesi, Ankara, Turkey; 6Vector Psychometric Group, LLC, Chapel Hill, NC.

**Background:** Cognitive Function and Abilities (CFA) are important factors in health-related quality of life (HRQOL) of dialysis patients and a prerequisite for performing hemodialysis (HD) at home. Congruence of self- and observer-rated CFA is debated especially among acutely ill hospitalized individuals receiving maintenance dialysis. We surveyed 223 hospitalized individuals undergoing maintenance dialysis (59% response rate) at Strong Memorial Hospital, an academic tertiary care center. Our sample included 120 patients (53%) over 65 years, 105 women (47.1%), and 91 (41%) White, 82 (37%) Black/African American and 36 (16%) patients from other self-identified racial groups. Patients had been on dialysis for an average of 3.16 years (SD ± 2.369, IQR 1–4). Physician trust was assessed using the validated Primary Care Assessment Survey (PCAS) trust scale. Dependent variables included quality of life measured by Kidney Disease Quality of Life Scale (KDQOL-36) and 30-days self-reported hospitalizations. Co-variates, included age, gender, race, education, annual household income and time on dialysis.

**Results:** Out of the 223 respondents, 72 (32%) reported not trusting their doctor, and 91 (41%) reported not trusting their doctor’s judgments about their medical care. Linear regression analysis revealed a statistically significant correlations between trust and symptom burden subscale (estimate 0.1, CI 0.05-0.016, p<0.0002) and number of hospitalizations in the last 30 days (estimate -0.56, CI -1.10, -0.03, p<0.007). Female participants reported lower trust scores than their male counterparts (estimate -1.56, CI -3.07, -0.05, p<0.043).

**Conclusions:** Mistrust of physicians is prevalent among hospitalized patients receiving maintenance dialysis. Hospitalized women receiving maintenance dialysis were more likely to mistrust their physicians than men. Higher trust scores were associated with lower symptom burden while lower scores were associated with greater number of hospitalizations in the last 1 month. Interventions to improve patient-physician communication and patients symptoms may improve trust.

**Conclusions:** The Turkish translation of PROMIS-CFA is reliable and may support valid inferences regarding cognitive functioning and abilities in this population. Self-rated CFA is more closely related to HRQOL than observer-rated CFA. Future outcome studies should therefore include both assessments in larger samples. Telephone interviewing with T-Cog-S is not an alternative to hospitalization to evaluate cognitive dysfunction due to high ceiling effects.

**Funding:** Commercial Support - Fresenius Medical Care Deutschland GmbH.

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**FR-PO413 Association Between Perceived Social Support and Health-Related Quality of Life in Hemodialysis Patients: Results from the TACare Study**

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**Background:** In patients with End Stage Kidney Disease (ESKD), high symptom burden and the demands of thrice weekly hemodialysis (HD) contribute to limitations in their daily lives, including a negative impact on their interpersonal relationships. However, there is limited research exploring associations of social support with symptom burden and health related quality of life (HRQOL) among HD patients.

**Methods:** The Technology Assisted Stepped Collaborative Care (TACare) was a randomized controlled trial to compare the effectiveness of a stepped collaborative care intervention for symptom management in chronic in-center HD patients. The current study is a secondary, cross-sectional analyses of baseline data to examine the sociodemographic and clinical factors that affect perceived social support (Multidimensional Scale of Perceived Social Support; MSPSS), and its association with symptom burden and HRQOL (SF-12 Mental Component Score (MCS) and Physical Component Score (PCS)).

**Results:** For the 160 randomized patients: mean (SD) age 58 ± 14 years; 45% female; 28% Black, 13% American Indian, 18% Hispanic; 88 % high school education; 27% married; 4 ± 4 years on dialysis. Mean baseline levels of MSPSS from family, friends, significant other, and total were: 21.3 (5.5), 19.8 (6.1), 22.0 (5.3), and 63.1 (14.0), respectively, comparable to other chronically ill populations. High school education (p = .01) and being married (p = .05) were associated with higher total MSPSS. Higher MSPSS scores were correlated with lower levels of fatigue (r = -.21, p < .01), pain (r = -.17, p = .03), depressive symptoms (r = -.23, p < .001), anxiety (r = -.23, p < .001), and better sleep quality (r = .32, p < .001). Higher family, friend, significant other, and total MSPSS support scores were all associated with higher MCS (r = .20, p < .01; r = .25, p < .01; r = .20, p < .01; and r < .26, p < .001, respectively); and higher MSPSS friend support was associated with higher PCS (r = .2, p < .04). After adjusting for age, sex, race, ethnicity, and Charlson morbidity index, MSPSS total scores were associated with MCS (β = .04, p < .001).

**Conclusions:** Because of the associations between MSPSS and HRQOL, particularly mental health, social support appears to be an important intervention target.

**Funding:** NIDDK Support.
Hemodialysis: Quality of Life, Symptoms, Palliative Care

**FR-PO417**

**Improved Quality of Life in Postdilution Compared to Precedition Hemodiafiltration in a European Cohort of Dialysis Patients**

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**Background:** Precedition and postdilution hemodiafiltration (HDF) affect solute removal differently, but the effect on patient reported outcomes is not well described. We describe differences in quality of life in prevalent hemodialysis (HD) patients with precedition and postdilution HDF.

**Methods:** In a cross-sectional study of 18,018 European prevalent HD patients from an international dialysis network, we identified 5,227 patients with HDF. All 317 patients with precedition HDF were compared to 317 propensity-score matched patients with postdilution HDF. KDQOL-SF36 results were compared between groups. Multivariable regression models were used to identify independent predictors of symptom/problem list, physical health composite (PHC), and mental health composite (MHC).

**Results:** Patients were comparable with respect to age, gender, diabetes, comorbidity, vascular access, dialysis vintage, and BMI. Patients with postdilution HDF demonstrated better results for symptom/problem list, PHC, MHC, and most KDQOL SF-36 domains (Figure 1). Multivariable regression revealed independent associations of precedition HDF with lower results for symptom/problem list (coefficient B (95% confidence interval) -6.6 (-9.5 - -3.7), p<0.001), PHC (-3.1 (-4.6 - -1.6), p<0.001), and MHC (-2.4 (-4.1 - -0.7), p=0.006).

**Conclusions:** We demonstrate improved quality of life in postdilution, compared to precedition HDF in a cross-sectional analysis of a multinational European prevalent hemodialysis population.

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**FR-PO418**

**Psychometric Validation of the CONVINCE Inter- and Intradialytic Symptoms Questionnaire**

Le Hong Ngoc Pham,1 Kristier Cronm,2,1 Yan Zhang,1 Anna Schappert,1 Gregor Liegl,1 Kathrin I. Fischer,2 Felix Fischer,1 Matthias Rose.3 CONVINCE Scientific Committee and CONVINCE Investigators.1 Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; 2Charite Universitätsmedizin Berlin, Berlin, Germany.

**Background:** Symptom assessment, especially from the patient perspective, is crucial in dialysis treatment. A comprehensive questionnaire is needed that covers different symptom types. In the CONVINCE study, we developed a survey based on the KDQOL symptoms scale with an adapted recall period of 7 days for interdialytic symptoms and extended inter- and intradialytic (IDS) items based on literature review and patient interviews.

**Methods:** A patient-reported outcomes data of 1264 hemodialysis patients were extracted from CONVINCE, an international randomized controlled trial comparing high-dose hemodiafiltration with high-flux hemodialysis, including baseline and quarterly follow-up data up to 24 months. The IDS questionnaire consists of 17 items covering interdialytic symptoms (11 based on KDQOL-SF36) and 5 newly developed items mainly covering intradialytic symptoms. Reliability, item, and validity analyses were conducted to assess the psychometric properties of the questionnaire. Correlations between IDS and Health-Related Quality of Life (HRQL) domains, measured with the PROMIS questionnaires, were calculated.

**Results:** Reliability analyses showed high internal consistency, stable over time (Cronbach’s α=.86 at baseline, .85-.90 for follow-up visits). Most item-total correlations yielded values from .37-.73, indicating good relationships between individual items and overall scale. Item difficulty ranged from .14-.73, revealing a diverse range, ensuring coverage of the symptom spectrum. The survey also showed good validity as correlations between HRQL domains and IDS ranged from .36 to .61. Factor analyses identified 3 symptom clusters (Table 1).

**Conclusions:** The IDS questionnaire demonstrated good psychometric properties which supports its use in clinical and research settings. By providing a more comprehensive assessment, it is a useful improvement to the KDQOL symptoms scale. Symptoms identified with the questionnaire could be managed in clinical practice and help tailor individualized care.

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

![Figure 1. Differences in KDQOL SF-36 domains between pre- and postdilution HDF](image)

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**FR-PO419**

**Patient-Reported Benefit of Relief from CKD-Associated Pruritus**

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**Background:** Chronic kidney disease-associated pruritus (CKD-aP) is a substantial burden for the physical and mental well-being of patients with kidney failure. Various instruments have been utilized to assess the impact of itch relief in clinical trials, but regular use in dialysis practice is still uncommon.

**Methods:** Phase-3 double-blind, placebo-controlled clinical studies KALM-1 and KALM-2 evaluated the use of IV difelikefalin (DFK) after each dialysis session for 12 weeks compared to placebo (Pbo). Itch intensity at baseline was assessed with the weekly average of the Worst Itching Intensity Numerical Rating Scale (WI-NRS, range 0 [no itch] to 10 [worst itch imaginable]) and defined as moderate (KALM-1: ≥4 to <7; KALM-2 ≥5 to <7, N=378) or severe (≥7; N=473). The 5-D Itch scale (range 5 to 25) assessed itch-related quality of life (QoL) and the Patient Global Impression of Change (PGIC) asked patients after 12 weeks how their itch changed (1 [very much improved] to 7 [much worse]).

**Results:** While PGIC benefit was relatively consistent with WI-NRS and 5-D Itch, more patients with moderate vs. severe CKD-aP reported clinically meaningful improvements on validated scales WI-NRS and 5-D Itch, the share reporting that they feel very much or much improved is notably higher. Asking...
Patients verbally for their perceived improvement could therefore be more meaningful than clinical scales in daily dialysis practice. 

**Funding:** Commercial Support - CSL Vifor

FR-PO420

**Exploring the Skin Symptom Cluster in a Prevalent Hemodialysis (HD) Cohort: The Dominance of CKD-Associated Pruritus and the Association with Fatigue**

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**Background:** Haemodialysis (HD) patients have a high symptom burden. Different symptoms may precipitate or intensify others, generating a symptom cluster: the co-existence of ≥2 symptoms. This work explores the skin symptom cluster (itching, restless legs, skin changes, difficulty in sleeping) in prevalent HD patients.

**Methods:** We present prospective symptom data (POS-S Renal) from the CYCLE-HD trial (ISRCTN11299707). Spearman’s rank correlations were considered, alongside linear regression (cluster sum score) and proportional odds logistic regression (fatigue subscore), both adjusted for age, sex, dialysis vintage and BMI.

**Results:** 118 participants provided symptom data. 77 (65.3%) participants reported ≥2 skin cluster symptoms at baseline. There were positive correlations between each symptom in the skin cluster (all coefficients ≥0.36). A one point difference in baseline itch was associated with a 0.87 increase in total skin cluster score at 6-months; these data, as well as relationships with other symptoms in the cohort, are outlined in Table 1.

**Conclusions:** Reporting of symptoms from within the skin cluster is common in the HD population. CKD-aP is the predominant symptom in predicting the persistence and exacerbation of the skin cluster. The skin symptom cluster and fatigue often co-exist and are interdependent. This highlights the importance of elucidating symptom clusters in routine care to improve management of intrusive symptoms.

**Funding:** Other NIH Support - CYCLE-HD was funded by the National Institute of Health and Care Research (NIHR)

FR-PO421

**The Impact of Intradialytic Cycling on the Symptom of CKD-Associated Pruritus**

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**Background:** CKD associated pruritus (CKD-aP) is an extremely common symptom amongst haemodialysis (HD) patients. The pathophysiology of CKD-aP is complex and multifactorial; chronic inflammation has been hypothesised as a key contributor.

Individuals on maintenance HD experience high levels of chronic inflammation. Previous research has demonstrated that regular intradialytic exercise (IDE) may have an anti-inflammatory effect. This suggests that IDE may reduce levels of CKD-aP in the HD population. This work aimed to ascertain the effect of 6-months of regular IDE on CKD-aP.

**Methods:** Post hoc analyses of data from the CYCLE-HD (ISRCTN11299707) study. 130 HD patients were randomised to standard care or IDE for 6-months. Data regarding CKD-aP were available from 118 participants who completed the Palliative care Outcome Scale-Symptoms (POS-S) Renal at baseline and 6-months. Statistical testing included proportional odds logistic regression adjusting for baseline itch, age, sex, dialysis vintage and baseline BMI.

**Results:** At baseline CKD-aP was present in 68.1% of participants (control=66.1%, IDE=70.0%). CKD-aP was classified as mild (27.1%, n=32), moderate (24.6%, n=29), severe (13.1%, n=13), and overwhelming (3.4%, n=5). There was no statistically significant impact of group assignment on 6-month itchiness; however, the odds of a one category increase in CKD-aP severity was lower (13%) in participants assigned to the IDE group after 6-months (OR=0.87, 95% CI: 0.42, 1.81; p=0.7163). Alluvial plots (Figure) of baseline vs 6-month CKD-aP score categorised by group further demonstrated that group assignment had no marked impact on CKD-aP severity at 6-months.

**Conclusions:** These results demonstrate that CKD-aP is common in the HD population and 6-months of IDE did not impact on the prevalence or severity. As such, pharmacotherapy should be considered as a primary treatment option.

**Funding:** Other NIH Support - CYCLE-HD was funded by the National Institute of Health and Care Research (NIHR)

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

**Underline represents presenting author.**

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Continued Improvement of Itch-Related Quality of Life in CKD-Associated Pruritus (CKD-aP) Patients Treated with Difelikefalin

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Background: Chronic kidney disease–associated pruritus (CKD-aP) is a serious complication seen in patients with kidney failure. Difelikefalin (DFK) has been approved to treat moderate-to-severe CKD-aP in adults on hemodialysis (HD) based on KALM-1 and KALM-2 randomized, double-blind, placebo (Pbo)-controlled phase-3 trials.

Methods: In KALM trials HD patients received either IV DFK or Pbo 3x per week (wk) for 12 wks followed by an up to 52 wks open-label extension (OLE) for all patients receiving DFK. Baseline itch intensity was defined based on the weekly average of the Worst Itching Intensity Numerical Rating Scale (WI-NRS, range 0 [no itch] to 10 [worst itch imaginable]) as moderate (KALM-1: >4 to <7; KALM-2 ≥5 to <7) or severe (≥7). Itch-related quality of life (QoL) was assessed by the validated 5-D Itch scale (range 5 to 25). This analysis assesses the 5-D Itch total score at the end of the DB period and wk 12 of the OLE.

Results: At wk 12 patients treated with DFK achieved a significantly greater improvement of QoL compared to Pbo, independent of baseline itch intensity (p < .001). After an additional 12 wks therapy in the OLE patients continued to improve, independent of prior exposure to DFK or Pbo and those with severe vs. moderate itch at baseline saw a numerically greater improvement of 5-D Itch scores. Differences between the groups were no longer statistically significant.

Conclusions: Patients with severe CKD-aP benefit from continued treatment with DFK. After an additional 12 wks of treatment they achieve a similar level of benefit as patients with moderate itch severity.

Funding: Commercial Support - CSL Vifor

Real-World Experience with Difelikefalin to Treat CKD-Associated Pruritus at a Large Dialysis Organization

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Background: Chronic kidney disease–associated pruritus (CKD-aP), is a common and burdensome symptom in dialysis patients, however it is often overlooked and underestimated. Difelikefalin (DFK) has been shown in phase 3 clinical trials to decrease pruritus among hemodialysis (HD) patients with moderate to severe CKD-aP after 12 weeks of treatment. The goal of this retrospective database analysis is to assess the effectiveness and prescription pattern of DFK in reducing pruritus in HD pts in routine clinical care.

Methods: Patients (Pts) included in the analysis were Fresenius Kidney Care in-center HD pts aged 18-89 who received ≥1 dose of DFK before 11/15/2022 and were administered ≥1 Worst Itching Intensity Numerical Rating Scale (WI-NRS) assessment before first DFK administration. Pts who received ≥50 DFK administrations within 74-84 days were classified as Complete Regimen Group (CRG), while pts with fewer administrations were Incomplete Regimen Group (IRG). Changes in itch were measured by WI-NRS at 12 weeks compared to the baseline (before DFK start). Safety events were collected through routine post-marketing pharmacovigilance reporting methods.

Results: Patients (Pts) included in the analysis were Fresenius Kidney Care in-center HD pts aged 18-89 who received ≥1 dose of DFK before 11/15/2022 and were administered ≥1 Worst Itching Intensity Numerical Rating Scale (WI-NRS) assessment before first DFK administration. Pts who received ≥50 DFK administrations within 74-84 days were classified as Complete Regimen Group (CRG), while pts with fewer administrations were Incomplete Regimen Group (IRG). Changes in itch were measured by WI-NRS at 12 weeks compared to the baseline (before DFK start). Safety events were collected through routine post-marketing pharmacovigilance reporting methods.

Conclusions: AI 12 weeks there is a significant difference in WI-NRS scores between CRG and IRG patients (p<0.0001), moreover CRG pts are more likely to continue treatment beyond 12 weeks. Confirming that treatment as prescribed in the pivotal studies ensure more pronounced itch relief and therapy adherence. A better understanding of the reasons for IRG is needed for better patient support.

Funding: Commercial Support - CSL Vifor

Assessing the Quality of Life in Hemodialysis Patients with CKD-Associated Pruritus in Clinical Practice

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Background: The detrimental impact of chronic kidney disease–associated pruritus (CKD-aP) on the quality of life (QoL) of hemodialysis (HD) patients has been well established in epidemiologic studies. However, diagnosis of CKD-aP and its consequences is not yet routine dialysis practice and no standard instrument is established.

Methods: KALM-1, KALM-2 and 3105 are phase-3 clinical studies evaluating safety and efficacy of difelikefalin in adult HD patients with moderate to severe CKD-aP. Itch intensity and baseline were assessed with the weekly average of the Worst Itching Intensity Numerical Rating Scale (WI-NRS, range 0 [no itch] to 10 [worst itch imaginable]) and defined as moderate (KALM-1: >4 to <7; KALM-2 ≥5 to <7; N=448) or severe (≥7; N=625). We set out to compare the association between itch severity and QoL domains in this cohort. Itch-related QoL at baseline was assessed with Skindex-10 (Sk-10; range 0 to 25) and 5-D Itch (5-D; range 5 to 25) scales with higher values indicating worse impact on itch-related QoL.

Results: Patients experiencing moderate / severe itch reported scores of 15.0 / 18.2 (Sk-10) and 29.3 / 39.7 (5-D), equivalent to 60.1% / 72.8% and 48.8% / 66.2% of the maximum for the corresponding scale respectively. Individual domains show a similar pattern. 5-D domains are relatively evenly balanced with Duration being an outlier at the lower end. Sk-10 was most influenced by the disease domain (Figure).

Conclusions: Either instrument can be useful in clinical practice: Sk-10 to complement WI-NRS with a differentiated measure of QoL and 5-D as a standalone option by combining itch intensity and impact on daily activities.

Funding: Commercial Support - CSL Vifor

Characterization of Common Adverse Reactions Observed with Intravenous Difelikefalin for the Treatment of CKD-Associated Pruritus in Adults Undergoing Hemodialysis

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Background: Managing side effects associated with medications is critical for optimizing outcomes. Here we describe the common adverse reactions with intravenous difelikefalin (IV DFK), a treatment approved in 2021 for chronic kidney disease–associated pruritus (CKD-aP) in adults undergoing hemodialysis.

Methods: Safety data were pooled from two randomized, double-blind, placebo-controlled phase 3 studies (KALM-1, NCT03422653; KALM-2, NCT03636269; DFK=424, placebo=424). The current analysis evaluated the safety of IV DFK administered immediately after dialysis.

Results: Common adverse reactions that occurred in ≥2% of subjects treated with IV DFK and ≥1% higher than with placebo are reported; few were categorized as serious and few led to treatment discontinuation (Table). Median time to onset of diarrhea, dizziness, and nausea associated with DFK was 22.5, 22.0, and 39.5 days; median duration
was 3.0, 1.0, and 2.0 days, respectively. Dizziness occurred more often in subjects using concomitant CH depressant medications, as depressive risk (ORR) 2.09% hyperkalemia and sonnusness were more frequent with concomitant opioids (ORR 1.79 and 2.73, respectively) versus without these medications.

**Conclusions:** IV DFK was well tolerated with most common adverse reactions reported as mild to moderate, did not lead to discontinuation compared with placebo, and rarely occurred during dialysis sessions. Diarrhea, dizziness, and nauscea occurred mostly during the first month of therapy; the duration was ≤3 days, suggesting they typically resolved while IV DFK treatment was ongoing. Concomitant medication use may increase the likelihood of certain adverse reactions. These findings provide additional information to prescribers on the common side effects of IV DFK, which could improve the management of CKD-ap in dialysis patients.

**Funding:** Commercial Support - Cara Therapeutics

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**FR-PO427**

**Burden of CKD-Associated Pruritus and Adverse Clinical Outcomes in Patients Receiving Dialysis: The SREAM Project**

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**Background:** Pruritus, a strong sensation of itching, is a common complaint of patients on dialysis, but their prevalence and consequences are not well known. We aimed to quantify the burden of clinically recognized pruritus and associated adverse clinical outcomes in a region-representative cohort of patients on dialysis.

**Methods:** Observational study of all patients receiving maintenance dialysis in Stockholm, Sweden, during 2006-2021. Pruritus was identified by clinical diagnoses, two consecutive dispenses of pruritus-medications, or use of UV-therapy. Study outcomes were incident diagnoses of depression and sleep disorders, serious infection-related hospitalizations (composite of endocarditis, peritoneal dialysis-related peritonitis, hemodialysis/ peritoneal dialysis-related catheter infection, sepsis due to Staphylococcus aureus, or skin infection), and all-cause mortality. Multivariable Cox regression models with time-varying exposures explored the association between prevalent/new-onset pruritus and adverse clinical outcomes.

**Results:** Among 3281 dialysis patients (median age 66 years, 66% men, 69% on hemodialysis, mean dialysis vintage 2.2 years), 456 (13.8%) had pruritus at enrollment. During median follow-up of 8.3 [IQR: 4.2-13.2] years, additional 637 (22.3%) patients developed pruritus. Prevalent and new-onset pruritus patients were at a higher risk of suffering sleep disorders (N=1294, HR: 2.02 [95%CI 1.70-2.41]), developing depression (N=752, HR: 1.70 [1.40-2.07]) and being hospitalized for serious infections (composite N=872, HR: 1.30 [1.23-1.60]), the latter attributed to higher risk of catheter-related infections, peritonitis and sepsis. No association was observed with endocarditis or all-cause mortality.

**Conclusions:** At least one third of dialysis patients suffer from CKD-associated pruritus during their lifetime. Patients with pruritus are at increased risk of infections, depression and sleep disorders.

**Funding:** Commercial Support - Vifor Pharma

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**FR-PO428**

**Dialyzer Performance and Associations in Self-Reported Pruritus and Fatigue: Results from the eMPORA III Trial**

John W. Larkin,1 Bettina Griesshaber,2 Ansgar Erlenkotter,2 Maria Krizsan,4 Petra Ronova,5 Jennifer Braun,2 Manuela Stauss-Grabo,2 Fresenius Medical Care, Waltham, MA; 2Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; 3Fresenius Medical Care Deutschland GmbH Werk Sankt Wendel, Sankt Wendel, Germany; 4Fresenius Nephrocare Praha 9 - Vysoocany, Prague, Czechia; 5FMC, Péterfy II. Dializis Központ, Budapest, Hungary.

**Background:** eMPORA III was a prospective, multi-center, open, crossover trial with 4-week randomized treatment sequences comparing the clinical performance and hemocompatibility of dialyzers (FX CorAL 600 vs FX CorDiax 600 and xevonta Hi 15) in post-dilution online hemodiafiltration (HDF). Primary outcome of beta-2 microglobulin (B2M) removal showed FX CorAL 600 was non-inferior vs its comparators and superior vs xevonta Hi 15 in post-dilution online hemodialfiltration (HDF). Primary outcome of beta-2 microglobulin (B2M) removal showed FX CorAL 600 was non-inferior vs its comparators and superior vs xevonta Hi 15. We assessed the additional patient-reported outcomes on sleep quality and dialyzer hemocompatibility of dialyzers (FX CorAL 600 vs FX CorDiax 600 and xevonta Hi 15).

**Methods:** We recruited clinically stable adults on HDF from 8 centers in Europe (NCT04714281). PSQI was measured at baseline and at the end of each 4-week treatment sequence. PSQI survey assesses impairment of sleep quality in the prior month on a 0 (worst) to 21 (best) point scale and has 7 component subscales. PSQI scores >5 points show poor sleep quality. A linear mixed model adjusted for random effects of the center and patient estimated the effect of the dialyzer on PSQI scores.

**Results:** Study enrolled 82 subjects (76 in the ITT group, mean age 67.0±15.6 years, 26.3% female, 34.2% diabetes). Mean total PSQI score was 5.7±3.77 (Figure 1). FX CorAL 600 showed a -0.07 and -0.02 point lower PSQI scores vs FX CorDiax 600 (p=0.75) and xevonta Hi 15 (p=0.93). The 7 PSQI component scores showed consistent patterns with the total score, no differences by dialyzer.

**Conclusions:** PSQI scores were consistent between dialyzers. Total PSQI values indicate borderline poor sleep quality among trial participants; this appeared to be driven by small additive disturbances in all domains of component scores, especially for subjective sleep quality, latency, duration, and disturbances. FX CorAL 600 has previously shown higher B2M removal vs. comparators. Higher middle molecule clearance may not affect sleep quality outcomes, yet further studies are needed with longer follow-up times and could consider severity of symptoms (i.e., need for improvement).

**Funding:** Commercial Support - Fresenius Medical Care

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**FR-PO429**

**Clinical Performance and Patient-Reported Sleep Quality Associated with Dialyzer Types: Results from the eMPORA III Trial**

John W. Larkin,1 Bettina Griesshaber,2 Ansgar Erlenkotter,2 Petra Ronova,1 Maria Krizsan,1 Jennifer Braun,2 Manuela Stauss-Grabo,2 Fresenius Medical Care, Waltham, MA; 3Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; 4Fresenius Medical Care Deutschland GmbH Werk Sankt Wendel, Sankt Wendel, Germany; 5Fresenius Nephrocare Praha 9 - Vysoocany, Prague, Czechia; 6FMC, Péterfy II. Dializis Központ, Budapest, Hungary.

**Background:** eMPORA III was a prospective, multi-center, open, crossover trial with 4-week randomized treatment sequences comparing the clinical performance and hemocompatibility of dialyzers (FX CorAL 600 vs FX CorDiax 600 and xevonta Hi 15) in post-dilution online hemodiafiltration (HDF). Primary outcome of beta-2 microglobulin (B2M) removal showed FX CorAL 600 was non-inferior vs its comparators and superior vs xevonta Hi 15. We assessed the additional patient-reported outcomes on sleep quality and dialyzer hemocompatibility of dialyzers (FX CorAL 600 vs FX CorDiax 600 and xevonta Hi 15).

**Methods:** We recruited clinically stable adults on HDF from 8 centers in Europe (NCT04714281). PSQI was measured at baseline and at the end of each 4-week treatment sequence. PSQI survey assesses impairment of sleep quality in the prior month on a 0 (worst) to 21 (best) point scale and has 7 component subscales. PSQI scores >5 points show poor sleep quality. A linear mixed model adjusted for random effects of the center and patient estimated the effect of the dialyzer on PSQI scores.

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**Conclusions:** PSQI scores were consistent between dialyzers. Total PSQI values indicate borderline poor sleep quality among trial participants; this appeared to be driven by small additive disturbances in all domains of component scores, especially for subjective sleep quality, latency, duration, and disturbances. FX CorAL 600 has previously shown higher B2M removal vs. comparators. Higher middle molecule clearance may not affect sleep quality outcomes, yet further studies are needed with longer follow-up times and could consider severity of symptoms (i.e., need for improvement).

**Funding:** Commercial Support - Fresenius Medical Care

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

Underline represents presenting author.
FR-PO430
Risk Factors for Impaired Cerebral Autoregulation and Its Relationship to Cognitive Decline and Brain Atrophy in Hemodialysis Patients
Max J. Goodman, Dawn F. Wolfgang. Medical College of Wisconsin, Milwaukee, WI.

Background: The hemodialysis (HD) population has evidence of increased cerebral atrophy and cognitive impairment. Understanding if cerebral vascular function and cerebral perfusion during HD may help us understand the pathophysiology of brain atrophy and cognitive impairment. We evaluate cerebral autoregulation (CA) in HD patients in relationship to cerebral structure and cognitive performance.

Methods: In a cross-sectional study, HD patients age 50 years and older receiving incident HD were included. Cerebral perfusion during HD was measured using cerebral oximetry and an index of CA was calculated based on the correlation between concurrent cerebral oxygen saturation and intradialytic blood pressure. Potential risk factors for worse CA were measured through linear mixed model with predicting impaired CA when adjusting for demographics, albumin, dialysis treatment, and oxygen saturation with an OR > 0.75. The CA index was negatively correlated with worse picture vocabulary scores at 12 months ($r = -0.44$, p < 0.03). There was no association between CA index and brain integrity including white and gray matter volume, gray matter thickness, and abnormal voxels at either baseline or 12 months.

Conclusion: Diabetes is associated with worse CA during HD. A worse (higher) CA index correlated to declining cognitive function in HD patients. Further research is needed to understand these relationships in order to reduce cerebral atrophy and cognitive impairment in HD patients.

Funding: NIDDK Support

FR-PO431
Association of Cognitive Impairment with Subsequent Cardiovascular Disease (CVD) Hospitalization: A Prospective ESKD Cohort Study
Jennifer Y. Park, Jessica Estrella,1,2 Jennifer Y. Park,1,2 Jessica Excellent,1,2 Mark A. Gallo,1,2 Ricardo F. Lima,1,2 Marissa Z. Chaves,1,2 and Michelle M. Farley,1,2

Background: Old age is a major risk factor of stroke and other cardiovascular disease (CVD) events in patients with ESKD. It is unknown if stroke is an indicator of increased risk of stroke, increased risk of CVD, and increased risk of all-cause mortality in ESKD patients.

Methods: Participants were incident hemodialysis patients from a prospective cohort study, the PACE Study. To assess CI, we used validated tests, the Multiple Mini- Mental State Exam (3MS) and Trail Making Test (TMT) Parts A and B. We used proportional-hazards regression models to evaluate the association of CI at baseline with incident CVD events, adjusting for demographic characteristics, education, depression, and hypercholesterolemia.

Results: Among 568 participants, the average age was 56.3 years (SD: 13.5 years; range: 20-90 years), and most participants are black (n=395; 69.2%) or white (n=161, 28.3%). Over a median follow-up of 2.9 years, 120 (21%) CVD hospitalizations occurred among the 568 participants. Worse TMT-A scores, indicating more severe CI, were associated with subsequent CVD hospitalization on an adjusted analysis (HR=1.08; 95% CI: 1.02-1.06). Similarly, those classified as cognitively “deficient” were at higher risk for subsequent CVD hospitalization, even after further adjustments for a history of diabetes, smoking, prevalent stroke, and atrial fibrillation (HR=1.53; 95% CI: 1.13-2.08). Outcomes were consistent in analyses of patients without diabetes (HR=1.38; 95% CI: 1.02-1.87) were associated with future CVD events. The 3MS test and TMT-B results did not show an association between CI and future CVD hospitalization.

Conclusion: In this study, patients with ESKD new to hemodialysis with impaired CI are more likely to have future CVD hospitalizations. Further studies should gauge whether this practical bedside test case helps predict a patient’s cardiovascular health.

Funding: NIDDK Support, Private Foundation Support

FR-PO432
Plasma Refill and Changes in Cognition During Hemodialysis

Background: Rapid ultrafiltration during hemodialysis has been associated with impaired cerebral perfusion. The effects of dialysis-associated hypoperfusion may be enhanced during acute situations to factors that impair the ability to refill the vascular space (i.e., plasma refill). We sought to investigate whether changes in plasma refill are associated with detectable changes in cognitive function in hospitalized patients receiving intermittent hemodialysis.

Methods: We conducted a prospective pilot study of hospitalized patients receiving intermittent hemodialysis at the University of Pennsylvania. Blood pressure was monitored every 15min throughout hemodialysis. Hematocrit monitoring (using CritLine-IV) and ultrafiltration volumes were used to calculate interval plasma refill rates. Digitized cognitive tests were administered at regular intervals during each session; specifically, the Psychomotor Vigilance Test was used to measure reaction time (delayed reaction defined as the bottom 25% or >50ms slower performance) and the Trail Making Tests A/B were used to measure executive function (impaired function defined as the bottom 25% or >10s difference in completion time). Mixed effects logistic regression was used to examine the relationship between interval change in cognitive function and plasma refill rate.

Results: In interim analysis, among 92 participants enrolled, 60 participants were able to complete at least two sets of cognitive testing. The mean age was 56.9±14.9 yr, 50.5% were female, 53% were Black and 40% were White, and 67% were receiving maintenance hemodialysis versus 33% for acute kidney injury. In the first half of hemodialysis, low plasma refill rate, defined as a plasma refill-to-ultrafiltration ratio < 0.75 was associated with delayed reaction time (OR 4.56, 95% CI 1.11-18.90, p = 0.033) and slower executive function but the latter did not reach statistical significance (OR 2.53, 95% CI 0.51-12.47, p = 0.253). These associations were independent of age, sex, acute versus chronic hemodialysis, and blood pressure.

Conclusions: These preliminary results offer insight into how changes in plasma refill might relate to tissue perfusion leading to detectable changes in cognition, particularly areas affected by the frontotemporal regions of the brain that are particularly susceptible to ischemic injury. Further evaluation in a larger cohort is needed to better evaluate the potential link.

Funding: NIDDK Support

FR-PO433
Sexual Dysfunction in People Treated with Hemodialysis
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Background: End Stage Kidney disease is associated not only with increased mortality, but also with higher symptom burden, particularly for people treated with hemodialysis (HD). Sexual dysfunction (SD) is common but often underrecognized among people with kidney disease. SD is a person’s inability to fully engage in sexual activities in one or more categories: desire, arousal, orgasm, and pain disorders. Reported rates of SD vary widely, between 5%-50%.

Methods: This is a secondary analysis of a project describing symptom burden in patients on HD (Anxiety, Comorbid Depression, and Dialysis Symptom Burden) with a focus on the prevalence of sexual dysfunction. In total, 92 people being treated with hemodialysis in New York City answered questions about their sexual functioning as measured by the Dialysis Symptom Inventory.

Results: The sample was comprised of 44% women (60.8 years ± 14.1) and 56% men (60.0 years ± 17.1). 38% of the total sample reported Decreased Interest in Sex (31% of the women, 45% of the men) and 32% reported Difficulty Becoming Aroused (21% of the women and 43% of the men). Of those that indicated Decreased Interest in Sex, 81% of the women and 45% of the men described being significantly bothered by it. Of those that indicated Difficulty Becoming Aroused, 25% of the women and 60% of the men described being significantly bothered by it.

Conclusions: There has been some debate as to whether decreased interest in sex should be categorized as a sexual dysfunction in people with ESKD being treated with HD. Our data find that Decreased Interest in Sex is both present and bothersome in 25% of the women surveyed and 19% of the men. Clinically significant Difficulty Becoming Aroused was reported by 5% of women and 26% of men. More detailed assessments of all the domains of SD are needed, and an exploration of the interest in intervention.

Figure 1: Prevalence and Associated Distress for Decreased Interest in Sex by Gender
FR-PO434

Engagement in CBT-I in the SLEEP-HD Trial for People on Long-Term Hemodialysis with Insomnia

Daniel Cukor,1 Susan M. McCurry,2 Tessa Rue,2 Maria-Eleni Roumelioti,3 Patrick J. Hegarty,4 Mark L. Unruh,2 Rajnish Mehrotra,2 Jagmohan C. Arora,2 Rossignol Institute, New York, NY; University of Washington, Seattle, WA; 3University of New Mexico School of Medicine, Albuquerque, NM.

Background: Patients with end-stage kidney disease treated with hemodialysis (HD) often experience distressing symptoms including sleep disturbances. Unique aspects of HD treatments and schedules possibly contribute to the high prevalence of insomnia. Cognitive-behavioral therapy for insomnia (CBT-I) is a first-line therapy but largely inaccessible to HD patients, partly due to significant dialysis treatment time. CBT-I delivered by telehealth could overcome barriers to access, but the level of engagement has not been tested for these patients.

Methods: SLEEP-HD was a parallel-group randomized controlled trial (RCT) wherein 126 HD patients treated in community-based dialysis facilities in Seattle and Albuquerque were randomized 1:1:1 to 6-week treatment with telehealth delivered CBT-I, trazodone, or medication placebo. Primary goals were to compare the efficacy of a 6-week treatment with telehealth CBT-I vs. trazodone vs. placebo for the treatment of chronic insomnia at treatment conclusion and follow-up. Herein we describe data available on CBT-I engagement of the study participants.

Results: 43 SLEEP-HD patients were randomized to the 6-week CBTI telehealth intervention with 51% women and 49% men (average age: 60.1 years (SD 15.2)). The protocol called for 6 sessions over 6 weeks and 74% of participants had all 6 sessions, while 3% had none. Participants were asked to keep sleep diaries during the intervention period and 40% kept for all weeks and 19% kept none. After each session, study therapists rated their perception of the participant’s level of engagement and effort in following previous week’s treatment recommendations (“homework”). Engagement scores across the six sessions indicated that 98% of participants were, on average, at least somewhat engaged during the sessions and 83% were well-engaged. The average homework scores indicated that 18% of the participants were rated as not putting in significant effort, and 43% were rated as putting in considerable effort.

Conclusions: CBT-I can be demanding and patient engagement is an important part of the treatment model. In this telehealth administered CBT-I protocol adapted for people on long-term HD, overall levels of engagement in the sessions seemed high, although the level of skills practice and follow through on sleep recommendations was more limited.

Funding: NIDDK Support

FR-PO435

Reducing Frequency of Surveillance Bloodwork in Chronic In-Centre Hemodialysis (ICHID) Patients from Every Six to Eight Weeks: A Quality Improvement Study

Tina Kung,1 Epstein Shaine-Vasanathan, Huda Al-Walsh, Jennifer M. MacRae, Julliya Hemmott, Sophia Chau, Elena Qijiai, University of Calgary, Cumming School of Medicine, Calgary, AB, Canada.

Background: Regular surveillance bloodwork is vital for hemodialysis patients to monitor complications such as anemia, chronic kidney disease-mineral and bone disorder (CKD-MBD), and electrolyte abnormalities. Previous studies have shown that reducing the frequency of bloodwork from every 4 to 6 weeks did not negatively affect the achievement of anemia and CKD-MBD targets. However, the impact of further reducing routine bloodwork frequency to every 8 weeks has not been explored. This study aims to assess the impact of reducing routine bloodwork frequency from every 6 to 8 weeks in chronic in-center hemodialysis (ICHID) patients on achieving anemia and CKD-MBD targets.

Methods: In this prospective cohort study, the Alberta Kidney Care—South program, which includes 7 hemodialysis centers in Calgary, reduced routine bloodwork frequency to every 8 weeks. There were 43 SLEEP-HD participants randomized to the 6-week CBT-I intervention with 51% women and 49% men (average age: 60.1 years (SD 15.2)). The protocol called for 6 sessions over 6 weeks and 74% of participants had all 6 sessions, while 3% had none. Participants were asked to keep sleep diaries during the intervention period and 40% kept for all weeks and 19% kept none. After each session, study therapists rated their perception of the participant’s level of engagement and effort in following previous week’s treatment recommendations (“homework”). Engagement scores across the six sessions indicated that 98% of participants were, on average, at least somewhat engaged during the sessions and 83% were well-engaged. The average homework scores indicated that 18% of the participants were rated as not putting in significant effort, and 43% were rated as putting in considerable effort.

Conclusions: CBT-I can be demanding and patient engagement is an important part of the treatment model. In this telehealth administered CBT-I protocol adapted for people on long-term HD, overall levels of engagement in the sessions seemed high, although the level of skills practice and follow through on sleep recommendations was more limited.

Funding: NIDDK Support

FR-PO436

Impact of 10-Step Sleep Hygiene Intervention on Insomnia and Muscle Strength of ESRD Patients: A Quasi-Interventional Study

Syed Muhammad Kashif Kazmi,1 MUzzamn Ahi,2 Misbah F. Shaikh,3 Umm-e Rabab Alizeh Zaidi,4 Maheerah Q. Khan,5 Mahmoor Luni,6 Finza Kanwal,7 NIKUD Research Hospital, a Project of the Kidney Foundation, Karachi, Pakistan.

Background: End-stage renal disease is a significant health issue that affects millions worldwide; the 10-step sleep hygiene interventions provide a low-cost strategy for better sleep habits that can potentially enhance the overall health of this patient group. The purpose of this study is to evaluate the impact of a 10-step sleep hygiene intervention on hemodialysis patients and simultaneously evaluate its impact on insomnia severity and muscle power. There is dearth of research in this specific area therefore our study can provide valuable insights in this regard.

Methods: The study used a pre-post quasi-interventional design. Participants’ demographic data, sleep quality, physical activity, depression score, medication and addiction history were collected using structured questionnaire before, and 1 month after the intervention. The muscle strength was measured using a handheld dynamometer. The intervention was a validated 10-step sleep hygiene strategy, which was delivered in a face-to-face physician-patient interview.

Results: Out of the 146 patients recruited, 141 completed the study. Majority of the participants were male, married, aged 35-55, had secondary education, and were retired. All of them engaged in mild physical activity, with average dynamometer readings of 10kg, and most were non-smoker with moderate insomnia, sleeping 5-6 hours per night. After the intervention, insomnia scores significantly improved (p=0.004), and muscle strength improved in only about 15% of participants and only 8% reported some improvement in depression score.

Conclusions: The study underscores the importance of sleep hygiene in routine care for hemodialysis patients. The 10-step sleep hygiene intervention was found to effectively improve sleep quality and slightly improve muscle strength in this population. The intervention was particularly effective in reducing insomnia in women and improving muscle power in men. Younger participants (18-35 years) showed the greatest overall improvement. This suggests that tailored, age-specific sleep hygiene interventions can yield better results in the future.

FR-PO437

Holographic Biology Theory-Based Auricular Acupoint Therapy Relief Insomnia Symptoms in Hemodialysis Patients

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Background: Insomnia is a common symptom among patients undergoing hemodialysis, which significantly affects their mental and physical well-being. Several studies, including DOPPS have found that sleep quality is not only related to the quality of life but also impacts patient survival rates.

Methods: A total of 42 hemodialysis patients who did not regularly take sleeping pills such as zolpidem were selected as study subjects, including 15 males (35.72%) and 27 females (64.28%), aged 46-83 years with a mean age of 63.76±25.54 years. Following the PFEIO principle, an treatment team was set up to process the treatment. Hamilton Anxiety/Depression Scale (HAMA/HAMD), polysomnography (PSG), and the Pittsburgh Sleep Quality Index (PSQI) and Sleep Rating Scale (SRSS) were used to assess sleep quality and self-rated insomnia severity. Ear acupuncture treatment was performed once a week, 4 weeks for a course. The TCM physician carried out a preliminary evaluation of the ears, based on tongue diagnosis, and the senior nurse performed the treatment.

Results: PSG showed that total sleep time (TST), sleep efficiency (SE), NREM stage 2 sleep as a percentage of TST (N2%), NREM stage 3 sleep as a percentage of TST (N3%), and REM sleep as a percentage of TST (REM%) of TST were all increased after treatment, and sleep time was longer than before treatment (P < 0.05). Refer to Table 1 for details. PSQ scores showed improvement in sleep quality, increase in sleep duration and efficiency, reduction in sleep disturbances, decrease in the use of hypnotic drugs, and improvement in daytime functioning. The overall score was statistically significant (P < 0.05). Refer to Table 2 for details. SRSS showed decrease in insufficient sleep time, significant improvement in sleep quality.

Conclusions: The application of auricular acupoint therapy based on holographic biology theory to relieve insomnia symptoms and effectively improve the sleep quality of HD patients with insomnia. The therapy has the advantages of safety, convenience, and low cost, and can be easily promoted and popularized in clinical practice. However, The specific mechanism needs further study.

Comparison of PSQ-related data in 42 hemodialysis patients with insomnia.

<table>
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<th>Number of cases</th>
<th>Group</th>
<th>TST</th>
<th>N2% of TST</th>
<th>N3% of TST</th>
<th>REM% of TST</th>
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<th>REM % of TST</th>
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<td>42</td>
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<td>31.54±13.14</td>
<td>0.63±0.23</td>
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<tr>
<td>42</td>
<td>After treat</td>
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<td>0.25±0.06</td>
<td>0.004</td>
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</tbody>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO438

Frailty in Patients on Dialysis Surviving for More than 40 Years Is Common and Severe: A Nationwide Study
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Background: The number of end-stage kidney disease (ESKD) patients on dialysis for 40 years or more and the associations between dialysis vintage and frailty using the JSDT Renal Data Registry database.

Methods: A cross-sectional study was conducted. The analysis included data of 221,136 patients aged over 40 years on dialysis in 2018. The dialysis vintage exposure was categorized as: 0–<5 years; 5–<10 years; 10–<20 years; 20–<30 years; 30–<40 years; and above 40 (≥40 years). The primary outcome was frailty, defined as grade 2 or higher according to the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale. The second outcome was bedridden, defined as grade 4 on the ECOG PS scale. Modified Poisson regression models adjusted for potential covariates were used to estimate the adjusted prevalence ratios (aPRs) for frailty and bedridden. The clinical characteristics of patients with dialysis vintage of 40 years or more were compared with those in other dialysis vintage categories.

Results: Total 809 (0.36%) ESKD patients were on dialysis for 40 years or more. This group showed a lower proportion of men and presence of diabetes. Histories of fractures and carpal tunnel syndrome were more frequent in the 40– years group (54.6%), and the prevalence of bedridden was similar (9.9%). The dialysis vintage 40 years vs. 0–<5 years was associated with increased frailty (aPR [95% confidence interval]: 2.41 [2.25-2.58]), and bedridden (aPR [95% confidence interval]: 2.12 [1.72-2.60]).

Conclusions: This large nationwide study found an association between dialysis vintage and frailty in dialysis patients. Long-term dialysis therapy, particularly for over 40 years, may accelerate the decline of physical function, probably due to unmeasured vintage and frailty in dialysis patients. Other groups. The prevalence of frailty was most common in the 40– years group (54.6%), and the prevalence of bedridden was similar (9.9%). The dialysis vintage 40 years vs. 0–<5 years was associated with increased frailty (aPR [95% confidence interval]: 2.41 [2.25-2.58]), and bedridden (aPR [95% confidence interval]: 2.12 [1.72-2.60]).

FR-PO439

“A Ray of Hope”: A Qualitative Study of Hemodialysis Patients’ Attitudes Toward a Clinic-Based Animal-Assisted Intervention
Meredith L. Stensland,1 Adrian E. Elorriaga,2 Martha Block,2 Geoffrey A. Block,3 Don D. Mcgeary,1 Jacie Flaman,1 Selena Lugosi.1 1The University of Texas Health Science Center at San Antonio, San Antonio, TX; 2US Renal Care Inc, San Antonio, TX; 3The University of Texas at San Antonio, San Antonio, TX.

Background: Adherence to one’s hemodialysis (HD) regimen is paramount to overall health and well-being for individuals receiving HD in the U.S. Patients may struggle maintaining the strenuous regimen, and ways to effectively reduce rates of missed treatments are needed. The purpose of this study was to explore HD patients’ attitudes toward a clinic-based animal-assisted intervention (AAI).

Methods: HD patients from 4 outpatient clinics were involved in 1-on-1 in-depth semi-structured interviews, which were audio-recorded and transcribed verbatim. Interviews took place at the dialysis clinics, including while patients were dialyzing. Within a framework of iterative content analysis, the Matrix Method was utilized in combination with line-by-line coding to thematically analyze data.

Results: Twenty patients aged 57 ± 7.93 years participated in interviews. Their narratives collectively illustrate the perceived value of AAI in the HD setting. Under the larger theme “Therapy dogs are a source of hope”, there are 4 subthemes: (i) The dread and suffering of endless treatment; (ii) Yearning for the presence of therapy dogs at the clinic; (iii) Therapy dogs can aid in the internal battle of treatment adherence; (iv) The logistics of incorporating therapy dogs into the HD care routine.

Conclusions: This study improves our understanding of how HD patients feel about receiving clinic-based therapy dog visits while also offering helpful insights for implementing this intervention in future research. Incorporating therapy dogs into HD patients’ healthcare routine may offer a complementary and integrative approach to improving patient outcomes. Findings highlight the importance of patient-centered care for this population.

FR-PO440

Animal-Assisted Intervention for Hemodialysis Patients’ Treatment Adherence, Pain, and Depression
Meredith L. Stensland,1 Adrian E. Elorriaga,2 Martha Block,2 Geoffrey A. Block,3 Don D. Mcgeary,1 Jacie Flaman.1 1The University of Texas Health Science Center at San Antonio, San Antonio, TX; 2US Renal Care Inc, San Antonio, TX; 3The University of Texas at San Antonio, San Antonio, TX.

Background: Maintaining adherence to one’s hemodialysis (HD) regimen is paramount to patients’ health and well-being. The purpose of this pilot study was to evaluate the feasibility of a clinic-based animal-assisted intervention (AAI) for improving HD patients’ treatment adherence, depression, and pain.

Methods: This study used a within-subject repeated measures design at 1 outpatient HD clinic with a primary outcome of unplanned missed treatments. Participants included prevalent HD patients, age 18+, who had depression (PHQ-2 ≥3) and chronic pain (Pain Enjoyment General activity score ≥4). Patients were randomized 1:1 into 2 groups: 1 dog visit (AAI1) or 2 dog visits (AAI2) per week for 10 weeks. The AAI took place in the waiting room immediately prior to HD, it involved socializing with and petting the dog. Patients completed pain and mood assessments before and after each dog visit. A generalizability linear mixed effects model was used for data analysis.

Results: A total of 17 patients were enrolled (n= 8 AAI1, n=9 AAI2) who cumulatively received 199 of 240 possible dog visits (83%), averaging 10.8 ± 4.8 minutes each. There were 9 missed HD treatments during the trial (1 in AAI1, 8 in AAI2), while there were 30 missed treatments in the 12 weeks prior to trial (6 in AAI1, 24 in AAI2). All patients who missed at least 1 HD treatment in the 12 weeks pre-enrollment had a decrease of at least 1 fewer missed treatments during the trial. The effect estimate for the reduction in probability of missing an HD treatment in the AAI vs pre-trial was OR 0.23 (95% CI: 0.09 to 0.57), p = 0.002. Pain severity rated 0-10 scores: pre-test = M 4.38 ± 2.63, post-test = M 3.46 ± 1.93 (AAI1); pre-test = M 3.52 ± 1.91, post-test = M 3.14 ± 2.04 (AAI2).

Conclusions: Including therapy dogs in HD patients’ healthcare routine may offer a complementary approach to improving outcomes. This safe and resource-minimal intervention received high patient approval and provides insight for determining the treatment effect of AAI in order to design larger controlled clinical trials on the clinical effectiveness of AAI.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
FR-PO441
Motivational Strategies to Empower African Americans to Improve Dialysis Nonadherence
Lindsey Theut,1 Zuri N. St. Julien,2 Devika Nair,2 Heather L. Prigmore,2 Robert Grevey,1 Marylou Wallace,2 Rachel B. Fissell,1 Julia Lewis,1 Rebecca Weinand,3 David G. Schlundt,4 Hilary A. Tindle,2 Collins Airhihenbuwa,1 Kerri L. Cavanaugh,2 Kenneth A. Resnicow,6 Ruth Q. Wolever,1 Ebele M. Umekuje1,1 Creighton University School of Medicine, Omaha, NE; 2Vanderbilt University Medical Center, Nashville, TN; 3Vanderbilt University Medical Center, Nashville, TN; 4Vanderbilt University Medical Center, Nashville, TN; 5University of Tennessee, Knoxville, TN; 6University of Nebraska Medical Center, Omaha, NE.

Background: Compared to whites, African Americans (AA) have four times the risk of ESKD. Hemodialysis (HD) nonadherence is common in AA and driven by low motivation. Motivational interviewing (MI), an evidence-based counseling style increases intrinsic motivation, and if culturally tailored, reduces nonadherence in AA. We hypothesized that culturally tailored MI would be feasible and acceptable for reducing HD nonadherence in AA.

Methods: Parallel arm [usual care (n=15) vs. MI (n=15)] pilot RCT of AA, a 18 years old, who missed HD or shortened HD by 15 minutes/month during the prior 3 months. Patients randomized to MI received 6 sessions over 8 weeks, culturally tailored to prioritize contributors to nonadherence: empowerment; support network; understanding ESKD, communication & trust; mental well-being; transportation; and racial identity. Coaches were assessed via the MI Treatment Integrity (MITI) scale. Coaches and patients provided feedback regarding their experience.

Results: We enrolled 30 AA; 57% male; median age [IQR]=57[17] years; median HD vintage [IQR]=6[6.4] years; and control groups respectively. Feasibility and acceptability were favorable: 76% enrollment-to-screening ratio; 73% MI attendance; 13% drop-out. Primary outcome was chart-reviewed HD adherence. In month 3 of follow-up, patients were prescribed a median [IQR] of 13 [12, 13] sessions and 2750 [2520, 3120] minutes, and completed 91.7% [80.8%, 99.1%] of prescribed HD. Patients completed 84.6% [63.6%, 92.3%] of prescribed sessions. Empowerment, support network, and understanding ESKD were most frequently discussed during MI per patients’ preference. Patients reported variability in the impact of racial identity on HD adherence. Some noted having low trust in, and feeling intimidated by the health system. Most viewed MI as an effective communication style. Health coaches demonstrated high fidelity on the MITI.

Conclusions: Health coach-delivered culturally tailored MI in AA is feasible and acceptable. Next steps will assess its efficacy in reducing HD nonadherence in AA.

Funding: NIDDK Support

FR-PO442
Managed Care Program Improves Hospitalization Rate in ESKD Patients
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Background: Care fragmentation, a lack of coordinated care for patients, is associated with reduced quality of care, increased costs, and poor clinical outcomes. End stage kidney disease (ESKD) patients are at increased risk of care fragmentation due to the complex collection of conditions that often accompany ESKD (i.e., diabetes, hypertension, etc.), and require care from multiple healthcare providers. Recently, managed care programs have started to defragment care for ESKD patients through collaboration across healthcare organizations in order to improve clinical outcomes. However, whether and to what degree these programs are effective is unknown.

Methods: This was a retrospective, observational study of dialysis patients with commercial or Medicare Advantage insurance treating with a dialysis provider in the United States from June 2021- June 2022. The primary exposure was enrollment in a managed care program. Expected hospitalization rates for enrolled patients were estimated by indirect standardization versus the non-enrolled patients.

Results: After accounting for differences in age, comorbidities, insurance type, and geography, we observed that enrolled patients had 0.11 admits per-patient per-year favorable hospitalization rate compared to non-enrolled patients. This resulted in an estimated 961, hospitalizations prevented among approximately 8,500 enrolled patients during the study period. Hospitalization reduction was similar between managed care programs done in partnership with government and private insurers.

Conclusions: A provider managed integrated kidney care program can be effective in improving clinical outcomes for ESKD patients for public or private payors.

FR-PO443
Perspectives on Preventability of Emergency Department Encounters for People Receiving Dialysis: A Qualitative Critical Incident Study
Meghan J. Elliott,1 Paul E. Ronksley,1 Maoliosa Donald,1 Eddy Lang,1 Jennifer M. MacRae,1 Andrew Merca,1 Shannan Love,1 Hana Kotani,1 Nancy Verdin,1 Brenda Hennemilgart,1 University of Calgary Cumming School of Medicine, Calgary, AB, Canada; 2University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; 3University of Calgary Department of Community Health Sciences, Calgary, AB, Canada.

Background: People receiving dialysis have disproportionately high rates of emergency department (ED) utilization. While certain conditions underlying ED encounters have been characterized as potentially preventable, little is known about how contextual factors may influence perceived need for ED care. We explored the perspectives of patients with kidney failure, their caregivers, and healthcare providers working with dialysis patients. We conducted semi-structured interviews in person or virtually, coded transcripts in duplicate across participant roles, and generated themes through an inductive thematic analysis approach.

Results: We completed interviews with 22 patients receiving hemodialysis and peritoneal dialysis, 8 caregivers, and 30 healthcare providers from nephrology, emergency medicine, and primary care disciplines. Across roles, participants discussed aspects of acute illness unique to people receiving dialysis and emphasized coordinated care across disciplines to prevent illness onset, deceleration, and ultimately need for urgent ED management. We characterized perceived preventability of ED encounters in relation to the following themes: (1) Connectedness of the acute condition to kidney failure; (2) Care continuity and engagement; (3) Reactions and behavioural responses to the acute illness experience; (4) Access to urgent care strategies outside of the ED.

Conclusions: Patients, caregivers, and providers identified how the interplay between kidney failure, the acute illness experience, behaviours, and support structures influence the perceived preventability of ED encounters. Findings will inform coordinated approaches to averting potentially unnecessary ED use among this medically complex population.

FR-PO444
Plasma B Cell-Activating Factor (BAFF) Levels Predict the Upcoming Depressive Symptoms in Hemodialysis Patients
Woojin Jang, Dong-Young Lee. Veterans Healthcare Service Medical Center, Seoul, Republic of Korea.

Background: B cell activating factor (BAFF) is a cytokine that plays a role in B cells’ maturation, homeostasis, and differentiation and is associated with mental disorders. Depression can often be caused by inflammation, with various cytokines playing a role. Chronic inflammation is common in hemodialysis (HD) patients, and depression is also prevalent among them. We hypothesize that BAFF may predict upcoming depressive symptoms in HD patients, so we evaluated their association.

Methods: Among 643 subjects who enrolled in a multi-center prospective HD cohort study, we investigated 72 patients who tested plasma BAFF levels, performed initial and follow-up Beck Depression Inventory, and had no depressive symptoms at first. We conducted a univariate and multivariate Cox regression analysis to calculate the hazard ratio (95% confidence interval (CI)) between upcoming depressive symptoms and BAFF levels.

Results: In both univariate and multivariate analyses, a 1 standard deviation (SD) increase in BAFF was significantly linked with a higher risk of future depressive symptoms. The HR was 1.437 (95% CI 1.034-1.996) and 1.699 (95% CI 1.037-2.784), respectively. Patients with higher BAFF levels experienced more depressive symptoms than those with lower BAFF levels for 2 years (p = 0.0048).

Conclusions: In HD patients, elevated levels of plasma BAFF showed a significant association with depressive symptoms up to two years later.

Hazard ratios of plasma BAFF and APRIL for depressive symptoms

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<th>HD</th>
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<td>0.575-1.302</td>
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Effects of Eating Meals During Hemodialysis Treatment on Depressive Symptoms: The FrEDI Randomized Controlled Trial

Masaki Okazaki,1,2 Connie Rhee,1 Yoko Narasaki,1 Jenny I. Shen,3,5 Ramanath B. Dukkipati,4,5 Tiane Daiz,1,6 Lili Tong,1 Sharon G. Adler,1 Joel D. Kopple,1,3 Kamyr Kalantar-Zadeh,1,2 University of California Irvine, Irvine, CA;1 Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan;2 VA Long Beach Healthcare System, Long Beach, CA;3 Harbor-UCLA Medical Center, Torrance, CA;4 University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA.

Background: Approximately one-third of patients undergoing hemodialysis (HD) suffer from symptoms of depression. HD patients with low serum albumin levels who ingest high- vs. low-protein meals during HD sessions display improved their protein-energy status. We examined whether their depressive symptoms were also alleviated with intradialytic high-protein meals.

Methods: We examined data from participants in the Fosrenol for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients (FrEDI Study) NCT01116997 who were randomized to weekly HD with serum albumin <4.0 g/dL. Participants were randomized to receive either high-protein (50–55 g) meals or low-protein (<1 g) meals during HD treatments for 8 weeks. The primary outcome was depressive symptoms measured by the Beck Depression Inventory (BDI)-II survey at 8 weeks. Data on change in Mental Component Summary (MCS) as assessed by the SF-36 were also evaluated. Differences between pre-to-post scores within each study arm were examined using Wilcoxon signed-ranks test.

Results: Fifty-seven participants completed the BDI-II assessment. The mean (SD) age was 55 (15) years; 56 % were female. The BDI-II score showed a statistically significant improvement among 26 participants in the high-protein meals (baseline, 11.5 [IQR, 5.20] vs. 8-weeks, 7 [IQR, 2.13], P = 0.01). In the low-protein meals, BDI-II scores among 31 participants showed a trend toward improvement (baseline, 10 [IQR, 4.22] vs. 8-weeks, 6 [IQR, 1.15], P = 0.077). The MCS showed no statistically significant changes either among 26 participants in high-protein meals (baseline, 37.2 [IQR, 16.5–48.7] vs. 8-weeks, 39.2 [IQR, 29.6–49.0], P = 0.64) or among 31 participants in low-protein meals (baseline, 30.1 [IQR, 15.6–53.3] vs. 8-weeks, 33.4 [IQR, 16.8–48.6], P = 0.97). Changes in BDI-II scores were not statistically different across meal composition.

Conclusions: Among HD patients who receive high- vs. low-protein meals during thrice-weekly HD, those eating high-protein meals exhibited a significant improvement in depressive symptoms. Further clinical trials are needed to conclusively determine the efficacy and safety of intra-dialytic eating and meal provision in the dialysis clinics on patient-reported outcomes including unpleasant symptoms.

Funding: Private Foundation Support

Underdiagnosis of Depression in Hemodialysis Patients

Raeesa Soomar, Reena Jose, Anuj Gupta, Morgan Davis, Janos G. Hajagos, Farrukh M. Koraishty, Stony Brook University, Stony Brook, NY.

Background: Depression is the most common psychiatric illness among dialysis patients. It has been associated with adverse outcomes in this population, and therefore routine screening is recommended. The Patient Health Questionnaire (PHQ)-9 scale has been validated for depression screening in patients on hemodialysis (HD) in controlled studies, but it is underutilized in dialysis centers. The utility of PHQ-9 in detecting depression in HD patients without an official diagnosis and its association with psychiatric care is not well studied.

Methods: In a single center observational study of HD patients, we used PHQ-9 scores ≥10 as an indicator for depression. This was compared to diagnostic code-based depression diagnoses. Two-tailed t-tests were used to compare continuous variables, while Fischer’s exact and Chi square tests were used to compare categorical variables.

Results: Among the 98 HD patients analyzed, the mean age was 61.3 years, mean days on HD were 2,005; 91% had hypertension, 59% diabetes and 87% had cardiovascular disease. Eighteen (18.4%) patients were diagnosed with depression using the PHQ-9. Of these, only six (33%) also had a diagnostic code-based depression diagnosis, nine (50%) had a follow-up appointment scheduled with a psychiatrist, and only five (28%) were being treated with an anti-depressant. Patients with depression were also more likely to have comorbid anxiety disorder and a greater number of previous hospitalizations (p=0.05).

Conclusions: Depression is underdiagnosed in HD patients. Better screening for depression will lead to improved medical care and potentially better health outcomes for this vulnerable population.

FR-PO447

“Dialysis Makes You Poor and Keeps You Poor”: Patient Perspectives on Health-Related Social Needs and Recommendations for Interventions

Tessa K. Novick,1 Michelle M. Osuna-Diaz,1 Daniel Ramirez, Francisco A. Barrios,1 Deidra C. Crews,2 Elizabeth Jacobs,3 The University of Texas at Austin, Austin, TX; 2 Johns Hopkins Medicine, Baltimore, MD; MaineHealth, Portland, ME.

Background: Dialysis patients with low socioeconomic status have worse outcomes, which may be due to health-related social needs. Patient perspectives on the impact of social needs and how to address them have not been explored.

Methods: We interviewed 32 people with low socioeconomic status receiving in-center hemodialysis on barriers and facilitators to care with an emphasis on social needs. The interviews were conducted at three dialysis facilities in Austin, Texas, from April to July 2022. We collected demographic information, and performed thematic analysis using the constant comparative method on interviews after they were audio-recorded, transcribed and have been underlined with a signature.

Results: Participants were mean (SD) age 56 (12) years, 18 (56%) identified as female, 15 (53%) identified as Hispanic/Latino/a/x, 30 (94%) were unemployed, 27 (94%) reported annual income ≤$25,000, and health-related social needs were common. Themes identified were (1) kidney failure was unexpected, (2) dialysis is detrimental, (3) powerlessness, (4) financial resource strain, (5) motivators, and (6) interventions should promote self sufficiency (Figure).

Conclusions: Dialysis exacerbates financial resource strain, and social needs exacerbate dialysis-related stress. Participants made recommendations to address social needs with an emphasis on increasing financial support and community resources for this population.

Funding: NIDDK Support

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Conclusions: Depression is underdiagnosed in HD patients. Better screening for depression will lead to improved medical care and potentially better health outcomes for this vulnerable population.
FR-PO448
Advance Care Planning in Patients with Advanced CKD on Hemodialysis in the Hospital Setting

Background: To explore the wishes and preferences of patients with advanced chronic kidney disease (ACKD) who receive hemodialysis through the application of the instrument “Dodecahedron of advance care planning” to improve the approach and medical care of these patients, promote communication between them and the healthcare professionals who attend to them. Advance care planning in patients with advanced chronic kidney disease on hemodialysis in the hospital setting.

Methods: Patients with advanced chronic kidney disease (ACKD) admitted to the Hemodialysis program of the General Hospital of Villalba were included. Demographic variables, knowledge about CAP and conversations about the end of life, comorbidity with the Charlson Index, and cognitive status using the Pfeiffer scale were collected. In addition, the dodecahedron of advance care planning was used as a clinical instrument through an interview.

Results: 70 patients were included; 35 completed CAP, 54.3% men and 45.7% women. Median age 72 years (44-89). Of all with Charlson Index >5, 14.2% had depression. The median dialysis time was 36 months (3-276). 100% had not discussed the end of their life with their doctor, and 25.75% had with their main caregiver. 31.4% NCPAL. Positive. The wishes of the patients were: 92.4% “to be cared for with respect and kindness,” 77.7% expect the best to be done at each moment of their illness, 25.4% did not want to talk about the end of life, 77.7% did not want to suffer pain, 96% “not to be a burden to their families,” 100% wanted to die accompanied by their family. 48.6% wanted to die at home, 14% in hospital, and 37.1% did not care. 80% wanted to be connected to machines “if their recovery is reasonable,” 68.6% wanted palliative sedation for refractory symptoms, 97.1% wanted to be reminded “as a good person,” and 85.7% were believers that gave meaning to his illness.

Conclusions: Most patients at the end of life wish not to be a burden to their family, to die accompanied, without pain, and at home. The dodecahedron tool is helpful for CAP in HD; it facilitates communication and decision-making aspects and has a positive impact on the patient.

FR-PO449
One-Year Survival and Hospitalization After Dialysis Initiation in Patients Aged Above 75
Patrick Saudan,1 David A. Jaquies,1 Anne Dufey Teso,1 Fadi Haidar,1 Belen Ponte,2 Sebastian Carballo,2 Sophie M. De Seigneur,1 Service of Nephrology, Geneva University Hospitals, Geneva, Switzerland; 2Service of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland.

Background: Implementation of dialysis in elderly patients is debated because of an unfavourable short-term prognosis. We therefore analyzed the one-year impact of survival of planned implementation versus emergency dialysis in this population.

Methods: All patients who started maintenance dialysis in our unit during the past 21 years were reviewed. Patient’s demographic and clinical characteristics were collected. Emergency implementation of maintenance dialysis was determined if there was no prior referral for a nephrologist one month before dialysis initiation.

Results: From 2000 to the end of 2021, 860 patients started maintenance dialysis in our unit, of whom 231 were aged 75 and above. Mean age was 80 ± 4 years. Hemodialysis was implemented in 83 % of the patients. There were 66% male, 41 % diabetics and median eGFR at start of dialysis was 7± 5 ml/min. Emergency dialysis was implemented in 36% (n=81) of the patients aged 75 and above. One-year mortality was 18% in patients who had planned dialysis and 36% in patients with emergency dialysis. One-year mean survival was 327±12 days in patients with planned dialysis versus 275±21 days in those who had emergency dialysis (p= 0.004).

Conclusions: In our dialysis population, one-month referral to nephrologists prior to dialysis implementation significantly increased one-year survival and hospitalization-free days in ESKD patients aged above 75.

FR-PO450
A Nationwide Survey of Conservative Kidney Management in Japan
Ken Sakai,1 Hirokazu Okada,2 Naoki Kashihara,1 Toho Daigaku, Ota-ku, Japan; 1Saitama Daigaku, Saitama, Japan; 2Kawasaki Ika Daigaku, Kurihashi, Japan.

Background: Even with our best possible efforts, death is an inevitable endpoint. The age of entering dialysis has reached over 70 years old in Japan. Withhold and withdrawal dialysis have emerged problem in elderly society. This article explains the selection and current situation of conservative kidney management (CKM) based on nationwide survey in Japan.

Methods: Questionnaire responses were collected in 2020, based on the 2-year period status from 2018 to 2019. A web-based questionnaire was sent to all members of 4 societies (Japanese Society of Nephrology, Society for Dialysis Therapy, Association for Palliative Care in Japan, and Society for Pediatric Nephrology), and one response was received from each facility to avoid duplication of cases. Thus, although the exact response rate could not be counted, responses were obtained from 451 facilities.

Results: Among the responses, 299 were from hospitals, 104 were from dialysis clinics, and 57 were from visiting physicians. In the past 2 years (2018-2019), the number of patients who opted for withholding of dialysis was 917, and that for withdrawal from dialysis was 492 (1409 in total). In patients who were 80 years or older, the increase in the number of patients who opted for withholding of dialysis was substantial, with more than twice as many patients than those who opted for withdrawing from dialysis. Among patients who withheld or withdrew from dialysis, the number of patients with poor cognitive function was approximately twice that of those with good, and poor cognitive function was prominent in patients who withheld dialysis. In terms of prognosis after withholding or withdrawal of dialysis, many patients died 1 month after withholding of dialysis and 7-14 days after withdrawal from dialysis. The contents of palliative care varied but pain management was a main component: not many patients were transferred to the palliative ward or home. Relevant confirmation document were obtained, but the explanation of CKM as a therapy option was provided at the time of therapy selection in just 40% of cases. Most patients treated with CKM is not well recognized as advance care planning, and thus, deliberation is still required for consensus-building on CKM, as well as on ACP. Adequate time must be also spent for full SDM in the elderly Japanese dialysis population.

Funding: Government Support - Non-U.S.

FR-PO451
Withdrawal from Dialysis: Seven-Year Experience in a Kidney Supportive Care Service
Kirsten S. Hepburn,1,2 Rebecca Hudson,1 Laura H. Austin,1 Louise Curtill,1 Nadine M. Ng,2 Ise R. Chia,1 Katrina M. Kramer,1 Anne Bonner,1 Helen G. Healy,1,3 Kidney Health Service, Metro North Hospital and Health Service, Brisbane, QLD, Australia; 2Faculty of Medicine, University of Queensland, Herston, QLD, Australia; 3Palliative and Supportive Care Service, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; 4School of Nursing and Midwifery, Griffith University, Southport, QLD, Australia; 5Research Development Unit, Caboolture Hospital, Caboolture, QLD, Australia.

Background: Withdrawal from dialysis is a common cause of death in patients on dialysis. Palliative care and supportive care (KSC) services have evolved to meet the palliative care needs of patients ceasing dialysis when it is no longer beneficial. This study examines the profile and survival of patients known to a KSC service who withdrew from dialysis.

Methods: Retrospective analysis of patients known to a KSC service between 2016 and 2023 who withdrew from dialysis (HD or automated peritoneal dialysis) were included. Demographics including age, sex, ethnicity, and Charlson Comorbidity index (CCI) were extracted from medical records. Reasons for referral to KSC and patient choices including advance care planning (ACP) documents and preferred place of death were recorded. Date of dialysis withdrawal, date and place of death, and referral to palliative care services were also collected. Results were analyzed descriptively.

Results: Over 7 years, 157 patients withdrew from dialysis with a mean age of 72.4 years (SD 9.88). 38% were female and 3% identified as First Nations people. 132 patients (84%) were on HD and 25 from PD. Among the patients referred to KSC, the median CCI was 7 (IQR 2.3), 31% had either ischaemic heart or congestive cardiac failure, and 5% had a diagnosis of dementia. Patients withdrew from dialysis a median of 205 days (IQR 440) after KSC referral. Following withdrawal from HD patients survived a median of 7 days (IQR 9.2), and 6 days after initiation of automated peritoneal dialysis in an acute hospital, 24% at home and 23% in a palliative care unit (PCU). Of the 74 who had indicated preferred place of death, 35 (47%) wished to die at home; of these 16 (46%) did. Only 16 patients (22%) wished to die in a PCU, but 11 (69%) did. Surprisingly 19 patients (26%) indicated they wished to die in an acute hospital and 14 (74%) of these patients did.

Conclusions: Our results indicate that patients typically survive around one week after withdrawal from dialysis, which is consistent with current literature. Most patients died in acute care settings, which was often not in keeping with their wishes. This may have been due to acute medical complications or sudden deterioration limiting transfer to their preferred place of death. Further work is needed to understand how best to provide care that concords with end-of-life preferences.

FR-PO452
Cultural Tailoring of Motivational Strategies to Improve Hemodialysis Nonadherence in African Americans
Melissa Ma,1 Erin Bergner,2 Ruth Q. Wolfever,2 Kemberlee Bonnet,3 Devika Nair,3 Rachel B. Fissell,2 Talat Alp Ikizler,2 Kerri L. Cavanaugh,2 Kenneth A. Resnicow,4 Derek M. Griffith,2 David G. Schlundt,2 Juliet Iwelunmor,2 Collins Airhihenbuwa,6 Ebele M. Umuekeje,2 California Institute for Science and Innovation (CIFI), Mill Valley, CA; 2Vanderbilt University Medical Center, Nashville, TN; 3Vanderbilt University, Nashville, TN; 4University of Michigan School of Public Health, Ann Arbor, MI; 5Georgetown University, Washington, DC; 6Saint Louis University, Saint Louis, MO; 7Georgia State University, Atlanta, GA.

Background: African Americans (AA) make up 33% of patients with ESKD and, compared to white patients, have higher hemodialysis (HD) nonadherence rates. Motivational interviewing (MI) improves nonadherence, and cultural tailoring centered...
on racial minorities reduces racial disparities. Informed by key themes derived from prior qualitative research focused on HD nonadherence in AA, we hypothesize that MI can be culturally tailored to improve HD nonadherence in AA.

**Methods:** During a facilitated community engagement studio, AA community experts (n = 7) with lived experience across each stage of kidney disease, reviewed key themes on HD nonadherence in AA. Themes were obtained from prior focus groups and interviews of 22 AA on HD, and 34 dialysis providers & researchers; mapped onto the PEN-3 cultural model; categorized as Perceptions (attitudes), Enablers (structural/societal factors), or Nurturers (support systems); and further categorized as Positive (facilitators), Negative (barriers). Community experts identified priority targets for an MI intervention. Health equity clinicians and researchers finalized the cultural adaptation process by examining the priority targets and providing additional input.

**Results:** AA community experts identified 6 major priority targets: empowerment; support network; understanding kidney disease; communication and health system-related trust/trustworthiness; mental well-being; and transportation. Health equity researchers added racial identity as a priority target. Key themes and illustrative perspectives are shown in Table 1.

**Conclusions:** Use of the PEN-3 cultural model for the cultural adaptation of MI is novel. Integrating input from AA community experts and content experts with perspectives from AA on HD to identify priority targets of MI, will likely increase the potential efficacy, adoption, and sustainability of MI to improve HD nonadherence in AA.

**Funding:** NIDDK Support

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**Figure:** Survival of incident hemodialysis patients from completion of depression survey to first hospital admission

**FR-PO454**

**Palliative Care and Advance Care Planning Integration into the Dialysis Team: A Quality Improvement Intervention at a Hospital-Based Outpatient Hemodialysis Clinic**

**Josha Hauser,1,2 Alejandro Gmurczyk,1,2 Joshua Hauser,1,2 Joanna R. Varghese,1 Julie Ozerzy,1 Tyra D. Oliver,1 Michael J. Fischer,1,3**

1 Jesse Brown VA Chicago Healthcare System, Chicago, IL; 2Northwestern Memorial Hospital, Chicago, IL; 3University of Illinois Hospital & Health Sciences System, Chicago, IL.

**Background:** Despite substantial symptom burden and high mortality, adults receiving maintenance hemodialysis (HD) infrequently utilize palliative care (PC). With most hospital-based outpatient dialysis clinics, Veterans Affairs (VA) is well-positioned to integrate access to PC services. At a large urban VA dialysis unit, we initiated a year-long intervention to improve Life Sustaining Treatment (LST) note and advance care planning (ACP) completion.

**Methods:** A PC physician was integrated into the dialysis care team at the Jesse Brown VA (JBV A) Medical Center to improve LST and advance directive (AD) completion. The PC physician worked with the dialysis team to provide palliative education and refine and bolster approaches to ACP. The PC physician contacted all patients needing an AD or LST note. After 12 months, we reassessed percentages of patients with LST and AD completion. Change in proportion with note completion pre/post PC intervention was compared.

**Results:** Among all outpatient HD patients at the JBVA, the average age was 71 years, 85% were Black, 99% were male, and the average time on HD was 4.7 years. Frequent consultation with the dialysis social worker was essential to targeting patients for the intervention. Most patients preferred private phone calls with the PC physician to discuss ACP. Integration of a PC physician into the dialysis care team significantly increased patient completion of an AD and LST note as noted in table.

**Conclusions:** Integrating a PC physician into the dialysis care team led to a substantial increase in LST and advance directives for maintenance HD patients. Future PC intervention plans should build on these gains in advance care planning, measure their impact on subsequent care and also extend to alleviating symptom burden.

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**FR-PO455**

**Importance of Living with a Spouse for Female Patients Undergoing Hemodialysis**

**Hiro Inoue,1,2 Mineaki Kitamura,2 Maiko Nakamura,1 Hiro Inoue,1 Satoshi Funakoshi,1 Tomoya Nishino,2 Nagasaki Renal Center, Nagasaki, Japan; 3Nagasaki Daigaku, Nagasaki, Japan.**

**Background:** An increasing number of elderly people are living alone owing to the aging population, and patients undergoing hemodialysis are no exception. Generally, patients living alone have poor prognoses. However, the significance of living with a spouse for patients on hemodialysis has been unclear. Therefore, we aim to clarify such significance among Japanese patients undergoing hemodialysis.

**Methods:** After excluding patients with an unknown family structure, we included patients undergoing hemodialysis at Nagasaki Renal Center, Japan, during 2011 and 2012. Patients were followed up until 2022. Log-rank tests and multivariate Cox regression analyses were conducted to evaluate the patients’ life prognosis.

**Results:** We included 333 patients undergoing hemodialysis (mean age: 67.2±13.3 years, 57% men, median dialysis vintage: 4.8 years). The proportion of those living with a spouse was 48%. The log-rank test for all patients showed that patients living with a spouse had a favorable prognosis compared with that of patients living alone (P=0.008). Notably, no significant difference was observed among male patients (P=0.22); however,

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

Underline represents presenting author.
a significant difference was detected among female patients ($P=0.004$). Even a patients’ background-adjusted multivariate Cox regression analysis showed that living with a spouse reduced the risk of death (hazard ratio 0.74, 95% confidential interval: 0.56–0.98, $P=0.04$).

Conclusions: Living alone was associated with poor prognosis, especially in female patients undergoing hemodialysis. The precise reason for this remains unknown. However, patients on hemodialysis living alone should not be isolated from society to improve their prognosis.

FR-PO456

Impact of Inpatient vs. Outpatient Dialysis Transition on Survival in a National Cohort of Advanced CKD Patients

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Background: Large population-based studies show advanced CKD patients transitioning to ESKD have high mortality in the first few months of dialysis initiation. It is unclear whether transitioning to dialysis in the inpatient vs. outpatient setting is associated with better survival in incident ESKD patients.

Methods: We examined advanced CKD patients (\(eGFR <25\) separated by \(\geq 90\) days) who transitioned to dialysis in the inpatient vs. outpatient setting matched by propensity score (PS) in a 1:1 ratio with a caliper distance of \(0.2\) to address confounding (C) and selection bias (SB). In this study we focused on a methodology that allows to analyze differences in clinical outcomes accounting C and SB.

Results: Among 20,655 patients who were PS-matched to 20,655 patients who transitioned to dialysis in the inpatient vs. outpatient setting, respectively, outpatient dialysis transition was associated with lower mortality risk vs. inpatient dialysis transition: HR (95%CI) 0.77 (0.75–0.79). Similar findings were observed in sensitivity analysis. A model using “modality” as treatment and baseline variables as covariates was built to estimate “average treatment effect” (ATE) on outcomes of interest using propensity score stratification (PSS), which estimates the risk/odd % change between treatment and control accounting for baseline differences and SB.

Conclusions: Since hemodialfiltration (HDF) provides higher clearance of middle molecules compared with hemodialysis (HD), several studies showed HDF may result in better outcomes than HD. However, these findings are prone to residual confounding (C) and selection bias (SB). In this study we focused on a methodology that allows to analyze differences in clinical outcomes accounting C and SB.
FR-PO458

A Qualitative Study Exploring the Role and Responsibilities of the Patient Care Technician in US Dialysis Care

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Background: Dialysis patient care technicians (PCTs) provide essential, frontline care for patients on dialysis. We aimed to qualitatively explore perceptions of the PCT job role, responsibilities, and training among current PCTs, other staff on the dialysis care team, and patients receiving dialysis.

Methods: Focus group discussions were conducted in March-May 2023 with U.S., PCTs, dialysis staff, and patients. Participants were recruited via email invitation and social media postings from professional organizations and were purposively sampled to capture diversity in demographics and years of experience. Discussions were audio-recorded and transcribed verbatim and thematic analysis was conducted using inductive and deductive strategies.

Results: Seven focus group discussions (n=36 participants) were conducted (3 with PCTs [n=19], 2 with dialysis staff [e.g., social workers, dietitians; n=6], and 2 with patients [n=1]). Preliminary analyses revealed that, although there is agreement that PCTs play a pivotal role in dialysis care for patients and colleagues, PCTs are often perceived as “helpers” or ancillary rather than an integral part of the care team. Participants reported that PCT job training and qualifications are not standardized and are often not commensurate with job expectations and responsibilities. Additional training and continuing education are needed and desired. Participants reported that the PCT-patient relationship is deeply valued, but boundaries can be fluid and blurred due to the frequency and nature of dialysis care and differences in the perception of relationship boundaries were observed among groups. Finally, it was noted that PCTs are vulnerable to multi-level workplace safety issues (e.g., unsafe staffing ratios, violence) but feel ill-prepared to manage them.

Conclusions: Preliminary findings suggest PCTs play a multifaceted role in dialysis care that is highly valued among patients and staff, but this is not always reflected in the multi-level policies that govern U.S. dialysis care. Future research should prioritize multilevel interventions aimed at equipping PCTs with the needed resources and support to provide quality care for patients and better prepare and integrate these critical members of the dialysis care team.

Funding: Other U.S. Government Support

FR-PO459

A Budget Impact Model (BIM) for Expanded Haemodialysis (HDx) vs. High-Flux Haemodialysis (HF-HD) in Two Major Public Health Sectors, Kingdom of Saudi Arabia (KSA)

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Background: Chronic Kidney Disease imposes economic costs on healthcare systems. The Saudi Center for Organ Transplantation (SCOT) in 2020 estimated that the number of patients undergoing dialysis (all modalities) is expected to increase by 5% per annum. While small-middle size molecules/uremic toxins have been shown to be associated with inflammation, vascular calcification, and increased risk of cardiovascular disease. While conventional HD will clear smaller middle molecules adequately; large middle molecules can be reduced by HDx. Theranova (Baxter Healthcare Corporation, Deerfield, IL, USA), a medium cut off dialyzer, allows for better clearance of large middle-size molecules/urate toxins in comparison to conventional HD, resulting in better patient outcomes.

Methods: An excel-based BIM was assessed the overall cost of HF-HD patients versus those on HDx over five-years from public payers’ perspectives. Input data were retrieved via a comprehensive literature search and expert interviews. These included epidemiology data, the costs of healthcare resources utilized in dialysis sessions and dialysis related complications management including physician visits, hospitals stay, and medications.

Results: As per 2021 SCOT report, 1,862 Patients are managed in these health sectors. HF-HD Therapy total cost per patient per year was $15,947 (US Dollars $, ± 3.75 Saudi Riyals [SAR]), while the total cost of HDx Therapy per patient per year was $12,019. The overall saving cost per patient per year of $3,928 were driven by reductions in hospitalization, $3,619, followed by reductions in dose of Erythropoietin Stimulating Agents (ESA), $232, per patient per year. Over 5 Years the cost savings for the patients treated in these health sectors was $3.4m.

Conclusions: This study demonstrated that choosing HDx as alternative line of therapy may result in better patient outcomes. In addition to HDx clinical benefits associated with better clearance of large middle molecules, the increased adoption of HDx with Theranova may provide further economic benefit.

Funding: Commercial Support - Baxter AG

FR-PO460

Assessing the Value of an Integrated Multidisciplinary Patient Centric Program for Patients in Hemodialysis

Shaira Martinez Vaquera,1 Sonia C. Molina,3 Teresa Martinez Sanchez,1 Maria Paz Sorribes Lopez,1 Ivan Fraile,1 Ignacio de Leon-Ponce de Leon,1 Oscar Martinez Perez,2 Helena Diaz-Cuervo,3 Jesus Cuervo,2 Jose Maria Ordóñez Martí Aguilar,2 Fernando Jose Gordinho R. Macario,1 Diaverum Catalonia PCC Team, 1Diaverum España, Madrid, Spain; 2Axentiva Solutions SL, Barcelona, Spain; 3Diaverum Renal Services Group, Lund, Sweden.

Background: Chronic kidney disease (CKD) constitutes a public health concern due to its notable morbidity&mortality and associated costs. The Patient Care Coordination program (PCC) provides comprehensive and personalized care to hemodialysis (HD) patients. This study evaluated the cost-effectiveness of PCC compared to standard of care (SoC).

Methods: The study included patients in 9 HD clinics (5 PCC, 4 SoC) in Catalonia, Spain, in 2020-2021. A comparative effectiveness evaluation was conducted to compare change in Individual Patient Performance Score (IPPS, score 0–100), evaluates parameters such as vascular access, adequacy of HD, anemia, mineral bone disease; arterial hypertension, nutrition/hydration status) and number of hospitalizations of PCC patients vs SoC during the first year of the program. Instrumental variables (IV) regression analysis was performed to address potential confounding; number of interactions with program specialists was a valid IV to estimate degree of PCC use. An incremental cost-effectiveness analysis (ICEA) through microsimulation was performed using the effectiveness data from the previous step, population data from the renal patient registry of Catalonia, and the cost of hospitalizations obtained from the Public Health System.

Results: 127 patients in PCC and 363 patients in SoC were included. The degree of PCC use and a positive impact on IPPS variation during the first year of the program (p= 0.012). In the iCEA the PCC program resulted in a mean gain of 3.4 additional IPPS points, a reduction of 0.2 hospitalizations per patient, and reduced mean costs of €1,265 per patient in the first year compared to SoC, resulting to be a dominant alternative (ICER= 0).

Conclusions: Use of PCC resulted in positive impact in outcomes and reduced costs compared to SoC for HD patients. The PCC program represents thus a dominant alternative, with greater effectiveness and total cost savings that could sum up to €5.5 million per year in the region due to reduced hospitalizations. The findings underscore the relevance of comprehensive and personalized care in addressing the challenges of CKD and optimizing healthcare resource allocation.

Funding: Private Foundation Support

FR-PO461

Long-COVID-19 in Hemodialysis Patients: A Prospective Study

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Background: Long-COVID (LC) is defined as persistent symptoms after COVID-19 infection. It has been reported that up to 40% of COVID-19 survivors experience LC (C.A. Holmes et al. The Lancet, 2023). We aim to determine if hemodialysis (HD) patients experience LC.

Methods: HD patients diagnosed with COVID-19 via RT-PCR test were enrolled from 01 to 04 2022 from 4 clinics in New York City: COVID-19 Yorkshire Rehabilitation Scale (C19-YRS) was administered at baseline, i.e. as soon as possible after diagnosis, and 1 and 6 months after baseline. C19-YRS also asks about pre-COVID symptoms; we used that symptom severity (SS) as baseline as comparator. While SS is graded from 0-10, 10 being the worst, global health score (GH) is reported with 10 being the best. Patient data were obtained from medical records. Paired t-tests were used examine differences in SS pre- and post- COVID-19 infection. Linear and generalized mixed models were used to examine the effect of time on continuous and discrete LC SS, respectively.

Results: We studied 16 patients (58±14 years old, HD vintage 2.7±3.4 years, 56% male, 86% Black, 19% Hispanic, no diabetic, 50 % hypertensive). Baseline C19-YRS was administered 43±23 days (range 9-108) after COVID-19 diagnosis. 5 patients were hospitalized. C19-YRS results are shown in Table 1. Compared to baseline, patients experienced significantly increased dyspea, anxiety, and PTSD at 1 month and fatigue at 6 months. Decreased mobility and activity of daily living were also observed, though not statistically significant. Lastly, patients reported decreased GH score at months 1 and 6 compared to baseline.

Conclusions: Following COVID-19 infection, patients report worsening LC symptoms. Further studies are warranted to investigate the long-term consequences of LC in HD patients.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
**FR-PO462**

**Risk of Hospitalization and Mortality Following Extreme Heat Events in Patients Undergoing In-Center Hemodialysis in the Western United States**

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**Background:** Climate change is increasing the frequency of extreme heat events (EHEs) and this trend is projected to continue into the foreseeable future. Previous research indicates that patients undergoing hemodialysis treatment are at an increased risk of both hospitalization and mortality following exposure to EHEs, although earlier analyses were limited in scope to the Northeastern U.S. Here, we investigated the risk of hospitalization and mortality following exposure to EHEs in the Western U.S. among patients that receive in-center hemodialysis treatment.

**Methods:** We identified EHEs as days where the daily maximum temperature (Tmax) exceeded the 95th percentile distribution of daily Tmax values specific to the location and calendar day over a 20-year baseline (1980-1999). We linked EHE data with health care encounters (ICD codes) from the Kidney Disease: Improving Global Outcomes (KDIGO) registry for patients on dialysis, strategies to increase the uptake of viable access are required.

**Results:** We observed a total of 7,242 EHE days at the county scale during the study period. EHEs were associated with a 7% higher risk of all-cause hospitalization (rate ratio (RR): 1.07, 95% CI: 1.02, 1.11), and a 6% higher risk of all-cause mortality (RR: 1.06, 95% CI: 1.00, 1.13).

**Conclusions:** We observed an increase in the risk of both hospitalization and mortality following EHE exposure in the Western U.S., which agrees with earlier findings from the Northeastern U.S. These findings indicate that interventions, such as the implementation of early heat warning systems, are needed to improve outcomes for patients undergoing in-center hemodialysis.

**Funding:** Other U.S. Government Support

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**FR-PO463**

**Global Variability and Patterns of Use in Vascular and Peritoneal Access for Dialysis: Analysis of the ISN-Global Kidney Health Atlas Data**

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**Background:** A well-functioning access (vascular or peritoneal) is key to adequate performance of dialysis. The International Society of Nephrology Global Kidney Health Atlas (ISN-GKHA) surveyed gaps in availability, patterns of use, funding models, and workforce for the provision of vascular and peritoneal accesses across countries.

**Methods:** Using the second iteration of the ISN-GKHA, countries were categorized by affiliations in the ISN regional boards and by World Bank income classification. Questions focused on availability of surgical aspects of care, access to education and availability of providers for the access creation.

**Results:** Data was available from 159 countries out of 160 that participated in the survey. Overall, public funding was available for hemodialysis (HD) central venous catheters in 92 countries (57%), for HD fistula or graft creation in 86 countries (54%), and for PD catheter surgery in 85 countries (54%). Public funding for the access types was highest in high-income countries than other country income categories. Overall, and in countries where HD was available, >75% of patients initiated HD with a temporary catheter in 21% of countries compared to patients commencing with a tunneled catheter (5%) or a fistula (5%) (Figures 1). Shortages of surgeons and radiologists were highest in low-income and lower-middle income countries.

**Conclusions:** There is significant variation in the availability, accessibility and patterns of use of vascular and peritoneal catheters across countries with significant limitations in the needed workforce. In order to improve the outcomes and survival of patients on dialysis, strategies to increase the uptake of viable access are required.

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**FR-PO464**

**Nitric Oxide-Releasing Nanomatrix Gel Inhibits Venous Intimal Hyperplasia and Improves Vascular Remodeling in Porcine Arteriovenous Fistula (AVF)**

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**Background:** Arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis, but a large proportion fails to mature due to venous intimal hyperplasia (HI) formation and impaired outward remodeling. End-stage kidney disease has been linked to endothelial dysfunction characterized by reduced nitric oxide (NO) in the blood vessel. NO delivery during AVF creation may improve AVF maturation. Our study tested an NO nanomatrix gel applied perivascularly during AVF creation in a porcine AVF model.

**Methods:** We identified AVF formation and impaired outward remodeling. End-stage kidney disease has been linked to endothelial dysfunction characterized by reduced nitric oxide (NO) in the blood vessel. NO delivery during AVF creation may improve AVF maturation. Our study tested an NO nanomatrix gel applied perivascularly during AVF creation in a porcine AVF model.

**Results:** We observed an increase in the risk of both hospitalization and mortality following EHE exposure in the Western U.S., which agrees with earlier findings from the Northeastern U.S. These findings indicate that interventions, such as the implementation of early heat warning systems, are needed to improve outcomes for patients undergoing in-center hemodialysis.

**Funding:** Other U.S. Government Support

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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: AVFs were created in Yorkshire pigs by anastomosing the jugular vein to the carotid artery, treated with NO-releasing nanomatrix or control gel at the anastomosis, and sacrificed at day 35. Immunohistochemistry, histomorphology and hemodynamic changes were evaluated to assess the efficacy of NO gel in reducing intimal hyperplasia and promoting outward remodeling.

Results: NO gel-treated group vs control gel demonstrated significantly reduced IH (p<0.0001) and type I collagen (p<0.05). The patency of open lumen within AVF region was significantly higher within NO gel, along with increased blood flow and AVF diameter (p<0.05). NO gel reduced intimal α-SMA, Vimentin, Desmin, CD68 and CD14 expression (p<0.05).

Conclusions: AVFs applied with an NO-releasing gel reduce intimal hyperplasia and promote outward remodeling, and could serve as a therapy to promote AVF maturation.

Funding: NIDDK Support

FR-PO465

Contrast Venography vs. Intravascular Ultrasound in Arteriovenous Access Dysfunction

Najia Idrees,1,2 Samir Haroon,3 Yichi Zhang,2 Joanna Crisa Mangio,2 Howard J. Cabral,2 Laura M. Denter,1 Vipul C. Chitalia,1,2 Veterans Affairs Boston Healthcare System, Boston, MA; 3Boston Medical Center, Boston, MA; 1University of Pennsylvania, Philadelphia, PA.

Background: Contrast venography, a standard approach for evaluating hemodialysis vascular access dysfunction, has several limitations that may be overcome by intravascular ultrasound (IVUS).

Methods: Venography and IVUS were performed in a prospective study of 41 patients with arteriovenous access dysfunction. Radiologists estimated stenosis on venograms and annotated cross-sectional IVUS images (N=250) that were used to train a deep learning model to automatically score stenosis. The model was validated with independent cross-sectional IVUS images (N=250) that were used to validate the model's score. The model’s performance was compared to venography in terms of sensitivity, specificity, and positive predictive value.

Results: Among the 33 patients with high quality images, 20 had a single stenosis and 13 had two stenoses of any severity (total of 46 stenoses). Twenty-four stenoses with >50% lumen reduction were detected by both venography and IVUS, and 14 additional stenoses were detected by IVUS but not by venography. A discordance between the two modalities was observed (McNemar ratio 7.11, p=0.0076; kappa 0.163). The severity of stenosis (%) was lower by venography (mean±SD 51.7±14.1) compared to IVUS (64.9±18.1, p=0.002). IVUS image analysis showed higher eccentricity and homogeneity indices for stenotic lesions compared to the reference segments. Metrics comparing stenoses and reference segments demonstrated substantial variability in the distribution of both indices.

Conclusions: Compared to IVUS, venography underestimated severity of stenoses in ~30% of patients presenting with arteriovenous access dysfunction. Further studies are needed to confirm the superiority of IVUS over venography and to establish the clinical utility of morphological indices for predicting stenosis progression and response to intervention.

Frequency distribution of stenoses severity detected by both modalities

<table>
<thead>
<tr>
<th>Frequency of stenosis by venogram</th>
<th>Frequency of stenosis by IVUS</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5%</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>&gt;5%</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Total</td>
<td>8</td>
<td>38</td>
</tr>
</tbody>
</table>

Disagreement between venogram and IVUS

FR-PO467

Role of Neutrophil Extracellular Traps in Vascular Access Thrombosis in Hemodialysis Patients

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Background: A patent vascular access (VA) is a life-line for hemodialysis (HD) patients. However, vascular access is prone to thrombosis, which, if left untreated, can lead to permanent vascular access loss and increased mortality. Previous data have shown that neutrophil dysregulation and excessive release of neutrophil extracellular traps (NETs) may be a key mechanism in both venous and arterial thrombosis. The aim of this study is to evaluate the relationship between circulating NETs and VA thrombotic occlusion and their role in predicting permanent VA loss.

Methods: A total of 173 patients (73 arteriovenous fistula [AVF], 100 arteriovenous graft [AVG]) undergoing VA percutaneous transluminal angioplasty (PTA) with or without thrombectomy were included. Circulating nucleosome and myeloperoxidase (MPO)-DNA complexes were measured as markers of NETs. Serum von Willebrand factor (vWF) was measured as a marker of endothelial damage and thrombosis risk. VA loss was defined as access abandonment requiring dialysis catheter placement.

Results: Thrombectomy was performed in 81 patients. Patients who underwent thrombectomy were significantly older than those who underwent PTA only and used AVG more often than AVF. Circulating nucleosome levels were closely associated with MPO-DNA (r=0.354, p<0.001). serum vWF levels (r=0.172, p=0.025), and previous coronary artery disease (r=0.226, p=0.003). Nucleosome and vWF levels were significantly higher in thrombectomy cases than in PTA cases (nucleosome: 0.83 ± 0.70 vs. 0.35 ± 0.26, p<0.001, vWF: 9.0 ± 7.6 vs. 7.3 ± 6.2, p=0.038). The highest quartile of nucleosomes (Q4) was associated with an 11.4-fold increased risk of VA thrombotic occlusion (p<0.001). In addition, the risk of recurrent thrombotic obstruction within 6 months of PTA was also 3.1 times higher in the nucleosome Q4 group than in the Q1-3 group (p=0.020). During a median follow-up of 34 months, there were 25 cases of VA abandonment. The nucleosome Q4 was strongly associated with an increased risk of access loss (HR 2.56, 95% CI 1.23-7.44, p=0.016) even after adjustment for age, vascular access type, blood pressure, vWF, and duration of access use.

Conclusions: Higher circulating NETs are associated with thrombotic occlusion of VA and subsequent access loss in HD patients.
WavelinQ allow for non-surgical creation of AVFs. Published pAVF studies so far report higher patency rates (85-96%), less interventions, less surgical complications, and greater patient satisfaction compared to surgically created AVF. The percentage of Black patients varies from 0-20.6% in the literature, which vastly differs from our clinical population. We report a case series of real-world outcomes of pAVF in our urban predominantly Black HD patient population.

**Methods:** Retrospective chart review from 2021-2023 of patients from Emory Dialysis of all patients who received percutaneous AVF.

**Results:** Eleven patients had pAVF created by four proceduralists using either the Ellipsys or WavelinQ devices. Majority of patients were male (72.7%) and of Black race (91%). Common co-morbidities included hypertension (100%), diabetes mellitus (63.6%), and cardiovascular disease (36.4%). Mean age was 53.6 years, and the mean body mass index (BMI) was 34.6. Dialysis vintage ranged from 0.5 to 9 years, with mean duration of 2.7 years. 91% of patient had a tunneled dialysis catheter before having a fistula. Of 11 patients, 6 (54.5%) had their pAVF functioning adequately for HD, 4 (36.4%) did not, 1 had 3 angioplasties but her pAVF was not used. Irrespective of ultimate functional patency, all required multiple interventions, with 10 of 11 patients (91%) requiring 2 or more interventions.

**Conclusions:** Overall, this case series provides real-world data on the use of pAVFs in an urban predominantly Black US dialysis population. To our knowledge, our study has the largest percentage of Black patients in the study population published so far. Our results indicate that though pAVFs can be successfully created in this population, a majority of patients require multiple secondary procedures, and only 54.5% were able to achieve functional patency. Further research with larger sample sizes and longer follow-up is warranted to evaluate the long-term patency rates and complications associated with pAVFs.

**FR-PO468**

**Development of Senescence in the Rat Arteriovenous Fistula: Functional Effects of Heme**

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**Background:** As shown in our previous studies, the murine arteriovenous fistula (AVF) model in the presence of CKD (AVF-CKD) evinces markers of senescence in the venous limb [Am J Physiol Renal Physiol. 315(5):F1493-F1499, 2018]. We now assess whether an AVF fashioned in the rat also exhibits senescence, and whether heme, a prosenescent agent, alters rat AVF function.

**Methods:** Subtotal nephrectomy was performed in rats after which an AVF was created by anastomosing the femoral artery and vein. At 1 and 2 weeks after AVF creation, the AVF was assessed for evidence of senescence, including increased expression of cell cycle inhibitors (p16 and p21), senescence-associated β-galactosidase (SA-β-Gal) and senescence-associated secretory phenotype (SASP) factors. In additional studies, the effect of heme on AVF blood flow was assessed in the rat.

**Results:** One week after AVF creation, p16 and p21 mRNA levels were markedly elevated in AVF veins compared to sham veins, as were p21 protein levels; p21 protein in the AVF artery was also increased. At 2 weeks, p21 protein was again upregulated in the AVF vein and artery, and protein levels of p53, an upstream inducer of p21, were significantly increased in the AVF artery, and tended to be higher in the AVF vein (p ~ 0.083). Upregulation of SASP factors was also observed in the AVF vein at 1 week; PAI-1, IL-6, TNF-α and MCP-1 mRNA were all markedly induced compared with sham values. At this time point, miR21, (associated with vascular senescence) was also elevated in the AVF vein. Additionally, SA-β-Gal activity, an established senescence marker, was significantly increased in both the artery and vein compared to their sham counterparts at 1 and 2 weeks post AVF surgery. Finally, heme administration increased AVF blood flow at 5 days after AVF placement, but resulted in lower AVF flow rates at 3 weeks.

**Conclusions:** We demonstrate that the rat AVF in the presence of CKD exhibits a senescent phenotype, akin to the murine AVF-CKD model. We suggest that heme, administered over 3 weeks, reduces AVF blood flow because of its prosenescent effect of heme on AVF blood flow was assessed in the rat.

**FR-PO469**

**Levels of Interleukin 8 and Monocyte Chemotactrant Protein-1 Are Associated with Arteriovenous Fistula Events and Upregulated in the Endothelium by Indoxyl Sulfate and TGF-β Pathway**

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**Background:** Arteriovenous fistula (AVF) failure due to stenosis or acute thrombosis is a major concern in haemodialysis (HD) patients. Intimal hyperplasia responsible for AVF stenosis can be caused by several factors like endothelial dysfunction, uremic toxins, and inflammatory/proliferotic molecules. Studies suggest that endothelium-secreted inflammatory molecules Interleukin 8 (IL8) and Monocyte Chemotactrant Protein-1 (MCP-1) trigger intimal invasion of smooth muscle cells and enhance intimal thickening. We investigated the association of IL8 and MCP-1 serum levels with AVF events in haemodialysis patients and studied the ability of the uremic toxin indoxyl sulfate to upregulate IL8 and MCP-1 expression in endothelial cells.

**Methods:** We conducted a retrospective observational study in 205 haemodialysis patients with AVF. In vitro, we studied the mRNA expression of IL8 and MCP-1 in endothelial cells incubated with indoxyl sulfate at uremic concentration (200μM).

**Results:** During the study period of 731 days, 64 patients had an AVF event defined as a composite of the first occurrence of AVF thrombosis or AVF stenosis requiring endovascular treatment. Kaplan-Meier analysis revealed that patients with serum levels of IL8 > 0 pg/ml or MCP-1> 720 pg/ml had significantly more AVF events. Serum levels of IL8 and MCP-1 were positively correlated with the levels of the pro- fibrotic molecule TGFβ1 in HD patients. In addition, serum levels of MCP-1 were positively correlated with indoxyl sulfate. In vitro, indoxyl sulfate upregulated endothelial expression of IL8 and MCP-1 by activating its receptor, aryl hydrocarbon receptor, which in turn activated the non-canonical TGFβ pathway involving TAK1, p38 MAPK, and the transcription factor β-catenin. The stimulation of the TGFβ1 signaling pathway by TGFβ1 amplified indoxyl sulfate-mediated IL8 and MCP-1 expression.

**Conclusions:** We demonstrated that AVF events are associated with high serum levels of IL8 and MCP-1, which are upregulated in the endothelium by activation of the non-canonical pathway by the uremic toxin indoxyl sulfate. Our study could provide therapeutic targets to limit intimal hyperplasia and prevent AVF events in haemodialysis patients.

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

**FR-PO470**

**Uremia and a Lack of Krüppel-Like Factor-2 (KLF-2) Are Responsible for an Inadequate Positive (Outward) Venous Remodeling in a Mouse Model of Arteriovenous Fistula (AVF) Stenosis**

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**Background:** Although AVFs remain the gold standard for dialysis vascular access they have a maturation failure rate of over 50% at 6 months post surgery due to a combination of neointimal hyperplasia and an inadequate positive (outward) remodeling. A central molecule in the mechanotransduction pathways responsible for outward remodeling in response to increased flow is KLF-2. In order to better understand the mechanisms of inadequate outward remodeling in AVF maturation failure we aim to describe the impact of both uremia and the absence of KLF-2 in our mouse model of AVF stenosis.

**Methods:** AVFs were created between the carotid artery and jugular vein in (a) non-uremic WT C57Bl/6 animals (b) uremic WT animals (c) non-uremic KLF-2 KO animals and (d) uremic KLF-2 KO animals (n=3 in each group). The degree of outward remodeling was assessed by measuring the change in the venous perimeter from the juxta-anastomotic segment (0 microns from the anastomosis) to proximal vein 1200 microns downstream (proximal) to the anastomosis, using Image J morphometry.

**Results:** Non-uremic WT animals had a 48% increase (p=0.0001) in venous perimeter across the length of the venous segment (from 0-1200 microns). In marked contrast both the KLF-2 KO animals and the uremic animals (regardless of KLF-2 presence or absence) completely lost this increase in venous perimeter (outward remodeling).

**Conclusions:** Our results demonstrate that KLF-2 is likely a strong driver of positive (outward) remodeling in our mouse model of AVF stenosis. At the same time uremia appears to be a strong inhibitor of outward remodeling (likely as a result of endothelial dysfunction) such that the presence or absence of KLF-2 in uremic animals does not have any impact on the remodeling process. Looking to the future our data suggest that (a) creating a local milieu around the AVF which inhibits the impact of uremic toxins and (b) upregulating the KLF-2 gene two molecular approaches that could reduce AVF maturation failure.

**Funding:** Private Foundation Support
FR-PO471

Local Sirolimus Delivery Reduces Arteriovenous Graft (AVG) Stenosis in a Pig Model
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Background: Dialysis vascular access is currently the “Achilles Heel” of hemodialysis due to the high rate of stenosis in both arteriovenous fistulae and arteriovenous grafts (AVG). AVG stenosis is due to an aggressive venous neointimal hyperplasia (NH) that has been shown to reduce NH in the setting of coronary stenting. We have previously developed a local sirolimus (SRL) drug eluting cuff (DEC; 2mg/month) linked to an osteomimetic graft that can be used to deliver high concentrations of SRL to the GAV with minimal systemic SRL exposure. Herein we report on the use of the Sirolimus DEC (SDEC) versus a control solution (CDEC) in the setting of a validated pig model of AVG stenosis.

Methods: 10 AVGs (6 SDEC and 4 CDEC) were created unilaterally in Yorkshire Cross pigs. Animals underwent weekly ultrasound assessments for patency and were sacrificed at 8 weeks post surgery. At the time of sacrifice 1cm of graft downstream to the DEC and 1.5cm of downstream (proximal vein) was collected for analysis of average (avg) and maximal (max) stenosis (including any attached thrombus) across the entire graft-segment and also within the individual vein and graft segments, using Image J. Results: All 10 grafts were patent at the 56 day time point. Systemic SRL levels peaked at between 0.86 and 1.6ng/ml at 3d. Percentage average stenosis (SDEC=50.4% vs CDEC=50.8%; p=0.025) and max. stenosis (SDEC=60.1% vs CDEC=80.6%; p=0.02) across the entire-graft-vein segment was significantly reduced in the SDEC group. A similar pattern was found in the venous segment for avg. stenosis (SDEC=46.4% vs CDEC=72.9%;p<0.01) and maximal stenosis (SDEC=60.1% vs CDEC=80.6%; p=0.02) but not in the graft only segment for either avg. (SDEC=66.6% vs CDEC=72.7%;p=0.13) or max. stenosis (SDEC=9.9% vs CDEC=27.4%;p=0.19).

Conclusions: Our results (a) demonstrate the technical feasibility of using a SDEC for the local delivery of SRL to the GVA (b) document minimal systemic SRL exposure due to the SDEC device and (c) describe a significant reduction in both avg. and max. stenosis across the entire AVG segment. Future clinical development of the SDEC could significantly reduce AVG stenosis and make AVGs the preferred modality for dialysis vascular access.

Funding: Other NIH Support - NIA

FR-PO472

Association Between Vascular Access Type and Health-Related Quality of Life
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Background: The use of arteriovenous fistula (AVF), arteriovenous graft (AVG), or central venous catheter (CC) may differently affect patients’ quality of life (QOL). We assessed the association between vascular access (VA) type and Kidney Disease Quality of Life Short Form (KDQOL–36) in a large, multinational sample of dialysis patients.

Methods: We enrolled 10148 European dialysis patients participating in the ePROM improvement program initiated in 8 European countries since September 2021. We assessed the association between the active vascular access type and KDQOL-36 subscales with generalized linear regression. All models were adjusted for potential confounders. We accounted for the multicenter design by including a random-intercept subscales with generalized linear regression. All models were adjusted for potential confounders. We accounted for the multicenter design by including a random-intercept factor in the intercept term.

Results: Catheter use was associated with statistically significant quality of life penalty in all KDQOL-36 subscales. However, the difference in score was very mild and did not reach clinical significance based on minimal clinically important difference estimation for all scales but the physical composite score (PCS12). Specifically, AVF was associated with 2-point better PCS12 scores, a small effect size difference.

Conclusions: Improving HRQOL of dialysis patients has been an elusive task as it may be associated with a multitude of factors which may require a multifaceted management approach. We found a small PCS12 advantage for AVF users which may be barely perceived as clinical important. Expanding AVF use may contribute to HRQOL improvement in combination with optimization of other modifiable clinical parameters.

Funding: Other NIH Support - NIA

FR-PO473

Increase in Hemodialysis Initiation with a Catheter
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Background: Reliable vascular access is essential for hemodialysis (HD). Initiating HD with an arteriovenous (AV) access rather than a catheter is preferred for most patients. We modeled recent trends in the percent of patients initiating HD with a catheter and no maturing AV access.

Methods: Using data from the US Renal Data System, we included all adults initiating HD between January 1, 2012 and September 30, 2022. We estimated the proportion initiating HD with a catheter only in each quarter, identifying a breakpoint in the temporal trend using segmented linear regression. We then fit a generalized piecewise linear model with a binomial distribution and identity link to estimate the temporal trend in catheter use before and after this breakpoint, with adjustment for age, sex, race/ethnicity, and seasonal effects.

Results: The analysis included 1,169,323 adults. A breakpoint was identified in March 2017 (Figure). In 2012, the overall proportion of patients initiating with a catheter only was roughly 60%. This proportion increased by 0.5% (95% CI 0.4-0.6%) per year, on average, until Q1-2017. After the breakpoint, the proportion increased more rapidly, by an average of 2.5% (95% CI 2.4-2.6%) per year, with nearly 75% of patients initiating HD with a catheter and no maturing AV access by 2022. Trends in catheter use before and after March 2017 were similar across categories of age, sex, and race/ethnicity. Other than a transient increase during Q2-2020, there was no enduring change in the pattern of catheter use during the COVID-19 pandemic.

Conclusions: We observed a concerning increasing trend in HD initiation with a catheter in the absence of a maturing permanent access between 2017 and 2022. The emergence of this trend in 2017 coincided with reductions for vascular access services in the Medicare Part B Physician Fee Schedule. Given further reductions in vascular access-related reimbursements occurred in 2023, trends in catheter use should be carefully monitored.

Funding: NIDDK Support

FR-PO474

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Background: Reliable vascular access is essential for hemodialysis (HD) initiation to decrease catheter (CVC) dependence. We quantified changes in vascular access between 2015 and 2019.

Methods: Using the USRDS database, we identified 536,667 patients initiating HD from 2015-19. Patients starting HD with an AVF or with a CVC and a maturing AVF were considered to have undergone pre-HD AVF placement. We examined patient demographics, co-morbidities, functional status, insurance status, and duration of pre-HD nephrology care. HD with an arteriovenous (AV) access rather than a catheter is preferred for most patients. We quantified changes in vascular access between 2015-19.

Results: Patients starting HD with a catheter and no maturing AVF by 2022. Trends in catheter use before and after March 2017 were similar across categories of age, sex, race/ethnicity. Other than a transient increase during Q2-2020, there was no enduring change in the pattern of catheter use during the COVID-19 pandemic.

Conclusions: We observed a concerning increasing trend in HD initiation with a catheter in the absence of a maturing permanent access between 2017 and 2022. The emergence of this trend in 2017 coincided with reductions for vascular access services in the Medicare Part B Physician Fee Schedule. Given further reductions in vascular access-related reimbursements occurred in 2023, trends in catheter use should be carefully monitored.

Funding: Other NIH Support - NIMHD
Deprivation, Caucasian cohort. There is a suggestion that lower decile patients were initiated earlier on dialysis and that middle-decile patients may have better access to fistulas compared to deciles 1 and 10.

FR-PO476
Effectiveness of Custom-Made Under-Table Shield in a Mobile C-Arm Fluoroscopy Unit
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Background: It is emphasized that interventionists should adhere to the “As Low As Reasonably Achievable (ALARA)” principle and radioprotection strategies. However, radioprotection is limited when performing interventional vascular access procedures using mobile C-arm fluoroscopy, because the under-table shields are challenging to be mounted on an arm board of the table in a mobile C-arm angiography unit. We modified commercial tools and implemented custom-made under-table shields to overcome these limitations in the radioprotection strategy. This study aimed to quantitatively analyze the protective effect of the shields using real-time dosimeters.

Methods: Commercial shields were tailored and modified to completely cover the angiography table equipped with an arm board (Figure 1A). Custom-made under-table shields completely covered the table and arm board in all directions to protect operators and assistants (Figure 1B). There was no radiopaque material between the table and arm board, so the shields didn’t interfere with the fluoroscopy-guided procedures (Figure 1C). To quantitatively measure the dose equivalent of radiation, real-time dosimeters (RaySafe i2) were located one meter and two meters away from the table (Figure 1D).

Results: Digital subtraction angiography was performed five times with eight pulses per second mode using a mobile C-arm fluoroscopy (GE OEC 9900 system), and the mean radiation doses were compared before and after applying the customized under-table shields. After application of them, the dose equivalent (μSv) was reduced by 34% at a 1-meter distance and 82% at a 2-meter distance, respectively (Figure 2).

Conclusions: Optimizing fluoroscopy settings and implementing radioprotective shields are crucial for ensuring safety. Under-table shields play a significant role in radioprotection strategy and should be emphasized. We customized commercial shields to overcome the limitations of radioprotective strategies in mobile C-arm fluoroscopy settings, and the shields proved effective in reducing the radiation dose.
haemodialysis catheter rewiring practices among Australian nephrology services, and to determine whether rewiring was associated with infection.

Methods: In a post-hoc analysis of the national stepped wedge cluster randomized REDUCTION trial, encompassing 37 nephrology services and 6399 adult patients, we examined variation in the service-wide proportion of tunneled catheters that were replaced by rewiring, for infectious or non-infectious reasons. Given the findings, we compared the absolute risks of, and time to infectious removal between rewired and non-rewired (new exit site) catheters that replaced failing non-infected catheters. Marginal Cox and competing risk proportional hazard models, including catheter, patient, and service-level covariates were used. Confirmed bloodstream infections were assessed in sensitivity analysis. Competing risks included removal for dysfunction and death before removal.

Results: Services universally avoided rewiring infected catheters but varied widely in rewiring non-infected failing catheters (range = 0 – 80% rewired). Among new catheters that replaced failed non-infected catheters, 36 of 480 rewired (7.5%), and 36 of 372 non-rewired (9.7%) were removed for infection. At three months the cumulative incidence of premature infections and mechanical removals was 5% and 21% for rewired and 7% and 23% for non-rewired respectively. The hazard of infections removal did not differ between rewired and non-rewired catheters (adjusted HR 0.81, 95% CI 0.46, 1.42). The incidence of confirmed catheter-related bloodstream infections and catheter dysfunction requiring removal were similar between groups.

Conclusions: The practice of rewiring non-infected failing catheters varied widely between services, was not associated with catheter infection, and did not appear to affect the high rate of subsequent catheter dysfunction in this population.

Funding: Government Support - Non-U.S.

FR-PO478
Burden of Haemodialysis Catheter-Related Bloodstream Infections in Australia: A National Data-Linkage Study
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Background: Haemodialysis catheters are widely used and prone to infection, but the health impact of these infections is unknown. We aimed to quantify the health burden of haemodialysis catheter-related bloodstream infection (HDCRBSI) among chronic haemodialysis patients in Australia.

Methods: Patients who commenced chronic haemodialysis via a catheter in the REDUCTION trial (Dec 2016- Mar 2020) were followed from first catheter insertion to the time of catheter removal or end of the trial. Hospitalizations in all States and Territories (except WA) were probabilistically linked and classified using the principal ICD-10-AM diagnostic code. Same-day admissions were excluded. Hospitalizations for vascular access infection (VAI) or bacteraemia, with concurrent HDCRBSI reported at time of admission, were characterized.

Results: In REDUCTION, 4004 patients commenced chronic haemodialysis via a catheter and were followed for 968,783 days, with baseline characteristics comparable to the Australian haemodialysis population. Infection was coded as the primary reason for hospitalization in 16,10,154 days and accessed for 18,982 (24.1%) of 78,696 total days in hospital. Mean duration of hospitalization for VAI (3649 total days, 377 admissions) and bacteraemia (5981 total days, 391 admissions) were longer than for pneumonia (2183 total days, 361 admissions) or cellulitis (1535 total days, 139 admissions; all p<0.01). Concurrent HDCRBSI at time of hospitalization was reported in 148 admissions, 122 (82%) with primary code for VAI or bacteraemia. The median length of stay was 9 days (IQR 5-15), 19 (15.6%) admissions required intensive care (median 64 hours, IQR 27 – 110), 10 (8.2%) were complicated by metastatic infection, and 4 (3.3%) resulted in death.

Conclusions: Catheter-related infections are a major source of infectious hospitalization among Australians receiving chronic haemodialysis via a catheter.

Funding: Government Support - Non-U.S.

FR-PO479
The Magnetic Snare Endovascular Catheter System for Central Venous Stenosis
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Background: Central venous stenosis (CVS) is a common complication in patients with End Stage Kidney Disease undergoing hemodialysis, and most commonly occurs after exposure to tunneled dialysis catheters. CVS can lead to vascular access failure and can be associated with life threatening. Sharp needle recanalization is an option for recanalization when a lesion can be approached bi-directionally, i.e. from the femoral vein and the internal jugular vein, however this procedure carries a high-risk of mediastinal perforation, which can be rapidly fatal. A novel two catheter system, the Magnetic Snare Endovascular Catheter (patent pending PCT/US23/62960), utilizing magnets to approximate either end of the stenosis has recently been developed to address this problem and improve safety of the recanalization procedure.

Method: Mechanical engineering students at the University of New Mexico were recruited to develop an initial prototype of the catheter system. After initial success, one of the graduates was retained for further work and development of additional working prototypes.

Results: Three distinct prototype catheter systems have been developed for further testing. The first prototype utilizes a neodymium to neodymium magnetic tip and would traverse a central stenosis using thermal or radiofrequency energy. The second catheter design utilized a broad-based neodymium magnet on one catheter, and a needle fashioned from neodymium on the opposite catheter. The final prototype consists of a powerful electromagnetic tip that would be used to attract conventional steel needles and guidewires from the opposing side.

Conclusions: The Magnetic Snare Endovascular Catheter system is a promising technology to improve safety of central venous stenosis recanalization. Three working prototypes are now developed for additional testing.

Funding: Private Foundation Support

FR-PO480
Initial Testing of a Novel Vascular Access Device in a Rabbit Model
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Background: Ideal vascular access for dialysis is the arteriovenous fistula (AVF). However, AVF have delays in maturation or frequently fail to mature. Arteriovenous graft (AVG) mature more quickly but are prone to thrombosis and have higher incidence of infection. Tunneled dialysis catheters (TDC) can be placed rapidly but have the greatest incidence of infection. Recently, a novel vascular access device was created using a titanium needle guide to be inserted around an artery and separately a vein, allowing the placement of a modified removable shunt. The device could be usable for dialysis rapidly and obviate need for AVF or AVG placement. Feasibility of this device was achieved previously in a porcine model. A rabbit model is sought in this study to expand testing and to examine the effects of repeated arterial cannulation.

Methods: A male New Zealand white rabbit was obtained. After a 2-week acclimation, the animal was anesthetized, the right femoral artery dissected, and the vascular access device attached around it. The device was secured with dissolvable suture, and site closed in three layers. The animal was recovered uneventfully, and after two weeks the site was well healed. The femoral artery was then cannulated via the device twice per week, with 2.5 mL blood withdrawn during each cannulation, for a total of 4 weeks, after which the animal was euthanized and submitted to pathology for examination.

Results: The vascular access device installed easily and without complication. The surgical site healed well with no visible signs of ischemia, trauma, or discomfort. All arterial access cannulations were successful with bright red arterial blood aspirated. After euthanasia, the femoral artery within the device was found to be intact, without neointimal hyperplasia or thrombosis on histologic examination. No visible signs of ischemia in the femoral artery vascular bed were seen. A small amount of neointimal hyperplasia was seen within the adjacent femoral vein, felt most likely secondary to manipulation and dissection from initial surgical implantation.

Conclusions: The novel vascular access device was successfully implantable in a rabbit model. The device allowed for repeated arterial cannulations as intended. No visible damage of the femoral artery was observed after 8 repeated arterial cannulations over four weeks.

FR-PO481
Achromobacter xylosoxidans: A Potentially Serious Occult Dialysis Catheter-Related Infection
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Introduction: Hemodialysis(HD) catheter-related infection is one of the major causes of morbidity and mortality in HD patients. Achromobacter xylosoxidans (AX) is an aerobic, oxidase, and catalase-positive gram-negative bacillus that lives in various
aqueous environments. There are reported cases of AX endocarditis, bacteremia, and an outbreak of AX bacteremia in a hemodialysis unit; however, after thorough literature review, no case of isolated AX hemodialysis tunneled catheter infection was found. Therefore, we are reporting a case of an AX tunneled dialysis catheter infection causing sepsis.

Case Description: A 50-year-old African American man with a past medical history of end-stage kidney disease on hemodialysis for more than one year, hypertension, and hyperlipidemia, who had recently returned from Africa, presented with a low-grade fever, chills, and lethargy. While in Africa, the patient received hemodialysis via a right internal jugular catheter placed with an unknown antibiotic in Africa for 14 days. However, his fever never resolved. On return to the United States, peripheral and tunneled catheter blood cultures revealed no growth, and no other focus of infection was identified. Chest x-ray and CT scan abdomen were unremarkable for any focus of infection. Repeat blood cultures were negative for viruses and atypical bacteria. As an inputant, in spite of receiving ceftriaxone and vancomycin for more than two weeks, he was still febrile despite repeat negative peripheral blood and central line cultures; therefore, a decision was made to remove the tunneled catheter and send the catheter tip for culture, which showed growth of aeromonas xosoxidans(two too numerous to count). It was resistant to a variety of antibiotics; however, sensitive to meropenem. He was treated with meropenem, and his fever resolved following the removal of the tunneled catheter.

Discussion: Aeromonas xosoxidans is an aerobic, oxidase, and catalase-positive gram-negative bacillus living in various aqueous environments with low virulence. It can cause occult dialysis catheter-related infections and be challenging to identify and treat. Strains of AX are highly resistant to various antibiotics and should be treated with appropriate antibiotics, usually sensitive to antipseudomonal penicillin, levofloxacin, meropenem, and trimethoprin-sulfamethoxazole.

FR-PO482
Should Alcohol Lock Replace Antibiotic Lock in Catheter-Related Bloodstream Infection (CRBSI) Management?
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Background: Catheter related blood stream infection (CRBSI) is a dreaded complication of Tunneled Cuffed Catheter (TCC), with a reported incidence of 1-5.5 episodes/1000 catheter days. Patients with Staphylococcus aureus, Pseudomonas aeruginosa or fungal growth generally require catheter removal. As per the KDOQI clinical practice guideline for vascular access: 2019, Systemic antibiotics plus antibiotic lock is the current standard of care for CRBSI. This study was done to find the usefulness of 70% alcohol lock (in place of antibiotic lock) in patients with established CRBSI.

Methods: All dialysis patients with TCC as vascular access were the subjects of the study. As per our center’s protocol, all patients were given heparin lock after each session of dialysis. CRBSI was diagnosed as per CDC/IDSA criteria. In patients with CRBSI, 70% alcohol lock (2 ml in each port) was given for 3 consecutive days, in addition to systemic antibiotics. Outcome of these patients was studied and compared with retrospective controls, who were given ‘antibiotic lock with systemic antibiotics’.

Results: Over the last two years 188 TCCs were placed in 181 patients at our center. Our CRBSI rate was 1.38/1000 catheter days. We encountered 31 episodes of CRBSI in 23 patients. There were 16 males and 7 females, with mean age of 57.03 ±11.65 years. Presentation was with fever and chills in 80.6% and hemodynamic compromise in 20%. Relevant investigations showed raised leucocyte count in 23 (74.1%) and procalcitonin in 27 (87.9%) episodes. The etiological agents were gram positive organisms in 12 (38.7%) and gram negative infections in 19 (61%) episodes; Staphylococcus aureus was isolated in 11 and albus in 1, Pseudomonas aeruginosa in 6, Klebsiella pneumonia in 8, citrobacter in 3 and E coli in 2 episodes. Only 4 cases required catheter removal. Over a mean follow up period of 145 days after alcohol lock, neither heparin lock was functioning well. On comparison with our retrospective data of 22 patients with CRBSI who were given antibiotic lock, 15 required catheter removal. The difference in catheter salvage is statistically significant (p<0.001). Our study shows that alcohol lock with systemic antibiotics works as panacea.

Conclusions: Our single center data suggests that alcohol lock works wonder in the management of CRBSI and can be included in the current standard of care.

FR-PO483
Clinical and Demographic Characteristics Associated with Arteriovenous Access-Related Infections in US Patients Initiating Hemodialysis
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Background: End-stage renal disease (ESRD) patients are dependent on successful arteriovenous (AV) access for continual hemodialysis (HD). Infection risk can be reduced due to early initiation of HD therapy by patients in order to mitigate new risk associated with HD establishment. The aim of this study was to describe demographic and clinical factors associated with access-related infections (AVI) for patients initiating HD.

Methods: Patients aged 18+ years initiating HD at Fresenius Kidney Care (FKC) clinical facilities in the U.S. between 01/2018 and 01/2019 were followed for up to 18 months, with censoring due to death or loss to follow-up. Patient characteristics were compared between those who developed an AVI (defined as graft infection or bloodstream infection) to those who did not. Data were stratified by gender, age range, and diabetes status. Univariable models were constructed and odds-ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: Among the 87,707 HD incident patients, 43% were female, 56% were white, and 41% were 65 years of age or older. The incidence of AVI was highest among the youngest age group (18-45), particularly, women (Figure 1). At 18 months, women aged 18-45 (OR: 1.3, CI: 1.2-1.35 vs. aged 45-64) and patients with type 1 diabetes (T1DM) were at high risk for AVI (OR: 1.4, CI: 1.2-1.6 vs. non-DM patients) (Figure 2). AVI risk was highest among younger women with T1DM (OR: 1.65, CI: 1.24 - 2.2 vs similarly aged non-DM patients). Patients with multiple access changes whose initial vascular access was an AV graft were among the highest risk compared to the overall population. Indigenous patients also had elevated AVI risk (23% by month 18) and were more likely to have multiple AV access change.

Conclusions: Younger women with T1DM had the highest AVI risks compared to those without DM, men, and older patients. Multivariate modeling of this sub-population is required to assess the interplay of other factors mediating the risk of these poorer outcomes.

Funding: Commercial Support - Humacyce, Inc.

FR-PO485
The Vasa Vasorum Is the Gateway to Vascular Inflammation Determining Arteriovenous Fistula Outcomes
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Background: Postoperative vascular inflammation is believed to contribute to arteriovenous fistula (AVF) maturation failure. However, the cellular mechanisms controlling inflammatory cell recruitment and inflammation resolution after anastomosis remain obscure.

Methods: In this work, we used for the first time a combination of single-cell RNA sequencing (scRNAseq) and histologic validations to reveal the place of entrance of inflammatory cells into the venous wall following AVF creation.

Results: Analyses of vascular tissues collected in the first week after AVF creation demonstrate an extensive infiltration of leukocytes in the media and adventitia and less so in the intima. Interestingly, these AVF showed a notable expansion of vasa vasorum (VV) number and size. Next, we characterized the cellular composition of cells forming the VV of pre-access veins and AVF using scRNAseq and validated our findings by immunofluorescence. Single-cell profiling of endothelial cells (ECs) identified markers for arterioles, capillaries, and venules. Immunofluorescence staining demonstrated an abundance of capillaries throughout the entire wall, venules in the outer media and adventitia, and a comparatively smaller number of arterioles in the outer adventitia. Vascular ECs had significant upregulation of adhesion molecules with respect to the other endothelial subsets, indicating they may act as docking sites for leukocyte infiltration. This work demonstrates a diversity of VV in the walls of veins and constitutes an important foundation for the study of intramural vascularization in vascular access remodeling.

Conclusions: In our study, we strongly support the importance of the VV network, and particularly venules, in postoperative inflammation and AVF outcomes. These results also support the paradigmal delivery of drugs targeting neangiogenesis and microveSEL permeability as future treatments to improve vascular access outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

FR-PO486
Analysis of the Arteriovenous (AV) Fistula Maturation in Eastern North Carolina and Validation of the Failure to Maturity Equation
Akil S. Kavacoglu.1 Ikra Myser.2 East Carolina University Brody School of Medicine, Greenville, NC; 2East Carolina University, Greenville, NC.

Background: AVF is the preferred vascular access for hemodialysis patients but has a high maturation failure rate. Lok et al developed a clinical prediction tool to identify AVFs at risk for Failure to Maturity (FTM) and it has achieved good prediction accuracy. We aim to examine the AVF success rate at 6 months and validate the FTM equation in patients with AVF in Eastern North Carolina.

Methods: The retrospective cohort study was done to identify patients who received AVF as their first HD access from 12/01/2009 to 12/10/2020. The primary outcome variable was FTM. The operating characteristic (ROC) curve of the equation was compared to our patient cohort and compared with the observed clinical outcomes using Receiver Operating Characteristic (ROC) curve. Univariate and multivariate logistic regression analyses were used to assess the association between the clinical predictors and AVF maturation. A nomogram was developed based on the coefficients from the multivariable model, and the weight (point) was given based on the regression coefficient.

Results: A total of 162 patients were found; the mean age was 55 years (SD:13.3), 41% were females, and 89% were African American. The failure to maturation rate at 6 months was 3.5%. Compared to the FTM cohort, there were statistically significant differences in age, ethnicity, BMI, presence of diabetes, CAD, and PVD(p<0.05).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Ununderline represents presenting author. 536
Univariate logistic regression showed PVD was associated with increased arteriovenous fistula failure (OR = 2.07; 95% CI = 1.05–4.09; p = 0.05). When results were adjusted for confounders on multivariate analysis odds ratio was 1.8 with a p-value of 0.08 (CI 0.91-3.8). The failure to maturation equation failed to predict maturation outcomes with the area under the curve performance of 0.587. We also developed a different scoring system by using coefficient values of Hypertension, PVD, and CAD, calculated with multivariate analysis but AUC on the ROC was 0.63 with the new scoring system.

**Conclusions:** The failure to mature equation failed to predict fistula maturation failure in our cohort. The difference in characteristics between cohorts is the likely reason.

**FR-PO486**

Metabolomic Analysis of Plasma Samples Collected Before Arteriovenous Fistula Creation Reveals Metabolome Clusters that Associate with Maturation Outcomes

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**Background:** The Manchester Vascular Access study was a prospective observational study intended to investigate the natural history and maturation of arteriovenous fistulas (AVF). We aimed to identify biomarkers that predict maturation success already before AVF creation.

**Methods:** Plasma samples were obtained before AVF creation. Unassisted maturation was defined either by successful hemodialysis or a combination of ultrasound features (vein size > 4 mm with fistula flow ≥ 500 ml/min) and clinical assessment. Untargeted metabolomic analysis employed liquid chromatography-mass spectrometry. Hierarchical clustering and principal component analyses were performed to cluster patients using 819 metabolite features. We used Chi-square test to explore differences in demographics, comorbidities, and AVF maturation between clusters.

**Results:** We studied 44 patients. Metabolomic analysis revealed 2 clusters (Cluster 1: 21 patients, Cluster 2: 23 patients) with diverse levels of plasma metabolites (Fig. 1). There was a significant statistical difference in unassisted maturation rates between the two clusters (Cluster 1: 85.7% vs. Cluster 2: 43.5%; p=0.0095). No significant differences between the clusters were found with respect to variables commonly associated with maturation (age, sex, diabetes, and cardiovascular disease).

**Conclusions:** In this cohort, we observed 2 clusters of metabolomic signatures associated with successful and unsuccessful AVF maturation, respectively. If corroborated in a larger cohort, metabolomic analysis could help identify biomarkers that predict AVF maturation success or failure already prior to AVF creation, thus allowing individualization of vascular access planning. Future targeted metabolomic analysis may also shed light on biological pathways related to AVF maturation.

**Funding:** Commercial Support - Fresenius Medical Care

**FR-PO487**

Deficient Endothelial Autophagy Promotes Accelerated Atherosclerosis and Impaired Arteriovenous Fistula (AVF) Remodeling

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**Background:** Arteriovenous fistulas (AVFs) are the preferred vascular access for hemodialysis patients. Atherosclerosis is highly prevalent in arteries of patients with Chronic Kidney Disease undergoing hemodialysis. We investigated the role of macroautophagy in the venous region of the AVF in an atherosclerotic mouse model.

**Methods:** At 8-12 weeks of age endothelial cell autophagy-related 7 gene knockout mice with LDLR gene deletion (ecAtg7−/−) and mice where the LDLR gene was deleted (LDLR−/−) were introduced to a high fat diet for 3 months before AVF creation surgery. Subsequently, mice underwent AVF surgery using the carotid artery and jugular vein. At day 7 blood flow in the AVF vessels was measured and mice were sacrificed, and histology and oil red staining were performed.

**Results:** Intimal hyperplasia was significantly greater in the AVF vein in ecAtg7−/− and LDLR−/− mice compared to LDLR+− mice (p<0.04). Collagen deposition was significantly greater in the AVF arteries and veins in the ecAtg7−/−LDLR−/− mice compared to LDLR+− mice (p<0.01). Oil red staining in the AVF was significantly greater in ecAtg7−/−LDLR−/− mice compared to LDLR−/− mice (p<0.01). There was a trend towards increased blood flow in AVF vein and arteries in LDLR−/− mice compared to AVF vessels in ecAtg7−/−LDLR−/−.

**Conclusions:** Autophagy may play an important role in AVF maturation by worsening atherosclerosis and arterial remodeling, which subsequently impacts vein remodeling.

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

**FR-PO488**

Phenotypic Switch Study in Cultured Arterial and Venous SMCs: Messages for the Future Development of Novel Therapies for Vascular Access Dysfunction

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**Background:** Smooth muscle cell (SMC) dedifferentiation, proliferation, migration, and extracellular matrix protein secretion are key events in the progression of SMC phenotypic switch and the development of intimal hyperplasia (IH) as well as negative vascular remodeling, which is responsible for arteriovenous access (AVF and AVG) failure. Previous studies have demonstrated differences in proliferation between venous (vSMC) and arterial SMCs (aSMC) but have not attempted to characterize specific pathways in this process. We herein aim to characterize the role of IRS-1-KLF-4-p53 pathway and other dedifferentiation related pathways regulating SMC phenotypic switch in pig vSMCs and aSMCs.

**Methods:** To reach the SMC differentiation stage before applying phenotypic switch stimuli, confluent cells were exposed to differentiation medium (DM, containing 1%FBS, 1% P/S and 30μg/ml heparin) for different time periods. A hyperglycemic milieu was created through the addition of 20 mM glucose 24-48hr before harvesting/treatments. PDGFBB or IGF-1 was applied to create a dedifferentiation milieu for different durations. Cellular expression of proteins of interest were assessed using either immunofluorescence (IF) staining or Western blots.

**Results:** Hyperglycemia significantly suppressed myocardin expression and enhanced KLF-4 expression in both cell types. IRS-1 suppression in response to hyperglycemia,
Impact of Arteriovenous Fistula (AVF) Dysfunctional and Repeated Endovascular Procedures on AVF Intervention-Free Survival

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Background: Endoluminal and surgical procedure effectively re-establish patency of dysfunctional Arteriovenous Fistulas (AVF); however, repeated intervention may reduce overall vascular access survival. We previously developed a risk score predicting AVF failure within 3 months that shows high accuracy and reproducibility. To enhance score interpretability we sought to assess its association with AVF intervention-free survival among patients with previous intervention to re-establish vascular access patency.

Methods: We included all patients receiving in-center hemodialysis therapy with an AVF in Nephrocare Portugal network between January 1st, 2015 and December 30th, 2022. We abstracted data from the European Clinical Database (EuCliD). We used generalized linear models to assess the association between the AVF failure risk score and intervention-free survival by the number of previous endoluminal interventions.

Results: We included 4,668 AVFs from 4,355 patients in the analytical dataset. Whereas patients with previous multiple endovascular procedures were common, only a small minority had more than 3 procedures. Both the AVF risk score class (p=0.01) and the number of previous endoluminal interventions (p<0.01) independently predicted AVF intervention-free survival (Fig. 1).

Conclusions: AVF intervention-free survival was associated with both AVF risk score classes and the number of previous endovascular procedures; both factors should be considered in evaluating the risk-benefit ratio of additional endovascular procedure against alternative interventions for dysfunctional AVFs.

AVF intervention-free survival (in days) with respect to the number of previous endovascular procedures and AVF failure risk class

FR-PO491
Initial Vascular Access Flow Rate for Early Prediction of Need for Intervention: A Retrospective Cohort Study

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Background: Arterio-venous fistula (AVF) or graft (AVG) are lifelines for most hemodialysis (HD) patients. Low access flow rate (AFR) often requires intervention to prevent access failure. This study examines if AFR, measured at initial AVF/AVG cannulation, predicts need for intervention in the first year.

Methods: From 2012 to 2021, 52 (30.7%) of 169 patients with surgical AVF/AVG creation had AFR measurements. Up to three values were collected per subject. Need for access intervention within one year was documented.

Results: Of 52 subjects, 28 (53.8%) required access intervention. After stratification by need for intervention (data not shown), patient characteristics were not significantly different. However, first AFR was significantly lower in the group with access intervention (898±495 vs. 1471±777mL/min; P=0.003), as was average AFR (841±399 vs. 1506±700mL/min; P=0.001). Receiver-operating characteristic (ROC) curve analyses (Figure 1 and Table 1) showed that first AFR (area-under-the-curve [AUC] 0.743; 95% CI 0.608, 0.877) and average AFR (AUC 0.775; 95% CI 0.648, 0.903) predicted need for access intervention within one year.

Conclusions: In HD patients, early AFR measurements can predict access intervention within one year after initial access cannulation. Our results are limited by single center setting and small sample size. Further studies are needed to determine optimal AFR cut-offs that indicate AVF/AVG at higher risk of early stenosis.
Figure 1. Receiver operating characteristic (ROC) curve showing diagnostic performance of first and average access flow rates (AFR) in new arterio-venous fistulas (AVF) and grafts for predicting need for intervention within one year.

Table 1. Area-under-the-curve (AUC) shows good diagnostic performance of access flow rate (AFR) for predicting patent-assisted intervention within one year.

FR-PO493

Autosomal Dominant Polycystic Kidney Disease Results in Increased Flow in Murine Arteriovenous Fistulas


Background: Autosomal dominant polycystic kidney disease (ADPKD) is a renotubular disease caused by mutations in the PKD1/-2 gene. ADPKD is the most common monogenic kidney disorder, affecting 10% of end-stage kidney disease (ESKD) patients. The arteriovenous fistula (AVF) is the gold standard of hemodialysis vascular access, although non-maturation due to inadequate vascular remodeling is a major limitation of these conduits. Polycystins are expressed in endothelial and vascular smooth muscle cells, and involved in production of extracellular matrix supporting the vessel wall and mechanosensation. In the present study, we investigated whether reduced expression of Pkd1 impacts vascular remodeling in a murine model of AVF failure.

Methods: Unilateral jugular-carotid AVFs were created in adult B6OlaPkd1+/− mice and wild-type litter mates. Blood pressure was measured using a tail cuff, before and after six days after AVF-surgery. Flow volume was measured weekly over three weeks post-AVF creation using doppler ultrasound. After three weeks, the mice were sacrificed and AVFs were used for histological analysis and collagen analysis through multiphoton microscopy. Longitudinal flow data was analyzed using Mixed-effects model, histological data using the Mann-Whitney U test.

Results: B6OlaPkd1+/− mice show signs of renal failure, with cystic kidneys and elevated blood urea levels throughout the study. Pkd1−/− mice had elevated mean arterial blood pressure at both timepoints compared to WT mice (1.2 and 1.3 fold increase in ADPKD mice). Whereas arterial flow was comparable in both groups before surgery, AVF flow in Pkd1−/− mice was consistently higher post-AVF creation (1.9 fold difference, p=0.0002, at all time points). There was no difference in luminal area between the two groups, nor aneurysm formation in the afferent artery. Histological analysis revealed a reduction of collagen deposition in the venous outflow tract in Pkd1−/− mice at 21 days post-surgery.

Conclusions: AVFs in mice with ADPKD are characterized by a higher flow and reduced collagen deposition in the venous outflow tract, when compared to wild type mice. Clinical studies should reveal if ADPKD patients have better primary patency rates of their AVFs compared to patients with other causes of ESKD.

FR-PO494

Arterio-Venous Shunt and Right Heart Function and Structure


Background: Emerging evidence suggests that right ventricular dysfunction (RVD) is a major determinant of adverse health outcomes. Data regarding the effect of AV shunt (AVS) placement on right heart function (RHF) and right heart structure (RHS) are sparse.

Methods: We conducted a cross-sectional study on patients with advanced CKD or ESRD who were followed by URMC nephrology faculty. We identified subjects who underwent an ambulatory echocardiogram within 90 days of AVS creation (Pre) and another ambulatory echocardiogram at least six months after AVS creation (Post). Original echocardiographic images were re-read to focus on RHF and RHS. Measures of RHF included: Tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RVFAC). Measures of RHS included length and diameter in systole and diastole. Changes between first and second echocardiograms were assessed. Continuous variables were analyzed by paired T-test. Categorical variables were analyzed by the McNemar test.

Results: Between 1/1/2010 and 12/31/2022, 1319 advanced CKD or ESRD patients under our care underwent at least one echocardiogram and/or underwent AVS creation. Thus far we have identified 39 subjects who met the criteria of having Pre and Post ambulatory echocardiograms that have interpretable measurements for the right heart. Selected subject characteristics are summarized in table 1. Selected echocardiographic changes are summarized in table 2.

Conclusions: Changes consistent with worsening RHF and RHS are observed in patients who underwent AVS construction. The observed population deterioration may have been attenuated due to survival bias as only subjects with two ambulatory echocardiograms at least six months apart were considered for analysis. Future efforts include adding a comparator group of failed AVS creation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO495

Time-Dependent Efficacy of Percutaneous Angioplasty with Drug-Coated Balloon in the Treatment of Stenosis of Arterio-Venous Fistulae: A Retrospective Study
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Background: Percutaneous transmural angioplasty (PTA) is the first-line treatment for stenosis of the arteriovenous fistulae (AVF). Even if paclitaxel drug-coated balloon (DCB) has become the standard of care, trials testing efficacy in comparison with standard PTA has provided conflicting results. We tested the hypothesis that conflicting findings from trials may result from the effect of DCB being short-lived.

Methods: We enrolled all patients undergoing angioplasty AVF stenosis with PTA or DCB 01/2011 to 04/2022 at the Parma dialysis centre. The choice of PTA vs. DCB depended on the temporary supply of each device. AVF patency was assessed after the procedure and at monthly intervals until month 12. We compared the hazard of AVF failure using interval-censored Cox multiple regression model, with the procedure (DCB vs. PTA) being included as a time-varying effect (i.e. interacted with time), and the standard errors adjusted for accounting of multiple procedures within the same patient.

Results: We retrospectively examined 146 procedures (in 143 subjects), 69 with PTA and 77 with DCB. Baseline features were similar between groups, apart from DCB performed most often in patients with multifocal stenosis (22.1 vs. 1.4%; P < 0.001) and with previous AVF (76.6 vs. 58%; P = 0.021), but less often with cardiovascular disease (46.8 vs. 69.6%; P = 0.007). Figure 1 shows crude AVF patency over the follow-up: survival curves diverged shortly after the procedure and eventually converged. Adjusted for different variables, the hazard of AVF failure was halved with DCB compared to PTA after the procedure (adjusted hazard ratio aHR 0.48 [95% CI: 0.26–0.97; P = 0.016]); then, benefit vanish over time and aHR increasing (toward the null value of 1) by 1.20 per every month elapsed since the procedure (95% CI: 1.07–1.34; P < 0.001).

Conclusions: Compared to PTA, DCB provides significant short-term benefit which vanishes by 12 months after the procedure.

FR-PO496

Differences in Vascular Access Can Influence the Level of Thrombo-Inflammation and Oxidative Stress in Patients with Hemodialysis
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Background: Patients undergoing hemodialysis require vascular access which includes arteriovenous (AV) fistula, AV graft, and tunneled catheter. At these sites, changes in the vessel wall result in a positive feedback loop that propagates inflammation and cell proliferation which can progress to stenosis and thrombosis. This study was designed to compare the levels of biomarker of thrombo-inflammation and oxidative stress in patients with ESRD requiring different vascular access sites.

Methods: A prospective cohort of 95 patients undergoing hemodialysis at Loyola University Chicago were compared to 50 normal healthy individuals. The ESRD patients were stratified according to the vascular access sites. All plasma samples were analyzed for D-Dimer, PAI-1 antigen, vWF, CRP, annexin V, MPO, nitrotyrosine, eNOS, IL4, IL6, IL10, VEGF, and EGF by using sandwich ELISA methods and Random Biochip Array.

Results: The ESRD patient cohort included 48 male and 47 female, with the median age 66-years, weight 77-kg and BMI 27.2-kg/m². The levels of thrombo-inflammation and oxidative stress marker were significantly (p < 0.05) higher in ESRD patients while MPO, IL4, and IL10 were significantly (p < 0.05) lower in ESRD patients compared to normal controls. The biomarker profiles demonstrated that various markers of thrombo-inflammation and oxidative stress were significantly elevated in patients with various vascular access types (table 1).

Conclusions: These studies suggest that ESRD patients with the AV fistula are at high risk of fibriolytic deficit, inflammation, and oxidative stress they are at low risk of thrombosis. Patients with AV graft and tunneled catheter are at high risk of inflammation, oxidative stress, and thrombosis.
105.3±SD-53.6d; 21 patients undergone Fistuloplasty. Mean patency of AVF -1.03Yr. peritumstomastic stenosis -71.4%, outflow stenosis -19.04%, inflow stenosis-9.52%. Fistuloplasty was successful in 85.7% cases. Mean fistula flow volume-110.47ml/min(SD-79ml/min)(pre) 438ml/min(SD-244.9 ml/min)(post). 4 cases developed restenosis complications-minor bleeding-6 cases, venous rupture in 2 and brachial artery pseudoaneurysm in 1 case.

Conclusions: This outcome analysis suggests that central venoplasty and fistuloplasty have very good outcome in the management of access issues in ESRD patients, but cost and restenosis are the main limiting factors.

Types of AVF

<table>
<thead>
<tr>
<th>Access Type</th>
<th>Fistuloplasty</th>
<th>Pseudoaneurysm</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Patients</td>
<td>57.14%</td>
<td>26.57%</td>
</tr>
</tbody>
</table>

FR-PO498

Safety and Efficacy of a Novel Compression Hemostatic Device for Vascular Access: A Quality Improvement Study

Mohamed Modar Abidian,1 Rodella Broxton-Key,2 Forest Rawls,2 Vandana D. Niyyar,1 Emory University School of Medicine, Atlanta, GA; 2Emory Healthcare, Atlanta, GA.

Background: Arteriovenous fistulas (AVF) and arteriovenous grafts (AVG) are common types of vascular access for chronic hemodialysis (HD) patients that require frequent needle cannulations. Proper cannulation and decannulation techniques are important for achieving hemostasis and preventing complications from bleeding. After decannulation, most protocols require manual pressure at vascular access sites to prevent bleeding. A novel compression device with a simple manual inflation/deflation pump has been developed to achieve post decannulation hemostasis. The purpose of this quality improvement (QI) study was to assess the safety and effectiveness of such a device in our clinical practice.

Methods: Our protocol for using the device is detailed in Figure 1. All patients who had HD with either AVF or AVG and were having manual pressure for hemostasis were eligible for the study. Efficacy outcome was achieving post decannulation homeostasis within 15 minutes. Safety outcome measures were prolonged bleeding (more than 15 minutes), access thrombosis, and local infection. Patient satisfaction surveys were performed using the Likert scale.

Results: We evaluated 166 HD sessions using the compression device in 28 patients. There were no access infections or thrombosis. Only 1 (0.03%) episode of prolonged bleeding post decannulation in a patient who was on warfarin therapy. Almost all patients preferred the device to manual compressions and the average satisfaction rate was 4.6/5.

Conclusions: This novel device was safe and effective in achieving post-decannulation hemostasis and was preferred to manual compression by patients at our center.

Funding: Commercial Support - No financial payment was received by the manufacturing company Sun-Scientific as the device was donated free of cost.

Table 1. Incidence Rate of Complications

<table>
<thead>
<tr>
<th>No of patients</th>
<th>Total No. of HD sessions performed using the device</th>
<th>No. of prolonged bleeding (1/5 per patient)</th>
<th>No. of access infections</th>
<th>No. of local infections</th>
<th>Average patient satisfaction (1-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>166/5.3 per patient</td>
<td>1 (0.06%)</td>
<td>0.0%</td>
<td>0.0%</td>
<td>4.5</td>
</tr>
</tbody>
</table>

FR-PO499

Brachial Artery Pseudoaneurysm (BAP): A Rare Cause of Median Nerve Neuropathy

Huy Truong, Hira H. Al-adroos, Mohamed Z. Ghyaz, Dalia Dawoud. Riverside Community Hospital, Riverside, CA.

Introduction: BAP, a complication in long-term hemodialysis (HD) patients, often develops without symptoms but can rarely lead to median nerve neuropathy. Differentiating between causes of the neuropathy is crucial due to distinct treatment approaches, but it is challenging and can result in severe consequences. This case report aims to raise awareness of BAP as a possible diagnosis for HD patients with the neuropathy.

Case Description: A 53-year-old man with end-stage renal disease undergoing HD via a left brachiobasilic arteriovenous fistula (AVF) presents to the hospital with pain and weakness in his left first three fingers for three weeks. Patient had a history of difficulty with AVF cannulations, but his HD sessions were able to be completed fully. During a thrombectomy for AVF thrombosis outpatient, a brachial artery pseudoaneurysm was incidentally discovered through a retrograde arterial angiogram. The patient underwent surgical intervention, which relieved the pain but did not fully restore motor function due to prolonged compression of the median nerve.

Discussion: BAP warrants prompt recognition in patient’s presenting with median nerve neuropathy or pain at AVF sites. Symptoms may mimic other etiologies such as distal hypoperfusion ischemic syndrome. However, BAP can develop when there is arterial infiltration, especially in the patient whose AVF body overlaps with the feeding arteries. Therefore, it is crucial to educate dialysis staff not only on proper cannulation techniques but also on the mentioned anatomical variation. Additionally, physicians should consider arteriography to exclude the presence of arterial pseudoaneurysm in patients with progressing neuropathy, particularly those who have a history of difficulty with cannulation, to prevent prolonged nerve ischemia.
FR-PO501

mTORC2 Coordinates Renal Gluconeogenesis and Glucose Reabsorption


Background: The proximal tubule is uniquely responsible for both gluconeogenesis (GNG) and glucose reabsorption from the filtrate. Insulin signaling in the proximal tubule suppresses gluconeogenesis and stimulates glucose transport. However, the coordinated regulation of these processes is poorly understood. The kinase mTORC2 is regulated by insulin signaling in multiple cell types, but its mechanistic role in proximal tubule glucose homeostasis is unknown.

Methods: Rictor is a critical component of the mTORC2 complex. Inducible tubule-specific Rictor knockout (TRKO) mice were made with Pax8-rtTA TetOCre Rictorflx/flx. Male and female TRKO mice and wild-type (WT) littermates were fasted for 18 hours then refeed 4 hours before sacrifice. Whole kidney relative mRNA was measured via RT-PCR. Kidney plasma membrane and cytosolic proteins were separated using the BioVision Plasma Membrane Protein Extraction Kit, and protein abundance was measured with western blotting.

Results: There were no differences in serum glucose between TRKO and WT mice during refeeding (n=6–10 per group for all experiments). However, the mean ± standard error of the mean urine glucose excretion was 1824.9±768.5 μg in TRKO mice compared to 69.2±15.0 μg in WT animals during refeeding (p<0.05). TRKO kidneys compared to WT had significantly higher relative PEPCK protein abundance (0.54±0.05 vs 0.28±0.03 AU; p<0.001) and mRNA levels (0.54±0.17 vs 0.17±0.01 AU; p<0.05). TRKO kidneys compared to WT had statistically similar G6Pase protein abundance and significantly higher relative mRNA levels (0.58±0.17 vs 0.18±0.05 AU; p<0.05). Refeed TRKO kidneys showed a decrease in plasma membrane SGLT2 after refeeding (0.64±0.07 vs 1.22±0.24 AU; p<0.05) and no significant difference in SGLT2 mRNA levels compared to WT mice. There were no significant differences in plasma membrane protein abundance or mRNA levels for SGLT1 or GLUT2 between TRKO and WT kidneys.

Conclusions: TRKO mice have glycosuria with normal serum glucose. TRKO mice fail to suppress renal GNG and have decreased plasma membrane SGLT2. Coordinated suppression of GNG and stimulation of glucose reabsorption by mTORC2 is critical to conserve glucose by preventing excessive glucose production. Future studies will examine changes in the insulin and mTORC2 signaling pathways which mediate these findings.

Funding: NIDDK Support, Private Foundation Support

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FR-PO500

Pseudoaneurysms in Arteriovenous (AV) Fistulas: A Common Complication or a Rare Occurrence?

Nicole Wyatt, Naief Abudaff, Megha Salani. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Although pseudoaneurysms are primarily a complication seen with arteriovenous grafts (AVGs) with repeated localized cannulation, they can more rarely be seen in arteriovenous fistulas (AVFs). The incidence of AVF pseudoaneurysms remains largely unknown and there is limited quality evidence to guide management. We present a case of pseudoaneurysm in a native AVF that required surgical correction.

Case Description: A 36-year-old male with end stage kidney disease on hemodialysis via right brachio basilic (BB) AVF presented with two days of shortness of breath and right upper extremity (RUE) swelling. He denied any inciting event or prior difficulty with right brachiobasilic (BB) AVF cannulation. Exam revealed unilateral RUE swelling and a tortuous right BB AVF. Fistulagram with AVF cannulation. Exam revealed severe stenosis of right innominate vein requiring venoplasty/stenting, as well as right pseudoaneurysm in the cannulation zone, the largest of which was 2.8 x 2.2 x 1.5cm. Surgery was consulted and recommended against cannulation of AVF given risk of rupture. The pseudoaneurysms were deemed too large for non-invasive treatment, therefore he had a tunneled dialysis catheter placed and underwent prompt AVF revision including pseudoaneurysm resection and conversion to AVG.

Discussion: This case highlights an important complication of AVFs which impacts patient safety. Though many AVF pseudoaneurysms may be asymptomatic, they pose risks such as rupture and infection. Despite this, the incidence of AVF pseudoaneurysms is scarcely reported and ranges from 0.3% to over 15% in available literature. In addition, there is insufficient literature on treatment results with poorly available evidence and no randomized control trials to guide recommendations for management. Treatment decisions are largely based on access type and etiology of underlying problem, with options including ultrasound-guided manual compression, direct thrombin injection, or surgical options such ligation and excision/repair with graft interposition. We present this case to encourage further research to define AVF pseudoaneurysm classifications, natural history, and optimal treatment guidelines.
Mechanisms of Renal Potassium Handling Sexual Dimorphism Resolved at Single-Cell Level

Hyun Jun Jung, Rick Grimm, Paul A. Welling, Lama Al-Quasair. The Johns Hopkins University School of Medicine, Baltimore, MD.

Background: A recent study revealed a rising trend of hypokalemia in the US general population, with women being more prone to hypokalemia. Our previous study revealed that the response to potassium (K⁺) deprivation in females is more active in reprogramming in males. Among the DEGs, transcript levels of pathways exhibited more active reprogramming in males. The apical localization of K⁺-secretory ROMK channel in the distal nephron is less abundant in males under basal conditions and decreased to a greater extent than in females in response to K⁺ deprivation. snRNA-Seq of whole kidneys from both sexes defined 45 cell-type clusters. Given the key role of the distal nephron in K⁺ regulation, we initially analyzed distal tubular cells. Cell type-dependent transcriptome profiling revealed that connecting tubule (CNT) cells exhibited striking sex-dependent changes in response to K⁺ deprivation. Pathway enrichment analysis of the CNT differentially expressed genes (DEGs) between control and K⁺-deprived animals revealed that cellular processes associated with the cytoskeleton and ion channel regulation.

Methods: C57BL6J wild-type male and female mice were randomized to a control or K⁺-free diet for 8 days. K⁺ balance and key transporters involved in renal K⁺ secretion were analyzed. The sexual dimorphic transcriptional responses to K⁺ deprivation were assessed using single nucleus RNA-Seq (snRNA-Seq) in whole kidneys.

Conclusions: Males exhibited a more robust reduction in renal K⁺ excretion in response to K⁺ deprivation compared with females. The apical localization of K⁺-secretory ROMK channel in the early distal nephron was less abundant in males under basal conditions and decreased to a greater extent than in females in response to K⁺ deprivation. snRNA-Seq of whole kidneys from both sexes defined 45 cell-type clusters. Given the key role of the distal nephron in K⁺ regulation, we initially analyzed distal tubular cells. Cell type-dependent transcriptome profiling revealed that connecting tubule (CNT) cells exhibited striking sex-dependent changes in response to K⁺ deprivation. Pathway enrichment analysis of the CNT differentially expressed genes (DEGs) between control and K⁺-deprived animals revealed that cellular processes associated with the cytoskeleton and ion channel regulation.

Funding: Other NIH Support - O'Briens Centers, Private Foundation Support

FR-PO504

Changes in Renal Acid-Base Handling in Megalin-Knockout Mice


Background: Megalin is a ~600 kDa receptor abundantly expressed in the renal proximal tubules. It facilitates reabsorption of a great variety of proteins avoiding their loss in the urine. Lack of megalin therefore leads to insufficient reuptake of its substrates, and thus low-molecular weight proteins. In addition, our preliminary data suggest that lack of megalin also causes impaired regulation of renal acid-base excretion.

Methods: Kidney specific mosaic megalin knockout mice Immunofluorescence Western blotting Liquid chromatography/mass spectrometry Biochemistry of mouse blood and urine

Results: Immunofluorescence showed a very marked increase of brush border carbonic anhydrase 4 (CA4) in proximal tubular cells lacking megalin compared to megalin-positive cells (Figure 1). This was confirmed by western blotting of cortex homogenates. To investigate if other proximal tubular proteins involved in acid-base handling were changed, we applied proteomics. We found a significantly decreased abundance of NBCe1a (−20%), V-ATPase and NHE3 (−20%) and confirmed an increased abundance of CA4 (32%) in megalin KO mice. Megalin knockout mice showed mild alkalosis during baseline conditions. Urine analyses showed a very unusually combination of high NH4⁺ excretion concomitant with reduced titratable acid excretion and increased bicarbonate excretion. Despite high NH4⁺ excretion net acid excretion was reduced.

Conclusions: Our data suggest that the absence of megalin has major effects on renal acid-base handling. We suggest that megalin KO mice have increased ammoniagenesis in PT-cells and that this causes a compensatory reduction in TA excretion and increase in bicarbonate excretion. Further experiments are necessary to solidify this hypothesis.

FR-PO505

LRBA Signalosomes Activate Vasopressin-Induced AQ2 Phosphorylation in Recyling Endosomes


Background: In dehydrated states, increased plasma osmolality stimulates the release of the antidiuretic hormone vasopressin from the posterior pituitary gland. Subsequently, vasopressin binds to vasopressin type 2 receptor in renal collecting ducts and then activates protein kinase A (PKA)/phosphatase-2 (AQ2) water channels signaling, which increases water reabsorption from urine. Lipopolysaccharide-responsive beige-like anchor protein (LRBA) is a protein kinase A (PKA) anchoring protein localized at renal intracellular endosomes that creates compartmentalized PKA signaling responsible for AQ2 phosphorylation. cAMP/PKA signaling phosphorylates AQ2, promoting AQ2 trafficking from intracellular endosomes to the apical plasma membrane; however, the molecular mechanisms by which LRBA mediates vasopressin-induced AQ2 phosphorylation remain unknown.

Methods: To elucidate the in vivo role of LRBA in vasopressin-induced AQ2 phosphorylation and endosomal trafficking, a density gradient ultracentrifugation technique was combined with an in situ proximity ligation assay (PLA) and superresolution structured illumination microscopy (SIM). Lrba−/− mice were used as negative controls for vasopressin-induced AQ2 activation.

Results: Surroce density gradient and SIM revealed that AQ2 was stored in the recycling endosome under resting conditions. Desmopressin phosphorylated AQ2, translocating it from the recycling endosome to the apical plasma membrane. In contrast, SIM and PLA demonstrated that LRBA was constitutively localized on Rab11-positive recycling endosomes in WT mice regardless of vasopressin stimulation. Therefore, LRBA and AQ2 were well-colocalized in the absence of vasopressin stimulation. The loss of LRBA/PKA signaling by Lrba knockout impaired vasopressin-induced AQ2 phosphorylation, resulting in AQ2 retention at the recycling endosome. Defective AQ2 trafficking reduced urinary concentrating ability in Lrba−/− mice.

Conclusions: AQ2 was found to be stored on the LRBA-containing recycling endosome, and LRBA-induced compartmentalization of PKA signaling efficiently phosphorylated AQ2 in response to vasopressin.

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

FR-PO506

Ghrelin Enhances Tubular Magnesium Absorption in the Kidneys

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Background: In animal models mimicking bariatric procedures, bone disease, decreased serum levels of Ca²⁺, Mg²⁺ and the gastric hormone Ghrelin were described. Ghrelin binds to the growth hormone secretagogue receptor (GHSR) which is expressed in renal tubules. We tested if Ghrelin modifies tubular calcium or magnesium absorption via the ion channels TRPV5 or TRPM6.

Methods: We expressed GHSR1 with TRPV5 or TRPM6 channel in HEK293 cells and treated them with purified Ghrelin. Whole-cell current density was analyzed by patch-clamp recording. Nephron-specific gene expression of Ghrelin, GHSR, and Trpm6, was determined in microdissected tubules. Tubular localization of GHSR was examined by immunofluorescent (IF) imaging of GHSR-GFP mice. As there is more Ghrelin secreted with fasting, we elucidated the effect of Ghrelin in tubular magnesium homeostasis in GHSR-null mice at baseline and after starvation.

Results: After Ghrelin exposure whole-cell current density did not change for TRPV5 but increased for TRPM6 in a dose-dependent fashion. While a Ghrelin-mimetic also increased TRPM6 current density, addition of a GHSR antagonist inhibited the effect. GHSR signals via protein kinase A (PKA) and applying the PKA inhibitor H89 abrogated TRPM6 stimulation by Ghrelin. In microdissected tubules of wild-type (WT) mice there was abundant Ghrelin and GHSR mRNA in the TAL with 50% lower levels.
Lithium-Associated Tubulointerstitial Nephropathy, Role of Collecting Duct Cell Proliferation
Marie Himbert,1,2 Melanie Try,1,2 Lydie Cheval,1 Samia Lasada,1 Luciana Morla,1 Emmanuelle Vidal-Petit,1 Martin Flamant,2 François Vrtovecnik,1 Gilles Crampet,1 Nahid Tabibzadeh,1,3 Centre de Recherche des Cordeliers, Paris, France;1 Assistance Publique - Hopitaux de Paris, Paris, France.

Background: Lithium salts are the main treatment for bipolar disorder, a common and serious illness. However, their effectiveness is offset by their renal toxicity, especially microcystic tubulointerstitial nephropathy, which can lead to end-stage renal failure. The aim of the present study is to identify and characterize this nephropathy, and to identify predictive biomarkers of renal outcome, especially GDF15, a growth factor known to be involved in the proliferation of intercalary A cells in an acid environment.

Methods: The project is based on a model of lithium exposure, for 1 month, of GHSR-null mice. The GHSR-null mice were followed prospectively in a metabolic cage allowing the analysis of urine, including the dosage of GDF15, by ELISA test. Cell proliferation was studied by immunofluorescence analysis of mouse kidneys collected at sacrifice. The role of GDF15 was also clarified in humans, from a prospective cohort of lithium treated patients, in whom GDF15 was measured in the urine and correlated with the clinicobiological phenotype.

Results: Plasma levels of GDF15 are increased in lithium treated mice (p=0.019). The phenotype of GDF15-/- mice is not different from WT lithium carbonate treated mice, while in lithium mono treated mice, diuresis and cell proliferation are significantly lower in GDF15-/- mice (p=0.0159 and p=0.0147 respectively). In patients, GDF15 urinary excretion is positively correlated with diuresis (p=0.0001) and natriemia (p=0.0001), but negatively with eGFR (p=0.0001).

Conclusions: GDF15 is both increased in lithium treated mice and patients, suggesting it as a prognostic marker of nephrothropy. There is a differential causal relation depending on the associated anion, requiring more investigations. It could be a protective mechanism to limit polyuria by increasing the proliferation of the principal cells.

Funding: Government Support - Non-U.S.

FR-PO507
Lithium-Associated Tubulointerstitial Nephropathy, Role of Collecting Duct Cell Proliferation

FR-PO508
WNK1 Is a Central Osmolality Sensor for Arginine Vasopressin Release and Acts Through OSR1/SPAK Kinase Cascade
Xin Jin,1 Yuan Xin,2 Xin-Chao Long,2 Huang, University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: Terrestrial animals are subject to constant stress of water deprivation. Maintaining internal osmolality constancy is essential for life. The circumventricular organs (CVO’s) of brain including the organ vasculosum of the lamina terminalis (OVLT) and subfornical organ (SFO) lack a blood-brain barrier. Neurons in OVLT and SFO detect changes in serum osmolality that stimulates the production of AVP in paraventricular nuclei (PVN) to be released in the posterior pituitary. We have recently reported that WNK1 in sensory neurons in CVOs functions as an osmolality sensor for AVP release (Xin et al., JCI, 2023). WNK1 activates Kv3.1 to increase action potential amplitude involved in this nephropathy, and to identify predictive biomarkers of renal outcome, especially GDF15, a growth factor known to be involved in the proliferation of intercalary A cells in an acid environment.

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Funding: Government Support - Non-U.S.
Histologically, *Vhlh* KO mice consistently exhibited higher food intake and solute diuresis, but decreased body weight. Food restriction led not different between deprivation. Water deprivation-induced, vasopressin-dependent urine concentration was urine volume and lower urine osmolality which could be partially ameliorated by water diuresis might be caused by destructed renal interstitium. But the mechanisms underlying dependent urine concentration was not impaired in *Vhlh* KO mice. *Vhlh* KO mice were bred to study the effect of HIF stabilization in Hoxb7-expressing renal epithelial cell. Littermate without *Hoxb7*-cre transgene was used as the control to compare body weight, blood and urine biochemistry, gene/protein expression and histology in kidney.

Background: Hypoxia-inducible factor (HIF) is one of important cellular responders when facing decreased oxygen tension or under hypoxia. HIF stabilization can improve anemia through erythropoietin production from kidneys; however, its overexpression could be seen in different cancer types, such as clear cell renal cell carcinoma. Previous studies have shown wide-spread HIF-1α-dependent hyperplastic, inflammatory and fibrotic lesions in the kidney of mice with von Hippel-Lindau gene (*Vhlh*) deletion in Hoxb7-expressing renal collecting duct (CD) epithelia. Interestingly, *Vhlh* deletion in *Ksp.l*-expressing renal tubular epithelia has also been reported to cause HIF-1α dependent diuresis in mice.

Methods: Tg(Hoxb7-cre);*Vhlh*Δ/Δ (Vhlh KO), Tg(Hoxb7-cre);*Vhlh*Δ/Δ;Hif1Δ/Δ (Vhlh KO;Hif1a DKO), and Tg(Hoxb7-cre);Vhlh*Δ/Δ;Hif2aΔ/Δ (Vhlh KO;Hif2a DKO) mice were used to study the effect of HIF stabilization in Hoxb7-expressing renal epithelial cell. Littermate without *Hoxb7*-cre transgene was used as the control to compare body weight, blood and urine biochemistry, gene/protein expression and histology in kidney.

**Results:** Compared to littermate control, Vhlh KO mice exhibited higher 24-hour urine volume and lower urine osmolality which could be partially ameliorated by water deprivation. Water deprivation-induced, vasopressin-dependent urine concentration was not different between Vhlh KO mice and littermate control. Vhlh KO mice exhibited higher food intake and solute diuresis, but decreased body weight. Food restriction led to similar excretion of urine solutes, but Vhlh KO mice consistently exhibited higher urine volume and lower urine osmolality than littermate control. Vhlh/Hif2a DKO mice exhibited higher urine volume and lower urine osmolality, but no more solute diuresis. Vhlh/Hif1a DKO mice did not exhibit abnormality in urine volume and osmolality. Histologically, Vhlh KO mice exhibited substantial tubulointerstitial injury.

**Conclusions:** Vhlh KO and hence HIF-1α/HIF-2α overexpression in renal CD epithelia led to HIF-1α-dependent decrease in renal concentrating ability. However, increase of solute diuresis was HIF-2α-dependent. Water deprivation-induced, vasopressin-dependent urine concentration was not impaired in Vhlh KO mice. HIF-1α-dependent diuresis might be caused by destructed renal interstitium. But the mechanisms underlying HIF-2α-dependent solute diuresis need further study.

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

**FR-PO512**

**Hypersmolality-Induced Cell Shrinkage in Renal Cells: What a Role for RhoB?**

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**Background:** The small Rho GTP-binding proteins are important regulators of cell morphology, function, and apoptosis. Unlike other Rho proteins, RhoB can be subjected to hyperosmolarity compared to mock and RhoB-wt-EGFP expressing cells. These findings alter the activity of RhoB.

**Methods:** To evaluate whether RhoB plays a role in volume reduction, by hyperosmolarity regardless of FTI exposure. By contrast, hyposmolarity did not by hyperosmolarity. To elucidate this gut-kidney axis.

**Results:** 545 J Am Soc Nephrol 34: 2023 Fluid, Electrolyte, Acid-Base Disorders: Basic Poster/Friday

**Conclusions:** Together, these findings revealed for the first time that exposure of renal collecting duct cells to lithium resulted in a significant reduction in the expression of tamoxifen counteracts the lithium-induced downregulation of HSP90 and RIP3. Treatment with tamoxifen attenuates the lithium-induced decrease in necroptosis in renal-collecting duct cells.

**Funding:** Government Support - Non-U.S.
RNAseq of Microdissected Collecting Ducts Revealing the Early Signaling Mediating the Loss of Aquaporin 2 After K+ Deprivation C. Chen, M. Hsu, S. Lin. Division of Nephrology, Department of Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Background: Potassium (K⁺) deficiency could cause a reduction in urinary concentrating ability, resulting in nephrogenic diabetes insipidus (NDI), but the detailed mechanism remains unclear. Recently, transcriptomic and proteomic data from acquired NDI models reveals that oxidative stress, apoptosis, and inflammatory signaling are associated with AQP2 loss. We aim to explore the early signaling after K⁺ deprivation in cortical collecting ducts (CCD).

Methods: Immunoblotting and bulk kidney RNAseq were performed at 0, 12, 24, and 48 hours after K⁺ deprivation in rats. Serum and urine biochemistry were also recorded. Based on immunoblotting and bulk kidney RNAseq, CCDs were microdissected from rats at 6 h after K⁺ deprivation versus time controls. Single-tubule RNA-Seq was carried out independently in K⁺ deprivation rats versus controls (n=4).

Results: Immunoblotting of bulk kidney showed a decrease in AQP2 protein abundance at 12 hours of K⁺ deprivation diet, and urine osmolality was significantly decreased at 24 hours, confirming the animal model of K⁺ deprivation-induced NDI. Preliminary bulk kidney RNA-Seq time course experiments also revealed that Aqp2 and other collecting duct markers such as Aqp3, Aqp4, and Fxyd4 mRNA started to decrease at 12 hrs. Single-tubule RNA-Seq data of CCDs at 6 hrs after K⁺ deprivation showed Aqp2, Aqp3, and Apol1 were significantly downregulated. It also revealed that chemokine transcripts (Ccl20, Cxcl10) were increased significantly. We also carried out analysis of Gene Ontology Biological Process terms that are statistically over-represented in the list of 88 “Increased Transcripts” at 6 hrs of K⁺ deprivation in CCDs, and many of the terms are related to glutathione metabolic process (Gstm1, Gsta1, Gsta3, Tran2), positive regulation of ERK1 and ERK2 cascade (Nrp1, Ccl20, FxR2, Fgfr4, Fgfr3), cell chemotaxis (Ccl20, Cxcl10, Hbdeg), cellular response to lipopolysaccharide (Ccl20, Fkg2, Cd14, Tjp1), consistent with an inflammatory response.

Conclusions: Our small samples RNA-Seq from microdissected CCDs in rats showed early cellular signaling changes in activation of oxidative stress and inflammatory signaling causing loss of aquaporin-2 in K⁺ deficiency induced NDI.

FR-PO516
Role of Paraoxonase 3 (PON3) in Regulating Epithelial Sodium Channel (ENaC)-Mediated Na⁺ Transport in Distal Nephron Shujie Shi, Stephanie Mutchler, Sarah Christine Whelan, Allison L. Marsczyn, Thomas R. Kleyman. University of Pittsburgh School of Medicine, Pittsburgh, PA.

Background: PON3 is expressed in the aldosterone-sensitive distal nephron, where ENaC plays an essential role in maintaining Na⁺/K⁺ homeostasis in the kidney. The aims of our study were to determine the physiological roles of PON3 in renal Na⁺ and K⁺ handling. We hypothesize that PON3 functions as a molecular chaperone to regulate ENaC expression and Na⁺ reabsorption in the kidney.

Methods: We have obtained a PON3 global knockout mouse model and examined the effect of PON3 on ENaC functional expression using several approaches, including biochemistry, immunohistochemistry, electrophysiology, and whole animal metabolic cage experiments.

Results: PON3 KO mice have normal kidney histology without evidence of inflammation or injury. AI baseline, PON3 KO mice have a significantly lower blood [K⁺] and higher blood [Na⁺] when compared to WT littermates. Amiloride-induced natriuresis was significantly greater in the KO mice, reflecting, in part, an upregulation in ENaC-dependent Na⁺ reabsorption in the absence of the PON3. Immunoblotting of whole kidney lysates indicated that the total abundance of ENaC subunits was not altered in KO mice. However, RNAseq was more apically distributed within the cortical collecting ducts (CCD) of the KO kidneys. Single channel recordings of ENaC in split-open tubules freshly isolated from WT or PON3 KO mice kidneys demonstrated that open probability (Pₒ) was similar between the two groups of animals. However, the number of active channels per patch (Nₒ) was significantly higher in the KO kidneys, resulting in a higher ENaC activity (NₒPₒ) in the distal nephron segments of PON3 KO mice. Consistent with this notion, we found that ENaC surface abundance was increased in mCCTD cells when PON3 expression was knocked down by siRNA.

Conclusions: Together, our data suggest that PON3 KO mice have upregulated Na⁺ reabsorption and K⁺ secretion, likely a result of increased ENaC functional expression in the absence of PON3.

Funding: NIDDK Support

FR-PO517
Circadian Rhythm Misalignment Induced Differential Expression of Mineralocorticoid Receptor Type I and Aldosterone in Kidneys and Urine of Male Rats Tyler Cholankerli, Margaret Roccati, Diana Martinez, Michael E. Disanto. Rowan University Cooper Medical School, Camden, NJ.

Background: Circadian rhythm misalignment (CRM) adversely impacts health and increases blood pressure (BP), especially in shift workers. Aldosterone (ALD) acting through mineralocorticoid receptor (mCR1) causes sodium retention and water reabsorption to increase BP. The aim of this study was to determine if CRM alters the expression of mCR1 in the kidneys and aldosterone levels in the urine of rats.

Methods: 32 young male rats were divided into control (CTL) and CRM groups. CTLs and CRMs were phase-advanced to 2 days for 22 days after which BP was measured at 6-hour intervals. Rats were sacrificed and kidney tissue and urine stored at 4°C. RNA was extracted and Real-Time PCR conducted. ELISA was utilized to quantitate urine ALD. The mCR1 expression was normalized to 18s ribosomal RNA. An independent sample two-tailed t-test was used to determine effects of variance in both directions for both ELISA and RT-PCR data.

Results: Overall mCR1 expression was ~7.5-fold higher in combined CRM groups compared to CTL (p = 0.00019). Subgroup analyses revealed significant in the 9AM CRM group with an ~18-fold higher mCR1 expression (p = 0.20). The 3PM, 9PM and 3AM CRM groups also exhibited higher expression but did not reach statistical significance compared to the CTL group (1). ALD secretion was ~1.8-fold higher in combined CRM groups compared to CTL groups (p < 0.0035). Subgroup analyses revealed the 9AM, & 3PM CRM groups with significantly higher ALD expression (~2.96-fold (p = 0.005) and ~ 2.87-fold (p = 0.011), respectively). 3AM also showed higher expression but the 9PM CRM subgroup did not differ from CTL.

Conclusions: mCR1 expression and ALD are upregulated in kidneys and urine of rats after CRM and may be a potential mechanism for CRM-induced renal and cardiovascular dysfunction (CVD). Additionally, mCR1 expression and ALD levels appear to vary over a daily 24-hour cycle. Shift workers, have an increased risk of impaired sodium excretion and water retention. We hypothesized that this impaired cycle is due to the improper activation of the renin-aldosterone-angiotensin system thus resulting in hypertension, renal dysfunction, and CVD.

Funding: NIDDK Support

FR-PO518
Proximal Tubule Regulates the Collecting Duct Response to Hypokalemia
Poster/FRiday
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Background: Hypokalemia induces phenotypic and remodeling responses in the collecting duct that increase net acid excretion. We showed recently that the proximal tubule, through an NBCe1-dependent signaling pathway likely involving ammonia, regulates the collecting duct response to metabolic acids. Because hypokalemia stimulates proximal tubule NBCe1-dependent ammoniagenesis, we postulated that a similar mechanism would control the collecting duct response to hypokalemia.

Methods: Male and female NBCe1⁻/⁻ knockout (KO) and wild-type (WT) mice were studied either on a K⁺-control diet or a nominally K⁺-free diet (KFD). Immunoblot analysis, immunohistochemistry, and cell counting evaluated phenotypic and remodeling responses.

Results: KO mice tolerated only four days of K⁺-free before developing life-threatening hypokalemia. After four days, K⁺-free increased the number of Type B intercalated cells (A-cell) in the inner stripe of the outer medullary collecting duct (OMCDs) and decreased the number of Type B intercalated cells (B-Cell) in the cortical collecting duct (CCD), and KO significantly blocked these remodeling responses. K⁺-free increased the number of A-cells in the CCD, and KO did not alter this response. Immunoblot analysis showed K⁺-free decreased cortical pendrin expression, and KO did not alter this response. In the inner stripe of the outer medulla (ISOM), K⁺-free did not significantly alter either AE1 or Rh B Glycoprotein (Rhbg) expression, and NBCe1⁻/⁻ deletion did not alter response to K⁺-free. ANOVA analysis showed no significant effect of sex on these immunoblots.

Conclusions: We conclude: (1) the CCD B-Cell and OMCDs A-cell remodeling responses to hypokalemia are present at four days and involves a proximal tubule NBCe1⁻/⁻-dependent response likely involving ammonia; (2) the ISOM collecting duct phenotypic response to hypokalemia that involves AE1 and Rhbg requires more than four days to develop; and, (3) the CCD pendrin response to hypokalemia occurs more rapidly than ISOM responses, and is independent of proximal tubule NBCe1⁻/⁻-expression.

Funding: NIDDK Support
However, only a partial FHH-like phenotype develops due to kidney injury. We hypothesized that DCT selective deletion of Jab1 led to an FHH-like phenotype. Interestingly, although Jab1 (DCT-Jab1) mice showed an FH-like phenotype with increased WNK4, SPAK, and pNCC abundance. CUL3 inactivation in the DCT-Cul3 mice caused an increase in both KLLH3 (the CUL3 substrate adaptor for WNK4) and WNK4 abundance. WNK4 accumulated in DCT-Jab1 mice due to hyperactivation of OSR1/SPAK and SGK1. Additional work reveals that Jab1 is a non-kinase scaffolding activity at the same time that it inhibits WNK kinase activity.

Methods: We utilized NCC-Cre-ERT2 mice to delete Cul3 (DCT-Cul3) and Jab1 (DCT-Jab1) only in the DCT. Blood was collected for plasma electrolyte analysis, and kidneys were collected for Western blotting and immunofluorescent staining.

Results: Both DCT-Cul3 and DCT-Jab1 mice showed an FH-like phenotype. Chronically, only DCT-Jab1 mice developed a large reduction in NCC abundance, suggesting the decrease is due to a direct JAB1 effect, or effects of JAB1 on other cullins.

Funding: NIDDK Support

FR-POS52
Regulation of NCC1, NCC2, and NCC69 by TSC1/TSC2 Complex

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Background: Na-K-2Cl cotransporters and ENaC play important roles in diverse physiological processes and several human diseases such as salt-losing tubulopathies, hypertension and cancer. In the kidney, NCC1 plays a pivotal role in K+ secretion in the collecting duct while NCC2 is the pacemaker of NaCl reabsorption in the thick ascending limb. Using the two-hybrid system, we identified tuberin (TSC2) as a binding partner of NCC2. We therefore sought to characterize the mechanism by which TSC2, with or without hamartin (TSC1), could regulate NCC2 and/or NCC1.

Methods: NCC1 and NCC2 protein expression was monitored in HEK cells transiently or stably transfected with the cotransporters using immunoblot and confocal imaging. The stability of the cotransporters was assessed by cycloheximide chase assay. NCC1 and NCC2 function in the Drosophila melanogaster renal tubule overexpressing TSC1 and TSC2 in a control of Ncc69 mutant background.

Results: Co-immunoprecipitation experiments showed robust interaction between TSC2 and the complex formed by NCC2 suggesting that the interaction takes a place at the post-Golgi level. TSC2 and/or TSC1 knock-down (KD) similarly increased total NCC2 protein. Cycloheximide assays and leupeptin treatment (lysosome inhibitor) revealed that TSC1/2 KD upregulated NCC2 by increasing its stability and maturation. Interestingly, similar to NCC2, the KD of TSC3/TSC2 reproduced the same effects on NCC1. To elucidate in vivo the role of TSC1/TSC2 in the regulation of NCC, we took advantage of the expression of NCC69, the fly NCC in the Drosophila melanogaster renal tubule. Importantly, while overexpression of either TSC1 or TSC2 alone had no effect, overexpression of TSC1 and TSC2 together resulted in decreased tubule K+ secretion in control tubules and in tubules lacking NCC69, strongly indicating that the two TSC function together to regulate NCC69 function.

Conclusions: We identified TSC1/TSC2 complex as a novel key player in the post-Golgi regulation of NCCs. Our results are consistent with a model whereby TSC1 and TSC2 act together to regulate the expression of the cotransporters via the lysosome pathway. A better understanding of the regulatory pathways acting on NCC1 and NCC2 will ultimately help to identify new “ druggable ” targets to prevent or treat several disorders in which these two cotransporters are involved.

Funding: Government Support - Non-U.S.

FR-POS51
Chloride-Induced Monomer to Dimer Transition Controls WNK1


Background: Although it is well established that WNK kinase activity is involved in controlling cation-chloride co-transporters, such as NCC and NCC1, recent findings demonstrate that WNK1 can also act as a scaffold, independent of its kinase function. It facilitates the interaction between mTORC2 and SGK1 and stimulates SGK1 phosphorylation thereby enhancing ENaC activity. Extracellular K+ stimulates this non-kinase scaffolding activity at the same time that it inhibits WNK kinase activity. Both of these effects are mediated by intracellular C1, which directly binds to WNKs. Previous studies have identified two conformational states of WNK kinases: a kinase inactive, unphosphorylated chloride-bound dimer and a kinase active monomer, which is not chloride bound. The dimer conformation is maintained by salt bridges between the monomers, which dissociate in low chloride conditions. This study explores the conformational changes in WNK1 that contribute to its catalytic and non-catalytic functions.

Methods: Salt bridge mutations were generated using site-directed mutagenesis. WNK1 knockout (WNK1 KO) HEK293 cells were transfected with either wild-type (WT) WNK1 or the salt bridge mutants of WNK1. Subsequently, the cells were adapted to either non-kinase or kinase active conditions in [35S]Methionine-labeled medium for processing for co-immunoprecipitation (co-IP) and immunoblot analysis. Whole cell lysates were also assayed for OSR1/SPAK and SGK1 phosphorylation.

Results: In cells transfected with wild-type (WT) WNK1, extracellular K+ stimulated mTORC2-dependent SGK1 phosphorylation, while inhibiting WNK kinase activity-dependent SPAK phosphorylation. In contrast, mutations disrupting the salt-bridge interface of WNK1 blocked the effect of K+ on mTORC2-dependent SGK1 phosphorylation but not SPAK phosphorylation, which became insensitive to changes in extracellular [K+] stimulated dimer formation in the WT WNK1, but it was significantly reduced or absent in mutant forms of WNK1.

Conclusions: Our data suggest that the C1 induced shift of WNK1 from monomer to dimer conformations both inhibits WNK kinase activity and enhances scaffolding activity, providing a parsimonious mechanism for its opposite regulation of cation-chloride co-transporters and ENaC.

Funding: NIDDK Support, Private Foundation Support

FR-POS52
Sexual Dimorphism in Vasopressin Signaling

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Background: Hypoamrenia is a life-threatening condition characterized by decreased body natrium (sodium) concentration due to water retention. For reasons not yet understood, women are more prone to hypoamrenic conditions, including exercise-associated hypoamrenia, post-operative hypoamrenia, and ecstasy-associated hypoamrenia. Recent reports suggest that compared to males, female mice concentrate their urine more effectively due to enhanced AQP2 apical membrane localization.

Methods: The sexual dimorphism of water balance was analyzed in C57BL/6J wild-type males and females at basal conditions and after 12 hours of water deprivation. The m-in vivo activation of vasopressin signaling was assessed using western blot (WB) and confocal imaging. Plasma copeptin, a surrogate marker of vasopressin secretion, was assessed using ELISA.

Results: Our data revealed that females exhibit higher urine osmolality at baseline and have an enhanced ability to further concentrate their urine following 12 hours of water deprivation. Plasma copeptin was higher in females compared to males under basal conditions. WB analysis of the renal cortex and medulla in both sexes under basal conditions revealed AQP2 total protein levels were similar between males and females. However, AQP2 phosphorylation at Ser256, in a protein kinase A (PKA) consensus site, was more enhanced in the renal cortex and medulla of females. This is consistent with higher AQP2 apical localization in females as revealed by confocal imaging. To assess a potential sex-dependent activation of vasopressin signaling in the principal cells, we analyzed phospho-PKA substrates in the AQP2-positive cells using phospho-PKA substrate (RRXS/T) antibody. Quantitative analysis of confocal images revealed that PKA-substrates were more phosphorylated in the principal cells of females compared to males, indicating more enhanced vasopressin signaling in females.

Conclusions: The sexual dimorphism in water balance is mediated, at least in part, by higher circulating vasopressin levels in females. Subsequently, vasopressin signaling in the collecting duct was more enhanced in females resulting in more robust AQP2 apical translocation.

Funding: NIDDK Support

FR-POS53
α-Epithelial Sodium Channel (ENaC) Proteolysis Regulates Channel Function In Vivo in a Sex- and Tissue-Specific Manner

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Background: Epithelial Na+ channels (ENaCs) facilitate Na+ and water reabsorption in the distal nephron and distal colon, while also controlling K+ secretion in the distal nephron. ENaC activity, in part, is regulated by cleavage of the channel’s α and γ subunits by furin, a serine protease, at two furin recognition sites during synthesis. As a result, an autoinhibitory peptide sequence is excised, thereby increasing the channel’s open probability (Po). However, the importance of α-ENaC cleavage with respect to Na+ and fluid handling in vivo is unknown.

Methods: We tested the hypothesis that α-ENaC cleavage is necessary for channel function in vivo by generating mice that lack a key furin cleavage site (229RSARΔ232) vs. wild-type (WT) α-ENaC (229RSAR). We examined ENaC function in α-ENaC versus wild-type (WT) littermates via electrophysiological and systemic analyses under normal and Na+-restricted dietary conditions.

Results: At baseline, male α-ENaC mice had elevated blood K+ versus WT littermates (α-ENaC vs. WT: 4.7 ± 0.1 vs. 4.3 ± 0.1 mEq/l; p<0.03), but this was not observed in females (α-ENaC vs. WT: 4.8 ± 0.1 vs. 5.0 ± 0.2 mEq/l; p>0.8). Otherwise, α-ENaC mice of either sex exhibited no baseline phenotype regarding blood electrolyte or metabolic parameters. Western blot analysis showed no differences in ENaC subunit expression in the kidney or distal colon. Patch clamp experiments revealed no differences in ENaC activity (P0) in isolated kidney tubules. However, short-circuit current (Isc) measurements revealed that male α-ENaC mice had diminished ENaC activity in the distal colon (α-ENaC vs. WT: Isc: tamolohie: -0.2 ± 0.3 vs. -17.7 ± 4.4 μA/cm2; p<0.01). Colonic ENaC activity in both genotypes was stimulated by dietary Na+ restriction (α-ENaC vs. WT: Isc: tamolohie: -104 ± 38 vs. 64 ± 19 μA/cm2; p<0.01).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
p<0.04) and plasma aldosterone levels were also similar following treatment (e11 and WT: 2.9±2.2 vs. 2.2±0.8 pg/mL). Body composition analysis showed that during Na+-restr., e11 mice maintained body water content, but lost total body weight more rapidly than WT littermates.

Conclusions: α subunit cleavage is required for full ENaC function in male mice. However, deletion of α-ENaC can be compensated by elevated aldosterone under Na+-restricted conditions to maintain salt and fluid balance.

Funding: NIDDK Support

FR-PO524

Inhibition of Calcium-Sensing Receptor in Mice Proximal Tubule Leads to Calcium Phosphate Crystaluria

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Background: The proximal tubular (PT) Ca2+ transport is crucial for maintaining tubular Ca2+ levels to prevent downstream calcium phosphate (CaP) crystal formation. While PT Ca2+ transport is often described as paracellular, we found a transcellular Ca2+ transport pathway in the PT that is mediated by the interaction of calcium-sensing receptor (CaSR) and transient receptor potential potential canonical type 3 (TRPC3) channel. TRPC3 knockout mice exhibited hypercalciuria and microlithifications arguing for a protective role of TRPC3 in preventing nephrolithiasis. However, the role of CaSR in CaP crystal formation is unclear. Thus, we used a renal-selective knockdown of CaSR by the renal subcapsular infusion of CaSR siRNA to sort out the CaSR-mediated Ca2+ transport in the PT and its contribution to urinary CaP formation.

Methods: Adult male C57BL/6J mice were uninephrectomized 1 week before the renal implantation of osmotic minipumps. Osmotic minipumps (100 µl.; flow rate 0.5 µL/h for 7 days) were filled with previously validated CaSR or non-silencing siRNA as control. siRNAs were dissolved in an AR pH 4.3 to detect CaP. Real time intracellular Ca2+ was measured in siRNA- or urine collection and ion measurements were performed and collected urine were stained with AR pH 4.3 to detect CaP. Real time intracellular Ca2+ was measured in siRNA- or transfected isolated mouse PT cells.

Results: In mice that underwent renal subcapsular infusion with siRNA for two weeks, 24h urine showed notable CaP crystal formations compared with that of control and scrambled SiRNA infused mice. Renal cortical knockdown of CaSR did not significantly affect Na+, K+, and Kc excretion (normalized by creatinine) except for Ca2+. Fura-2 intracellular Ca2+ measurements in CaSR siRNA-transfected PT cells revealed decreased or nearly complete absence of Ca2+ entry after application with L-phenylalanine (CaSR agonist), confirming the effects of the siRNA.

Conclusions: The decreased Ca2+ influx due to CaSR inhibition suggest diminished tubular Ca2+ reabsorption thereby diminishing CaSR’s involvement in PT Ca2+ regulation. This study thus enhances our understanding about transcellular regulation of PT Ca2+ and its role in regulating urinary Ca2+ levels and subsequently CaP stone formation.

Funding: NIDDK Support

FR-PO525

Mice Lacking P300/CBP-Associated Factor Have a Resistance to Salt-Induced Hypertension Probably Through Dysregulation of NKCC2 and Aquaporin 2

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Background: P300/CFB-associated factor (PCAF), a member of the GNAT acetyltransferase family, is involved in the modulation of differentiation and cell cycle progression. Several neurodegenerative conditions have been thought to be associated with an alteration of PCAF activity and subsequent histone acetylation, and patients with neurodegenerative diseases often experience hypotension although the consequence of dysfunctional PCAF on blood pressure remains unknown. This study investigated a potential role of PCAF in the relationship between blood pressure and urinary sodium and water excretion in the kidney.

Methods: PCAF knockout (KO) mice and wild-type (WT) mice received 8% or normal NaCl salt diet for 2 weeks.

Results: WT mice had higher blood pressure on a high-salt diet than on a normal salt diet, but changes of dietary salt did not affect the blood pressure of PCAF KO mice. Free water clearance (FWC) and electrolyte free water clearance (EFWC) in PCAF KO mice on a high-salt diet were higher than those of WT mice on a high-salt diet. Both PCAF KO and WT mice on a high-salt diet had higher expression of Na+/K+ exchanger isoform 3 (NHE3) compared with normal salt-fed groups. In PCAF KO mice fed a high-salt diet, there was an increase in renal expression of Na+-NHE1 cotransporter (NCC) and a decrease in renal expression of Na+-K+-2Cl cotransporter (NKCC2) compared with WT mice fed a high-salt diet. Although renal mRNA expression of aquaporin 2 (AQP2) was upregulated in all groups on a high-salt diet, the phosphorylated protein level of AQP2 at serine 261 was significantly increased only in PCAF KO mice on a high-salt diet.

Conclusions: A deletion in PCAF expression makes blood pressure less sensitive to salt, probably via inappropriate downregulation of NKCC2 and AQP2 in kidneys, indicating that genetically impaired PCAF activity is likely to affect how blood pressure responds to changes in dietary salt.

FR-PO526

TGR5 Activation Ameliorated Hypertension Through Inhibiting Epithelial Sodium Channel (ENaC) Expression in the Kidney of Deoxycorticosterone Acetate (DOCA) Salt-Treated Mice

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Background: Epithelial sodium channel (ENaC), located in the collecting duct principal cells of the kidney, plays a critical role in regulating sodium balance and blood pressure in the body. The G protein-coupled bile acid receptor (TGR5) is a cell-surface receptor mediating bile acid effects and is implicated in several kidney diseases. The current study aims to investigate whether activation of TGR5 by lithocholic acid (LCA) regulated renal ENaC expression and blood pressure in deoxycorticosterone acetate (DOCA)-salt induced hypertensive mice.

Methods: Hypertension was induced in mice by subcutaneous implantation of DOCA pellets with 1% NaCl in drinking water. LCA was given by gavage.

Results: LCA markedly decreased blood pressure induced by DOCA-salt in mice, which was associated with decreased expression levels of ENaC mRNA and protein in the kidney. Compared with wild type group, TGR5 knockout mice developed increased blood pressure and ENaC protein expression in the kidney after DOCA-salt treatment. Our data indicates H3K4me3, 2, 3 enrichment in the promoter of ENaC. DOCA-salt treatment was associated with increased H3K4me3 expression in the kidney cortex which was markedly inhibited by LCA, while TGR5 knockout caused further increased H3K4me3 expression mice with DOCA-salt. Interestingly the mRNA and protein expression of KDM5A, a lysine demethylase, was significantly decreased in the kidney of mice with DOCA-salt, which was also significantly prevented by LCA. These data likely suggests that TGR5 activation decreased H3K4me3 enrichment of ENaC thus downregulated ENaC mRNA and protein expression. In immortalized mouse cortical collecting duct cells (mpkCCD) cells treated with either Ang II or aldosterone, the protein and mRNA expression levels of ENaC subunits were dramatically increased in association with increased protein expression of H3K4me3 and decreased mRNA and protein abundance of KDM5A, which were all inhibited by LCA treatment. Inhibition of KDM5 or KDM5A knockdown in mpkCCD cells treated with Ang II or aldosterone prevented the downregulation of ENaC expression induced by LCA.

Conclusions: In conclusion, LCA decreased blood pressure and ENaC protein expression in the kidney of mice with DOCA-salt, likely through increased KDM5A-mediated H3K4me3.

Funding: Government Support - Non-U.S.
Deletion of Kcnj16 Disturbs Acid-Base Homeostasis in Dahl Salt-Sensitive Rats

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Background: The role of renal inwardly-rectifying potassium (Kᵢ) channels in regulating acid-base homeostasis has been suggested by various studies. Previous studies demonstrated that patients with loss-of-function variants of Kᵢ₅,1 presented with disturbed acid-base homeostasis. However, the underlying mechanisms are still not fully understood. Here, we aim to investigate the renal handling of acid-base balance under the deletion of Kᵢ₅,1 in Dahl salt-sensitive rats (SSKcnj16⁻/⁻).

Methods: To evaluate the baseline acid-base status of SSKcnj16⁻/⁻ rats, 12-week-old male SSWT and SSKcnj16⁻/⁻ rats were used (N=5 per group). 24 hrs urine and blood were collected for measurement of blood pH, HCO₃⁻ and urinary pH, NH₄⁺, titratable acid, and net acid excretion (NAE). At the end of the experiments, RNA-Seq and Western blot analysis were performed on extracted kidneys to evaluate the expression of key transporters related to renal HCO₃⁻, H⁺, and NH₄ handling.

Results: At baseline, SSKcnj16⁻/⁻ rats showed significantly lower blood pH and HCO₃⁻, but higher urinary NH₄⁺, titratable acid and NAE than SSWT rats. RNA-Seq and Western blot analysis revealed altered expression of several transporters essential for renal handling of HCO₃, H⁺ and NH₄⁺. For example, for HCO₃⁻ transport, both RNA-Seq and Western blot analysis demonstrated increased expression of NBCe1 while decreased expression of pendrin, which may suggest enhanced HCO₃⁻ reabsorption in the proximal tubule while inhibited HCO₃⁻ excretion in the collecting duct of SSKcnj16⁻/⁻ rats. For H⁺ transport, increased mRNA expression of Rhbg and Rhcg may indicate enhanced H⁺ excretion in the kidney of SSKcnj16⁻/⁻ rats. For H⁺ transport, elevated mRNA and protein expression of NHE3 may suggest enhanced H⁺ secretion in the proximal tubule. Additionally, although the RNA-Seq suggested increased expression of several subunits of V-ATPase, we didn’t observe any differences at protein levels.

Conclusions: Our data suggested that at baseline, loss of Kᵢ₅,1 initiated metabolic acidosis and altered the renal transport of HCO₃⁻, NH₄⁺, and H⁺ in Dahl SS Rats. The following analysis will further investigate the phenotype after the NH₄Cl challenge test in both genders.

Funding: Other NIH Support - NIH R35 HL 135749, Veterans Affairs Support

Physiologic Importance of Proteolytic Cleavage of Epithelial Sodium Channel (ENaC)γ Subunit in Na⁺ and K⁺ Handling

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Background: Proteolytic removal of a peptide inhibitory tract (IT) from the epithelial Na⁺ channel (ENaC) γ subunit’s extracellular domain increases channel open probability (Pₒ) in vitro. IT removal requires cleavage at a furin recognition sequence (RKRR/KRR) at a site distal to the IT (RKRR) that is not acted upon by furin. The role of furin site cleavage in vivo is not well understood. Here we investigate the effects of impaired furin site cleavage in ENaC’s γ subunit on fluid and electrolyte handling.

Methods: We disrupted the γ subunit furin cleavage site in mice (γ₁₄₀RKRRγ₁₄₃→γ₁₄₀RKRRγ₁₄₃) was also not different at a low flow rate. At a high flow rate, the Jₒ current was greater in WT than Q4 collecting ducts (6.0 ± 1.1 vs 3.8 ± 0.6 pmol min⁻¹ mm⁻²). K flux (Jₖ) was also not different at a low flow rate. At a high flow rate, the Jₖ magnitude was greater in WT than Q4 collecting ducts (6.0 ± 1.1 vs 3.8 ± 0.6 pmol min⁻¹ mm⁻²). p ≤ 0.01). In colonic epithelium, we observed no difference in amiloride-sensitive short-circuit currents (Iₛₙ) in Q4 vs. WT. Total body water (TBW), measured via quantitative magnetic resonance and normalized to starting TBW, declined more in Q4 than WT males. TBW change was not different in female Q4 mice compared with WT mice.

Conclusions: Impaired furin site cleavage in ENaC’s γ subunit did not influence blood electrolytes, colonic Iₛₙ, or collecting duct Pₒ or Jₒ but diminished flow-induced stimulation of Jₒ in the collecting duct, and impaired body fluid conservation in males. Differences, where observed, were relatively subtle, indicating that additional factors influence ENaC activity and Na⁺ and K⁺ balance in live animals.

Funding: NIDDK Support, Other NIH Support - NHLBI
Weidong with angiotensin II (300 ng/kg/min) for 2 weeks by osmotic minipump. We treated mice with FXR agonists or antagonists. To induce hypertension, mice were infused into the vasculature with FR-PO531. Our findings demonstrated FXR activation decreased renal ENaC and AQP2 protein levels by immunoblotting in WT-KO cells as well as AQP2 protein abundance.

Conclusions: We conclude that CREB and AQP2 are not necessary for the action of dDAVP to increase AQP2 gene expression, contrary to the conventional belief in the literature. Future studies will assess whether other dDAVP-responsive genes are regulated by CREB and AQP2, or whether other transcription factors might be involved in mediating dDAVP signaling, which may explain the upregulation of AQP2.

Acknowledgments: This work was supported by The National Key Research and Development Program of China (2018YFC1706101), National Natural Science Foundation of China (81971778), Science and Technology Commission of Shanghai municipality (19JC1402800, 20JC1405400), Shanghai Science and Technology Commission (20221150500, 2020YK140033), Shanghai Municipal Commission of Health and Family Planning (2020ZLYS004), and Shanghai Education Commission (202005007).

Background: Osmoregulation is a complex component of cell physiology, yet the initial transcriptional regulators of the osmotic stress response remain to be fully characterized. Here we studied the regulation of promoter-proximal RNA polymerase II transcriptional activity under osmotic stress.

Methods: We applied extracellular flux analysis (EFA) to investigate mitochondrial respiration and energy metabolism in isolated renal tubules. Briefly, after mice were sacrificed and perfused, renal tubules were microdissected and incubated at 37°C for 1 hour. The dynamic oxygen consumption and extracellular acidification rates (OCR/ECAR) were measured by Seahorse XFp analyzer.

Results: Isoflurane reduced the amount of ENaC at the plasma membrane of mpkCCDc14 cells. CDCA reduced the amount of ENaC at the plasma membrane of mpkCCDc14 cells, which indicated FXR activation inhibits the trafficking of ENaC to the cytomembrane. Interestingly, CDCA significantly reduced With-No-Lysine 1 (WNK1) and SGK1 expressions in renal tubules, which was associated with increased abundance of WNK1 and SGK1 and decreased abundance of NEDD4-2. In angiotensin II-induced hypertension, CDCA treatment lowered the systolic and diastolic blood pressure in mice. The increased expressions of ENaC in the kidne of mice, which was associated with increased abundance of WNK1 and SGK1, was prevented by CDCA treatment. Consistent to the in vitro study, CDCA downregulated the expressions of ENaC in the kidney induced by angiotensin II were prevented by CDCA treatment through the NEDD4-2 signaling pathway.

Conclusions: Our findings demonstrated FXR activation decreased renal ENaC expression likely through downregulation of WNK1 and SGK1 signaling, which may explain the upregulation of AQP2.
FR-PO534

Activation of BK<sub>α</sub> Channel Prevented the High Glucose-Induced Oxidative Stress in Human Proximal Tubular Cells

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Background: Hyperglycemia stimulates the production of reactive oxygen species (ROS) leading to oxidative stress. Oxidative stress could cause inflammation or fibrosis. Our previous study found that activation of the large conductance, calcium-activated potassium channels (BK channels) attenuated renal fibrosis in mice. We hypothesized that upregulation BK channel activity would suppress the high glucose (HG)-induced oxidative stress.

Methods: Human proximal tubular epithelial cell (HK-2) was cultured in DMEM/F12 medium. HEK-BKα cells (HEK293 stably expressing BKα) were cultured in DMEM with G418. Cells were cultured in the low glucose DMED (5.5 mM glucose) for 24 hours before treatments. NS1916 (10µM) was used to activate BKα channel. Two ROS products were measured: 1-hydrogen peroxide (H2O2) was measured by Amplex Red Hydrogen Peroxide Kit (cat # A22188, Molecular Probes): 2- DHE (Dihydroethidium) assay (Abcam ab236206) was used to detect superoxide. Superoxide Dismutase (SOD), a defense of oxidative enzyme, was measured using colorimetric activity kit (Invitrogen, EIASODC). Single channel recordings were used to analyze the activity of BKα channel.

Results: Using single channel recordings we showed that high glucose (HS, 25 mM D-glucose) inhibited BKα channel activity in HEK-BKα cells. As an osmolarity control 25 mM mannitol does not change the BKα activity. To determine the effect of BKα channel on HG-induced ROS production HK2 cells were treated with HS (25mM) with or without NS1916 (10µM). H2O2 and superoxide productions were significantly increased with high glucose treatment, whereas NS1916 (10µM) prevented the HG-induced H2O2 and ROS. In addition, HS (25mM) significantly decreased SOD activity in HK2 cells, whereas activation of BKα activity with NS1916 reversed the decreased SOD activity induced by HS.

Conclusions: High glucose inhibited BKα activity while increasing H2O2 and superoxide productions in HK2 cells. Activation of BKα channel activity attenuated HS-induced the ROS production. In addition, BKα reversed HS-induced down-regulation of SOD. These results suggest that activation of BKα channel has novel roles in preventing oxidative stress.

Funding: Veterans Affairs Support

FR-PO535

Neuropeptide FF Increases Na<sup>+</sup> and K<sup>+</sup>-ATPase Activity in Live Renal Proximal Tubule Cells

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Background: Neuropeptide FF (NPF), an amidated peptide, acts as a pain-modulator. However, the effects of NPF on renal Na<sup>+</sup> transport and blood pressure are unknown.

Methods: Intracellular Na<sup>+</sup> concentration in renal proximal tubule cells (H8 cells) was measured using the lifetime Na<sup>+</sup>-binding of NaTRIUM Green-2 (Green-2), monitored by fluorescence lifetime imaging (FLIM) and Fluo-3 tetramethylated, by spectrometry. Blood pressure and sodium excretion were also studied in mice.

Results: In glass-bottom cultured RPTCs, Green-2 (5 µM/1 hr) had a biexponential decay in time-resolved fluorescence measurements randomly selected regions of interest (ROI) in the cytoplasm of these RPTCs. In the basolateral membrane, the lifetime tα (Na<sup>+</sup>-binding decay time component, due to NPF was associated with a decrease in intracellular Na<sup>+</sup> concentration (NPF: 79±6.7, n=4 vs vehicle: 100±9.4, n=4). The NPPF-mediated decrease in intracellular Na<sup>+</sup> was due to an increase in Na:<sup>-</sup>K-ATPase activity, because ouabain (50 µM) which inhibits Na:<sup>-</sup>K-ATPase activity increased intracellular Na<sup>+</sup> (125±6.1, n=4) and prevented the NPPF-mediated decrease in intracellular Na<sup>+</sup> concentration (124±3.3%, n=4). The effect of NPF on other sodium transporters and exchangers was not determined. The stimulatory effect of NPF on Na<sup>+</sup> transport has physiological significance because in anesthetized C57Bl/6 mice (n=4), the acute bilateral renal denervation decreased (p < 0.05), peaked at 25 min (3.4±4.0% vs basal, 99±5.9%, P < 0.05), and gradually returned to baseline at 60 min. The chronic bilateral renal subcapsular infusion of NPF (9.25 µM, 0.5 ml/h, n=4) for 7 days also increased SBP and decreased urinary sodium excretion that were prevented by RP3, an NPPF antagonist.

Conclusions: NPF decreased intracellular Na<sup>+</sup> concentration in RPTCs by stimulating Na:<sup>-</sup>K-ATPase activity, decreased Na<sup>+</sup> excretion, and increased blood pressure in C57Bl/6 mice.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO536

Cell Volume-Sensitive Transcription Factor(s) Regulate Claudin-2 Expression in Epithelial Cells

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Background: The basolateral Na<sup>-</sup>/K<sup>-</sup>2Cl<sup>-</sup> cotransporter (NKCC1) plays a critical role in maintaining the intracellular concentrations of Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> ions, and cell volume. While it is well recognized that NKCC1 is critically important for vasoconstriction and blood pressure regulation, its role in transcellular ions transport and epithelial barrier function is not well understood. Here we ask whether loss of NKCC1 function affect kidney and intestinal epithelial tight junction permeability.

Methods: Wild-type MDCK I and NKCC1-deficient clones LKA3 and LKC1 were plated and polarized on transwell filters, and their TER was measured. Tight junction protein expression and localization was assessed by western blotting and immunofluorescence.

Results: The TER values of NKCC1-deficient MDCK I cells decreased by more than 20%, from 8000 ±100Ω·cm<sup>2</sup> in parental MDCK I to 3000 ±500Ω·cm<sup>2</sup> in LKA3 and LKC1 clones. Western blot analysis showed that genetic ablation or pharmacological of NKCC1 function increases the expression of the cation selective claudin-2. This is consistent with the observed decreased TER. In addition, growing MDCK I cells in C1-free, Na<sup>-</sup>-free or both C1 and Na<sup>-</sup>-free media upregulates claudin-2 expression.

Conclusions: Our data indicate that loss of NKCC1 function affects tight junction protein expression without affecting their localization. Particularly, claudin-2 was significantly upregulated. This led to an increase in paracellular flux of positively charged ions across the MDCK epithelial cell monolayers. Notably, this phenomenon is not unique to kidney epithelial cells, as loss of NKCC1 function in intestinal HT29 cells also led to significant decrease in TER and upregulation of claudin-2 expression.

Funding: NIDDK Support, Private Foundation Support

FR-PO537

Resveratrol Inhibits Proximal Tubular Sodium Reabsorption and Suppresses the Progression of Renal Injury

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Background: Resveratrol (RSV), a natural polyphenol compound, has demonstrated anti-inflammatory, anti-cancer, anti-oxidant, and anti-aging effects in vitro and in vivo studies. However, its effects on the proximal tubules (PTs) and kidney disease remains unknown. In this study, we evaluated the effect of RSV on Na transport in isolated PTs and its potential to inhibit the progression of chronic renal injury in rat models.

Methods: By using a pH-sensitive dye BCECF we measured the basolateral Na-HCO exchange activity of Na-H exchange (NHE) activity in freshly-isolated rat PTs. To evaluate the effect of RSV on the progression of kidney disease, 6-week-old OLETF rats that had undergone unilateral nephrectomy were fed a high-salt diet, administered aldobestone (Ald) continuously by osmotic pump, and compared to a group receiving 50 mg/kg BW RSV orally daily for four weeks. Comparisons were made by serum biochemical, histological tests and protein expression. Protein expression was determined by Western blot.

Results: In a concentration-dependent manner, RSV significantly inhibited the stimulatory effects of insulin on Na reabsorption on PTs, and inhibited insulin-induced phosphorylation of Akt. Moreover, continuous Ald administration resulted in severe albuminuria and renal dysfunction, whereas those treated with RSV exhibited a significant reduction in both albuminuria (p < 0.05) and renal dysfunction (p < 0.05). In the renal phosphorylation of Akt and expression of Rictor and Raptor were significantly decreased (p < 0.05).

Conclusions: RSV inhibits insulin-induced sodium reabsorption in PTs, and it could have a renoprotective effect.

Funding: Government Support - Non-U.S.

FR-PO538

Exposure of Junctional Claudin-3 Epitopes in the Thick Ascending Limb of the Rat Deficient Mice

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Background: The kidneys play a vital role in maintaining mineral balance. The reabsorption of calcium and magnesium in the renal thick ascending limb (TAL) is facilitated by CLDN16 and CLDN19 and mutations in either gene results in severe calcium and magnesium loss. Clinically, it is also expressed in TAL RNAseq databases, however some but not all studies localize the CLDN3 protein to the TAL. In our hands, using 3 distinct antibodies, we have been unable to detect CLDN3 expression in the TAL.

Methods: The pattern of expression of CLDN3 was evaluated using 3 distinct CLDN3 antibodies: 1. Anti-CLDN3 antibody (HPA014361 Sigma-Aldrich), 2. Anti-CLDN3 antibody (ST23159, St John’s Laboratory), and 3. Anti-CLDN3 Antibody (34-1700, Invitrogen), all produced in rabbit. Using these antibodies, we investigated the localization of CLDN3 in the kidneys of both wild-type and Cldn19 deficient mice on 2 um paraffin sections.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
Results: All antibodies showed immunoreactivity towards epitopes situated in the tight junctions of the renal tubular cells. In addition, the Sigma antibody labeled epitopes in the intercalated cells and the Invitrogen labeled epitopes in the perinuclear region of epithelial cells. With respect to the tight junction, CLDN3 was expressed in portions of the proximal tubule as well as distal nephron cells but was absent from the TAL in wild-type animals using all three antibodies. In contrast, in Cldn19 deficient animals, immunoreactivity was also found in the TAL in a mosaic pattern.

Conclusions: These findings suggest that CLDN3 localizes to the TAL where it may play a direct role in determining the permeability. Why immunoreactivity in the TAL is only seen in Cldn19 deficient animals remains to be elucidated. The findings could suggest that CLDN19 shields the epitope towards which CLDN3 binds in fixed tissue.

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

FR-PO539

A Novel R881S Mutant of Transporter NBCe1 Has Cytosolic Retention and Lacks Dominant Negative Effect

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Background: The electrogenic Na+ /HCO3- cotransporter NBCe1 is expressed in many organs including the brain, eye, and the kidney, where it controls sodium and bicarbonate reabsorption. NBCe1 homozygous mutation causes not only severe hypotension but also proximal renal tubular acidosis (RTA) in human and rodents. Here we characterized the functional significance of SNVs reported from NCBI database.

Methods: We identified the missense mutation R881S in NBCe1 variant A (kidney type) from the database. Given the report of R881C mutation in patients with RTA (JASN 2005), we conducted a comparative analysis of cellular localization and cell protein expression between R881S and R881C using confocal microscopy and Western blotting.

Results: Immunofluorescence analysis with confocal microscopy revealed that the R881S variant was present exclusively in the cytoplasm in both HEK293 cells and MDCK cells. Biotinylated western blotting in HEK293 cells confirmed that the cell-surface expression was completely abolished in R881S mutant. In total cell lysates, R881S-NBCe1 showed a lower molecular weight compared with wild-type, and deglycosylation study confirmed that R881S substitution impaired N-glycosylation. Moreover, co-immunoprecipitation study revealed that the interaction with wild-type NBCe1 was severely impaired in R881S compared with R881C.

Conclusions: R881S mutation inactivates the NBCe1 function without lack of dominant-negative effect. These data illustrate the diverse physiological consequences of distinct SNVs and underscore the importance of functional characterization in membrane transport proteins.

Funding: Government Support - Non-U.S.

FR-PO540

Estimation of Plasma Vasopressin Activity by AQP2 in Urinary Extracellular Vesicles

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Background: The antidiuretic hormone, vasopressin (AVP), activates protein kinase A (PKA) in the principal cells of the collecting duct via the V2 receptor. Activated PKA is known to phosphorylate the amino acid residues (S256 and S269) on the water channel, aquaporin 2 (AQP2). These phosphorylations are considered to promote water reabsorption by increasing the trafficking of AQP2 into the apical membrane. The measurement of the blood AVP concentration is difficult because of its instability and binding to the platelets. It has been shown that urinary extracellular vesicles (uEVs) contain AQP2 protein. Therefore, in this study, we investigated whether AVP activity could be inferred by measuring the total or phosphorylated form of AQP2 in uEVs.

Methods: In experiment I, male SD rats were divided into three groups: a control group (free-drinking tap water), a dehydration group (water deprivation; DH group), and a hydration group (free-drinking 20% sucrose; HY group). In experiment II, male SD rats were divided into two groups: a vehicle group (50% of 5% glucose, 50% of saline, s.c.) and a DDAVP group (300 mg/kg desmopressin, 2 VG, s.c.). Urine samples were collected for 12-24 hrs, and blood and kidney samples were collected at 24 hrs after the treatment. Total and phosphorylated (pS256, pS269) AQP2 protein levels in uEVs were evaluated by immunoblot analysis.

Results: In experiment I, urine volume was decreased in the DH group and was increased in the HY group. Moreover, urine osmolality was elevated in the DH group and reduced in the HY group. Total and phosphorylated AQP2 levels in uEVs were increased in the DH group, and only the pS269-AQP2 level was decreased in the HY group. In experiment II, urinary osmolality and AQP2 protein levels in the DDAVP group significantly increased in comparison with the control group. The total AQP2 level showed an increasing tendency, and the pS269-AQP2 level was significantly increased in the DDAVP group. On the other hand, the pS269-AQP2 level was not altered.

Conclusions: These results indicate that the pS269-AQP2 level in uEVs responded well to the physiological and pharmacological changes in V2 receptor activation. Therefore, pS269-AQP2 in uEVs may be a potential non-invasive biomarker to estimate plasma AVP activity.

FR-PO541

Elucidating the Diuretic Effect of Corticosteroids in Rats

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Background: Corticosteroids are widely used to treat kidney diseases such as nephrotic syndrome and glomerulonephritis. A few cases of polyuria following corticosteroid treatment have been reported in human patients with heart failure or hypopituitarism. In dogs, corticosteroids frequently cause polyuria and polydipsia (Ellkholly DA et al., Front Vet Sci. 2020). In experimental rat models, acute corticosteroid treatment is known to cause a potent diuretic response (Tunhors RL et al., Am J Physiol Renal Int Physiol 2007). However, the mechanisms by which corticosteroids cause polyuria is largely unknown. Here, we investigated the mechanism of corticosteroid-induced polyuria in rats treated with prednisolone (PSL).

Methods: Male SD rats aged 10 weeks were treated with PSL (0.3 or 1.0 mg/kg, s. c.) or vehicle (25% DMSO/75% Corn Oil, s. c.). Urine was collected for 6 hours after the treatment. Blood and kidneys were isolated at 6 hours post-treatment. The levels of electrolyte and osmolality in urine and blood were measured. Free water clearance was also calculated. The gene expression levels of sodium-dependent transporters and water channels were investigated by real-time PCR.

Results: The urine volume was significantly increased and the urine osmolality was significantly decreased after the treatment of PSL, in a dose-dependent manner. The total excretion of Na+, K+, Cl- and inorganic phosphorus was significantly higher in rats treated with PSL than in without it. The free water clearance value was negative in the PSL-treated rats. Real-time PCR revealed that mRNA levels of sodium/chloride cotransporters (NKCC2/Sli2a1 and NCC/Sli2a3), sodium/phosphate cotransporters (Slc34a1 and Slc34a3) and a water channel (AQP2) were decreased in the PSL group. In addition, significant negative correlations were observed between urinary sodium excretion and the gene expression of NKCC2 and NCC.

Conclusions: These results indicate that reduced renal expression of sodium-dependent transporters in response to PSL may contribute to the suppression of electrolyte reabsorption, leading to the diuretic and natriuretic effects in rats. Since the free water clearance value was negative, the contribution of AQP2 was considered modest in the diuretic effect of PSL.

FR-PO542

Colistin-Induced Acute Tubular Dysfunction: Toxicity Beyond Creatinine

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Background: Colistin is a relevant antibiotic for infections by multiresistant microorganisms. However, it is not exempt from serious renal adverse events, e.g.: acute kidney injury (AKI). The present study describes the hydroelectrolytic disorders associated with the prescription of colistin.

Methods: Retrospective cohort design. Data were obtained from January 2021 to December 2022. Patients who received colistin for at least 48 hours were included. Patients with chronic renal support therapy or acute kidney injury prior to starting colistin were excluded.

Results: 23 patients were evaluated, with an average age of 55.96 years, men 60.86%. The most frequently isolated microorganism was P aeruginosa (56.52%). The reported findings were: hyponatremia, hypokalemia (39.13%), hyperkalemia (45.8%), hypercalcemia (52.17%), hypocalcemia (100%), hyperphosphatemia (63.63%), and hypomagnesemia.
FR-PO543
Mechanisms of Thiazide-Induced Magnesium Wasting and Calcium Retention at Single-Cell Resolution
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Background: States of NCC inhibition, as in Gitelman syndrome and chronic thiazide treatment, present with hypokalemia, alkalosis, hypomagnesemia, and hypocalciuria. The mechanism by which loss of NCC function affects Mg and Ca handling remains very unclear. Here we combined single nucleic RNA sequencing with physiologic and morphometric analysis to unravel the causes of hypomagnesemia and hypocalciuria secondary to NCC inhibition.

Methods: 8 to 10-week-old male NCC-Cre-INTACT mice received 50 mg/kg/day metolazone (MTZ) orally for 4 days. Fluorescence-activated nuclei sorting was performed to select for DCT nuclei. Sequencing was done using 10X Chromium. Reads were analyzed using a transcriptomic bioinformatics pipeline with Seurat. We also performed tubule morphometrics.

Results: MTZ-treated mice had lower plasma Mg and lower urinary Ca excretion compared to controls, consistent with NCC inhibition. Our snRNA-seq dataset showed 2 clusters, DCT1 and DCT2, based on canonical markers consistent with published transcriptomic atlases. We curated Mg and Ca cassettes from known magnesiotropic and calcitropic genes and defined Mg and Ca scores from the pooled expressions of the genes and used them to indicate Mg and Ca handling capacity. The analyses showed that Mg handling is primarily a DCT1 process and Mg score was lower in the MTZ group. We also found that the DCT1 undergoes dedifferentiation leading to reduction in magnesiotropic gene expression. Additionally, 3D morphometrics showed that DCT1 was shorter in the MTZ group. Ca handling is primarily a DCT2 process and Ca score was lower in the MTZ group consistent with low distal delivery due to enhanced proximal Ca reabsorption. Yet, DCT2 cells maintained their cell state and were less vulnerable to NCC inhibition compared to DCT1 cells. Lastly, MTZ-treatment caused hypertrophy of the Ca-transporting connecting tubule (CNT).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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FR-PO544
WNT Ligands Drive PKD1-Mediated G Protein Signaling and Receptor Internalization and Downregulation
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Background: Autosomal Dominant Polycystic Kidney Disease is a genetic disorder caused by mutations in PKD1, which encode PKD1 and PKD2, respectively. PKD2 is a nonselective cation channel and forms a complex with PKD1 in which the channel is activated upon WNT binding to PKD1. Independently, PKD1 is proposed to act as an atypical G protein-coupled receptor (GPCR) for which the activating ligand is unknown. To investigate the role of WNTs in PKD1-mediated G protein signaling and receptor internalization and downregulation, we: (i) compared PKD1 and Gαq coupling in wild type and mutant PKD1 (PKD1ΔGαq) cells, and (ii) assessed PKD1-Gαq coupling functionally.

Methods: A WNT5A expression construct was cloned into a eukaryotic expression vector and cotransfected into HEK293T cells with Wnt3a or empty vector. Cell membranes were prepared and subjected to immunoprecipitation using anti-Gαq antibodies. Western blot analysis and densitometry were performed to compare wild type and mutant PKD1-Gαq coupling.

Results: PKD1ΔGαq showed a significant decrease in Gαq coupling compared to wild type PKD1, whereas PKD1ΔGαi coupling was similar to wild type PKD1.

Conclusions: Our findings highlight an important role for WNTs in the GPCR-mediated PKD1 internalization and downregulation. The results indicate that hypomagnesemia secondary to NCC inhibition results both from a disruption of genes involved in Mg handling and from aldosterone-induced hypertrophy of the CNT and relative preservation of DCT2 contribute to calcium retention.

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

FR-PO545
Addition of an N-Terminal SNAP-Tag Induces a Novel Hypomorphomic Pkd1 Allele
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Background: We engineered mice that express endogenous polycystin-1 (PC1) with an N-terminal, self-labeling SNAP-tag to facilitate the in vivo visualization of PC1 trafficking and co-immunoprecipitation of multiprotein complexes. While initial reports indicated that the allele is normal, follow-on work has demonstrated that addition of SNAP results in a hypomorph classical PKD1 Pkd1N-SNAP/V mice had kidneys with only a few very small cysts with a %KW/BW of 1.4% at 23-26 weeks. Interestingly, a female compound heterozygous Pkd1N-SNAP/V and PoKO mice had moderately cystic kidneys with a %KW/BW of 9.4%. Homozygous Pkd1N-SNAP/V mice had moderately cystic kidneys with a %KW/BW of 2.6% at 8 weeks, progressing to 5.2% at 23-26 weeks. In contrast to compound heterozygous Pkd1N-SNAP/V mice, which are severely cystic by 3 weeks, compound heterozygous Pkd1N-SNAP/V and Pkd1N-SNAP/V mice had kidneys with only a few very small cysts with a %KW/BW of 1.4% at 23-26 weeks. Interestingly, a female Pkd1N-SNAP/V mouse and a female Pkd1N-SNAP/V mouse used as breeders had a few large cysts at 23-26 weeks.

Conclusions: Addition of SNAP to the N-terminus of Pkd1 generates a hypomorph Pkd1N-SNAP/V allele. The cystic phenotypes in Pkd1N-SNAP/V and Pkd1N-SNAP/V mice suggest that the tag affects PC1 trafficking, stability, and/or a critical function of the polycystin complex. However, the very mild phenotype Pkd1N-SNAP/V mice suggest that the PC1-SNAP defect is functionally distinct from that of the defects caused by

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the V and RC mutations, allowing partial preservation of PC1 function when present in the same animal. Future experiments will determine the functionality of the SNAP-tag, the localization of the PC1\textsubscript{V}\textsubscript{RC} protein, and the nature of the defect caused by the SNAP-tag.

**Funding:** NIDDK Support

**FR-PO546**

Cleavage of PC1 Is Not Required for Embryonic Vasculature Development

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**Background:** Polycystin 1 (PC1) is a large membrane protein that undergoes an autophosphorytic cleavage at a G protein coupled receptor (GPR) site. PC1 cleavage at the GPR is essential for trafficking of the PC1/PC2 complex to the primary cilium. While homologous Pkd1 or Pkd2 knockout mice die at mid-gestation due to vascular and lymphatic abnormalities homologous Pkd1\textsuperscript{V/V} mutant embryos, harboring a mutation that abolishes PC1 cleavage, survive embryogenesis, suggesting that uncleaved PC1 (PC1\textsuperscript{u}) might play a role in embryonic vascular development.

**Methods:** We analyzed the vascular phenotype of Pkd1\textsuperscript{V/V}, Pkd1\textsuperscript{u} and control E14.5 embryos including placenta branching morphogenesis and epidermal lymphatic vessel development. Rescue experiments were performed using a transgenic BAC expressing HA-tagged-PC1\textsuperscript{u} (PC1\textsuperscript{u}u). We evaluated the impact of PC1 cleavage on cell migration/polarity via wound healing assay. Trafficking of PC1\textsuperscript{V} and the PC2/PC1\textsuperscript{u} complex was assessed by N-glycosylation studies and biotinylation assays. Localization of PC1 and PC1\textsuperscript{u} in the cilia was performed using immunofluorescence in endothelial cells (EC).

**Results:** Pkd1\textsuperscript{V/V} embryos lacked the vascular abnormalities observed in Pkd1\textsuperscript{u} embryos including hemorrhage, edema and polyhydramnios. The complexity of the placental labyrinth vasculature and the lymphatic vasculature were similar between embryos including hemorrhage, edema and polyhydramnios. We confirmed that PC1 and PC2 colocalized in the primary cilia of cultured embryos including hemorrhage, edema and polyhydramnios. The complexity of the placental labyrinth vasculature and the lymphatic vasculature were similar between Pkd1\textsuperscript{V/V} and controls but reduced in Pkd1\textsuperscript{u} embryos. Transgenic expression of PC1\textsuperscript{V}\textsubscript{u} was sufficient to rescue the vascular phenotype observed in Pkd1\textsuperscript{u} mutants. Using wound-healing assays we observed that Pkd1\textsuperscript{u} cells migrated properly and that front-rear polarity was similar to controls. We confirmed that PC1 and PC2 colocalized in the primary cilium of cultured ECs. In contrast, PC2 was undetectable in cilia from Pkd1\textsuperscript{u} cells. In addition, we showed that the pool of PC2 protein that co-immunoprecipitated with PC1\textsuperscript{u} was Endo H sensitive, indicating that PC1 cleavage is a pre-requisite for the protein complex to traffic beyond the Golgi in ECs. PC1\textsuperscript{u} was partially resistant to Endo H and able to reach the cell surface.

**Conclusions:** Our data suggests that expression and localization of PC1 and/or PC2 in the primary cilium of ECs is not required for a proper vascular/lymphatic vessel development. This is the first time that an extraciliary role for full length PC1 has been identified.

**Funding:** NIDDK Support

**FR-PO547**

Involvement of Glycolipids in Cyst Formation in Cystic Kidney Disease


**Background:** ADPKD is an important disease that can lead to end-stage renal failure, yet many aspects of the mechanism of cyst enlargement remain unclear. In this study focusing on cystic kidney diseases, we examined the differences in glycolipids, a post-translational modification of proteins. Previous studies have demonstrated the accumulation of sphingolipids, such as GlcCer, LacCer, and GM3, in cystic kidney diseases. However, their direct involvement in cyst formation has not been established.

**Methods:** Glycolipids were extracted from the kidneys of PCK rats, a model of ARPKD, and developed by thin layer chromatography. Total RNA was extracted from the kidney tissue of the model animals and expression of glycosyltransferase was confirmed by qPCR. The same was also confirmed by WB.

**Results:** Thin layer chromatography of glycolipids extracted from renal tissue revealed changes in gangliosides including GM3, an acidic glycolipid. In cystic kidney tissue, GD3 with malignant phenotype was detected. qPCR and WB showed decreased expression of B4galnt1, a glycosyltransferase, in the medullary tubules of cystic kidney tissue. Primary culture of kidney cells from ADPKD patients also showed decreased expression of B4galnt1.

**Conclusions:** In the kidneys of mouse models of cystic kidney disease, disturbance in the composition of glycolipids was observed. Accumulation of GD3 is said to be involved in signaling of cell proliferation and may contribute to cyst enlargement. Decreased expression of B4galnt1 could explain these disturbed glycolipids change.

**Funding:** NIDDK Support

**FR-PO548**

Role of FBW7 in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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**Background:** ADPKD, caused by mutations mostly in PKD1 or PKD2 genes, is a leading cause of end-stage renal disease. Deleting structural components/proteins of cilia in mouse models of Pkd1 inactivation ameliorates ADPKD progression, highlighting the importance of cilia regulation in ADPKD. Our lab has shown that FBW7, a substrate recognition receptor of the SCF\textsuperscript{E3} ligase, can regulate ciliogenesis. It recognizes proteins with a specific phosphorylated sequence called “phospho-degrons” and targets them for degradation via the ubiquitin-proteasome system. In this study, we sought to investigate the role of FBW7 in ADPKD.

**Methods:** We adopted an early-onset ADPKD mouse model where we induced Pkd1 and/or Fbw7 deletion in postnatal mice using a global tamoxifen-inducible Ubc-Cre\textsuperscript{E2/c}.

**Results:** We found that UbcCre\textsuperscript{E2/c}; Pkd1\textsuperscript{P16} P16 pups develop cysts and significantly increased the Two kidney weight/body weight (2KW/BW) and cystic index, along with the loss of kidney function measured by levels of three different markers, BUN, Creatinine, and cystatin C in the blood serum compared to the WT pups. Furthermore, UbcCre; Pkd1\textsuperscript{P16}; Fbw7\textsuperscript{P16} p16 pups also developed cysts and increased 2KW/BW and cystic index similar to UbcCre\textsuperscript{E2/c}; Pkd1\textsuperscript{P16} P16 pups. However, surprisingly, UbcCre; Pkd1\textsuperscript{P16}; Fbw7\textsuperscript{P16} and Fbw7\textsuperscript{P16} p16 pups showed significant rescue in the kidney function based on BUN, Cystatin C, and Creatinine levels in the serum compared to UbcCre\textsuperscript{E2/c}; Pkd1\textsuperscript{P16} P16 pups. Although the kidney function parameters in UbcCre; Pkd1\textsuperscript{P16}; Fbw7\textsuperscript{P16} p16 pups were still significantly higher compared to the WT pups, the fact that the UbcCre; Pkd1\textsuperscript{P16}; Fbw7\textsuperscript{P16} p16 pups displayed improved kidney function despite having no significant changes in 2KW/BW, and cystic index compared to UbcCre\textsuperscript{E2/c}; Pkd1\textsuperscript{P16} P16 pups was exciting. This protective effect on kidney function upon loss of FBW7 was persistent when we analyzed P21 pups. UbcCre\textsuperscript{E2/c}, Fbw7\textsuperscript{P16} p16 pups do not show any apparent kidney phenotype.

**Conclusions:** Loss of FBW7 ameliorates ADPKD progression via proteomic reprogramming that perhaps partially uncouples the kidney function and cystogenesis, challenging the prevailing dogma that kidney function is secondary to defects/cysts in kidney architecture.

**Funding:** NIDDK Support

**FR-PO549**

Anoctamin 3 Enhances Cystogenesis and Ciliary Dosage of Polycystins by cAMP Signaling in Renal Cilia

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**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is a ciliopathy which is characterized by abnormal tubular epithelial proliferation and fluid secretion. We reported Anoctamin1(ANO1), one of chloride channels family could accelerate both cilia formation and cilia trafficking of polycystins. Anoctamin3(ANO3) was recently shown to be involved in ADPKD progression in our research.

**Methods:** 1.Real-time RCR, IHC and Western blot to detect expression of ANO3 in kidney tissue of ADPKD patients and normal kidney. 2.3D culture to verify the function of ANO3 in cysts formation with siANO3 and ad-ANO3 treating in ADPKD cells. 3.MRI to calculate the separates normal tubule space from cystic fluid area. 4.MQAE to detect chloride ion flow by shANO3 and ad-ANO3 treating in kidney tissue of ADPKD patients and normal kidney. 5.Cyst fluid SA in PKD1\textsuperscript{flox/flox}CAG-cre-ER\textsuperscript{T} mice.

**Results:** 1.ANO3 located in renal tubules and cyst and upregulated in human and mouse ADPKD kidneys. 2.siANO3 could inhibited cysts formation. 3.ANO3 was puncta-like localization on cilia membrane and siANO3 increased the cilia length and the expression of PC2. 4.Chloride ion flow was lower by shANO3 treating than ad-ANO3 in ADPKD cells. 5.Cyst fluid SA in PKD1\textsuperscript{flox/flox}CAG-cre-ER\textsuperscript{T} mice was significantly decrease than which in PKD1\textsuperscript{flox/flox} mice.

**Funding:** NIDDK Support
Conclusions: ANO3 may aggravate ADPKD by regulating the renal cilia length and PC2 expression through cAMP signaling and provide mechanistic insights regarding the therapeutic potential of ANO3 pathway.

**Background:** The polycystin complex (PC-1 and PC-2) forms a non-selective cation channel and mutations within the polycystin complex cause Autosomal Dominant Polycystic Kidney Disease (ADPKD). The spatial and temporal regulation of the polycystin complex within the ciliary membrane is poorly understood, partially due to technical limitations studying the electrical properties of this tiny cellular compartment.

**Methods:** In this study, we used both whole-cell and ciliary patch-clamp recordings to measure the polycystin activity in the plasma or ciliary membrane. For carbenoxolone (CNX) injection study, we used intravenous and intraperitoneal injections to C57BL/6 strain mice from postnatal day 0.5 to 17.

**Results:** We identified a novel oxysterol binding pocket within PC-2 to modulate channel activation and showed that mutations within the oxysterol binding pocket disrupt 7β,27-DHC dependent polycystin activation. Pharmacologic and genetic inhibition of 11B-HSD enzyme that synthesizes oxysterol deplete channel activity in primary cilia and result in renal tubular dilation in vivo.

**Conclusions:** Our results identify the oxysterol binding pocket in PC-2 as an allosteric regulatory site in the polycystin complex, which may provide a specific target for novel ADPKD therapeutics.

**Funding:** NIDDK Support
Conclusions: These findings demonstrate that ouabain at levels similar to those circumscribing the cystogenic effect of ATP in vivo can contribute to cyst growth in vitro. Additionally, the ouabain affinity of NKA plays a key role in the hormone’s cystogenic effects.

Funding: NIDDK Support

FR-PO552

Cystotrophic Domain of Fibrocystin/Polyductin Suppresses CAMP-Induced Cyst Formation of Pkd1 Knockout (KO) Cells

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Background: Loss of ciliary protein function leads to defective control of epithelial homeostasis in hereditary polycystic kidney diseases. To address molecular aspects of epithelial physiology, monolayered epithelial spheroids can be used to analyze consequences of protein expression and pharmacological intervention. Here, we employed epithelial cell clones deficient for the protein fibrocystin/polyductin (FPC), the cause of ARPKD, to study the impact of FPC cystotrophic domain expression on cAMP/Src/cyclin cyst formation.

Methods: We used pl-MDCCK, sub-cloned principal-like cell lines, with CRISPR/ Cas9-based genetic knockout (KO) of Pkd1 / FPC, and corresponding controls. Cells were grown in matrigel to allow formation of epithelial spheroids within 3 days. Forskolin (Fsk) treatment was employed to induce CAMP-mediated cyst growth mimicking disease conditions. Proportional lumen, i.e. the ratio of lumen to spheroids, provided the measure to detect the enhanced water / ion transport across the barrier that is characteristic for cystic epithelia. Cellular signals known to stimulate cyst formation were modulated by viral expression of the FPC C-terminal domain and/or interventional treatment.

Results: In Pkd1-KO cell lines, enhanced CAMP levels resulted in massive lumen expansion of epithelial spheroids with no increase in cell number. Cyst induction was sensitive to inhibition of Src kinase and led to activation and increased Y705 phosphorylation of FPC.

Conclusions: Our data reveals that ARPKD patients who carry FPC knockout missense mutations may have a missense mutation on the second allele.

FR-PO555

Transcriptomics Analysis of ADPKD Cysts Shows Remodeling of Purinergic Receptors in Pkd1RC/RC Mice

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Background: Polycystic kidney diseases (PKD) are characterized by development of multiple cysts, dilations of nephron segments, which replace normal tissue and lead to kidney insufficiency.

Methods: To identify new gene pathways affected by cyst development in collecting ducts, we used a bulk RNAseq approach comparing gene expression of normal proportion of cysts with over 15,000 genes. Our data reveals that although cysts originate from normal collecting ducts, cystic epithelium show 2692 down-regulated and 2278 up-regulated gene level. We analyzed the contribution of FPC to cyst signaling expression of a membrane-bound FPC C-terminal protein domain was studied, and was sensitive to inhibition of Src kinase and led to activation and increased Y705 phosphorylation of FPC.

Results: In Pkd1-KO cell lines, enhanced CAMP levels resulted in massive lumen expansion of epithelial spheroids with no increase in cell number. Cyst induction was sensitive to inhibition of Src kinase and led to activation and increased Y705 phosphorylation of FPC.

Conclusions: Our data reveals that ARPKD patients who carry FPC knockout missense mutations may have a missense mutation on the second allele.

FR-PO554

Early Transcriptional Changes in Distal Convoluted Tubule Cells Are Evident in PKD1 (Poly cystin 1) Mutant Mice Prior to Cyst Development

Elizabeth D. Nguyen,1,2 Amrei M. Mandel,1,2 Scott R. Houghtaling,2 Sean Gombart,1 David R. Beier,1-2 University of Washington, Seattle, WA; 2Seattle Children’s Research Institute, Seattle, WA; 1Universitaet zu Koln, Koln, Germany; 2Universitätsklinikum Koln, Koln, Germany.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in PKD1 and PKD2 and is not diagnosed in patients until cyst formation has already occurred. Cysts arise mainly from distal portions of renal tubular segments but the mechanism of cyst formation is still unclear, and there are no treatment strategies to prevent formation of cysts. The PKD1 p.R5327C Pkd1-m1.1Pcha knockin mouse (RC/RC) develops gradual cystogenesis mimicking the features of ADPKD (Hopp K et al., JCI 2012). Here, we use this model to identify transcriptional changes at early timepoints; post-natal day 10 (p10), before gross cyst formation and p20, after cystic changes occur in the kidney.

Methods: Single nuclei RNA-seq was performed on kidneys from RC/RC and age matched control mice at p10 (n=3) and p20 (n=3). Sequencing data within the same condition were aggregated. Cluster identities were assigned using expression of known cell markers. Differentially expressed genes between p10 and p20 with correlating controls was performed on distal convoluted tubule (DCT) cell clusters using regression analysis with a cutoff of log2 fold change.

Results: Cells with unique molecular identifiers (UMI) ≥ 1000 ranged between 7000 to 10,000 for controls and 25,000 to 31,000 for kidneys from RC/RC mice. There were 20-26 clusters for each condition covering 12 kidney cell types, including >1500 DCT cells per condition. Genes with significant differential expression in the RC/RC mouse at p10 included genes associated with cystic disease (Nck1 and Pde3a) in addition to 34 other genes. Genes with differential expression within DCT cells at p20 include Hsf2bp in addition to 5 other genes.

Conclusions: This work identifies genes within distal convoluted tubule cells implicated in cyst formation in polycystic kidney disease caused by mutations in PKD1. The transcriptional landscape of the pre-cystic kidney is significantly different than control, indicating that molecular pathways are activated at early timepoints before structural changes in the tissue. Further characterization of differentially expressed genes at early timepoints will address an important gap in field of ADPKD by identifying pathways leading to cyst formation and potential targets for therapeutics before cysts occur.

Funding: NIDDK Support, Private Foundation Support

FR-PO555

Dynamics of the Renal Transcriptional Profile Through the Course of the Disease in Experimental ADPKD

Yahya Alswajj,1,2 Cassandra Trask,3 Sara Kazemnia,4 Alfonso Eirin,5 Maria V. Irazabal. Mayo Clinic Department of Internal Medicine, Rochester, MN.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a chronic disease spanning an affected individual’s life where earlier stages are marked by cyst development and kidney enlargement with preservation of renal function and later stages by increased kidney fibrosis and renal function decline. To understand the underlying molecular processes accompanying the dynamics of the disease phenotype, we comprehensively characterized the kidney transcriptomic profile in the slowly progressive hypomorphic Pkd1 mutant mouse (p.Arg3277Cys, Pkd1m1.1RC) across the course of the disease.

Methods: Pkd1m1.1RC and wild type (WT) mice (n=10, 5 males and 5 females each) were studied at 5 timepoints: embryonic day 18.5, adolescent, and adult (3, 5, 6, and 8 weeks of age). Disease severity and progression were evaluated by kidney weight/body weight (K/BW), cystic index (CI), fibrotic index (FI), and BUN. Renal tubular cell proliferation, inflammation, mitochondrial morphology, and metabolic function were assessed by immunostaining, western blot, electron microscopy, and metabolomics at all time points.

Results: K/BW and CI were higher in Pkd1m1.1RC versus WT kidneys, which was higher at 1- compared to 6-, but further increased at 12m (Figure). Functional analysis showed that while DE genes were primarily implicated in inflammation, immune response, and mitochondrial functions, different signatures characterized each timepoint. Confirmaory studies on cell proliferation, inflammation, mitochondria, and kidney metabolism agreed.

Conclusions: Our findings that the renal phenotype and transcriptomic landscape varied across the course of ADPKD may have significant clinical implications and suggest that different therapeutic strategies might be beneficial throughout the disease.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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FR-PO556
CRISPR Activation of PKD1 in Immortalized Cell Lines Is Limited by Its Heterochromatinized Proximal Promoter
Anubhav Chakraborty, Christopher J. Ward, Alan S. Yu. University of Kansas Medical Center, Kansas City, KS.

Background: Loss of function mutations in PKD1 are the predominant causes of autosomal dominant polycystic kidney disease (ADPKD). ADPKD is characterized by the progressive enlargement of renal cysts which leads to a decline in renal function. Cysts form when the functional levels of polycystin 1 (PC1), the protein product of PKD1, decrease below a critical threshold. We hypothesize that increasing the expression of PKD1 could potentially restore functional levels of PC1 and rescue the disease.

Methods: To increase the expression of PKD1 using CRISPR activation (CRISPRa), we designed and screened several guide RNAs (gRNAs) targeting the proximal promoter of the gene in mouse renal cortical collecting duct (M1) and HEK293T cell lines. We measured the abundance of PKD1 transcripts in these cell lines using qRT-PCR and assessed the chromatin accessibility of the PKD1 proximal promoter.

Results: CRISPRa-mediated PKD1 upregulation in M1 or HEK293T cells reached a maximum of 2-2.5-fold (p<0.001) using pooled gRNAs targeting the 100 bp region upstream of the transcriptional start site. In contrast, positive control genes (Klf1, Nkx2, Oct4, INS, and TTN1) displayed substantially greater increases in expression (5-6000-fold). Both cell lines exhibited low PKD1 mRNA abundance (~10 copies/cell). PCR-based chromatin accessibility assay showed less than a 4-fold enrichment in the PKD1 proximal promoter (in both cell lines), indicating a heterochromatinized region. Additionally, H3K27 acetylation and DNase hypersensitivity data from ENCODE showed that heterochromatization of the mouse or human PKD1 proximal promoter is common to most immortalized cell lines.

Conclusions: Our findings suggest that the heterochromatinized PKD1 proximal promoter poses a limitation on the extent to which the gene can be effectively upregulated by CRISPRa. Understanding these constraints is crucial for developing strategies to overcome heterochromatinization and enhance PKD1 expression, potentially enabling therapeutic interventions for ADPKD.

FR-PO557
Identification of Paracrine Factors in the Early Cyst Microenvironment in Polycystic Kidney Disease
Seventa A. Yasinoglu,1 Thomas B. Kuipers,1 Hester Bange,2 Michael Eikmans,1 Hailiang Mei,1 Hans J. Baalde,1 Dorien J. Peters.1 Leids Universitair Medisch Centrum, Leiden, Netherlands; 2Crown Bioscience Netherland B.V., Leiden, Netherlands.

Background: Initial cysts that are formed upon Pkd1 loss in mice impose persistent stress on surrounding tissue and trigger a cystic snowball effect, leading to the activation of PKD-related signaling which increases the likelihood of new cyst formation and disease progression. In the present study, we profiled transcriptomic changes that occur in the cyst microenvironment in PKD mice and identified paracrine factors with increased activity in PKD mice and in human ADPKD cyst cultures.

Methods: To perform an unbiased analysis of transcriptomic alterations that occur in the cyst microenvironment, microarrays were collected from iKsp-Pkd1+/- mice with scattered Pkd1-deletion using Laser Capture Microdissection. Based on F4/80 staining, collected microarrays were defined as either macrophage (MΦ)-low cystic, representing early alterations in the cyst microenvironment, MΦ-high cystic, with more advanced alterations, or non-cystic. Pathway and upstream regulator analyses were applied to identify dysregulated pathways and secreted factors that may play a key role in altered signaling. Finally, supernatants from 3D cultures of primary human ADPKD cells were harvested to analyze secreted paracrine factors using a Bio-Plex assay.

Results: When compared to the non-cystic microarrays, 953 and 808 genes were dysregulated in MΦ-low and MΦ-high regions, respectively. Several injury-repair, growth, and tissue remodeling-related pathways were activated in MΦ-low microarrays, accompanied by mild metabolic alterations. In the more advanced MΦ-high microarrays, these pathways were strongly poteniated and the metabolisms was more dysregulated. Using upstream regulator analysis, paracrine factors were identified with increased activity in the early cyst microenvironment, including IFNG, TNF, IL1B, TGFβ1, AGT, and PDGFB. In addition, we identified TNF-α, PDGFB-ß, and several other factors that were undetected by primary ADPKD cells in the culture medium.

Conclusions: Collectively, our data provide an overview of molecular alterations that occur specifically in the MΦ-low and MΦ-high cyst microenvironment. Also, paracrine factors were identified that may drive early epithelial cell-induced alterations and tissue remodeling, which potentially give rise to the formation of more cysts.

Funding: Private Foundation Support

FR-PO558
Identification of Early Transcriptional Markers of ADPKD Cystic Epithelial Cells
Victoria Rai, Laura Onuchic, Marcela A. Reyna-Neyra, Giorgia Schena, Joseph E. Craft, Michael J. Caplan. Yale University, New Haven, CT.

Background: Mechanisms driving ADPKD cystogenesis are not well understood, and reliable biomarkers are scarce. To explore molecular changes in cystogenesis, we performed single cell RNA sequencing on kidneys from an ADPKD mouse model at an early stage of cyst formation and from a model in which cystic disease was suppressed by expression of the polycystin-1 C-terminal tail (PC1-CTT).

Methods: Doxycycline inducible Pkd1fl/fl;Pax8rtTA;Teto-Cre ADPKD C57BL/6N mice expressing CTT (Pkd1+/-;CTT or not (Pkd1-/-) were induced between 4-6 weeks and aged to 10 weeks. Single cell kidney suspensions were pooled and processed for cDNA synthesis and library preparation with 10X Chromium technology. Reads were aligned using the 10X Genomics CellRanger pipeline and further processed using Seurat v4.3.

Results: Clusters corresponding to tubule segments were identified using established annotations. Several novel clusters defined by expression of multiple markers, including V Cad, Tmc2, and Filp1l1, were identified in the Pkd1-/- model. These clusters were sparsely populated in Pkd1+/-;CTT samples, suggesting that they may correspond to cyst epithelial cells that are suppressed by PC1-CTT expression. Each of these novel clusters included cells whose markers identified them from distinct tubule segments (e.g. Sgr2, Umod, S100g), suggesting that cells of different segments are clustered together by virtue of sharing the putative cyst cell transcriptional signature. The single cluster observed in Pkd1-/-;CTT model and not in the Pkd1+/-;CTT model is enriched in markers associated with metabolic processes including Uqgl2, Chr1, and Pck1. Importantly, at 10 weeks there are no significant differences in %K/W/BW or kidney morphology between the Pkd1+/-;CTT and Pkd1-/-;CTT models, suggesting that the cells belonging to the cystic epithelial cell clusters exhibit early identifiable differences in transcriptional programming.

Conclusions: scRNA-seq at an early timepoint reveals novel transcriptional markers of putative cystic epithelial cells. The protein expression levels of individual markers are being assessed. These results suggest that there are epithelial cells early in disease progression exhibiting a unique transcriptional signature that may elucidate the mechanisms of cyst formation and that may provide new candidate biomarkers.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

FR-PO559
Repression of Foxo3-Gatm Accelerates Cystogenesis by Increasing Reactive Oxygen Species (ROS) in ADPKD
Jaehee Jun, Jong Hoon Park, Je Yeong Ko, Yejin Ahn, Oh Chaewon, Jinu Min. Sookmyung Women’s University, Sookmyung Women’s University, Yonggan-gu, Seoul, Republic of Korea.

Background: The most common inherited renal disorder and leading cause of genetic end-stage renal disease is ADPKD. The relationship between ADPKD and oxidative stress have reported in in the early stage with disease progression, however the mechanism of correlation remains unclear.

Methods: We generate Pkd1flox/flox:Bmi1-Cre and performed integrative analysis. 3D cell culture produced in vitro cyst formation, and we observed differences in cyst formation.

Results: We explored the mechanisms associated with FOXO3 in ADPKD through screening by integrative analysis since FOXO3 regulates mitochondrial gene expression. And notably, GATM were significantly reduced in ADPKD patients. Furthermore, GATM was decreased by FOXO3 knockdown. Additionally, Inhibition of FOXO3 decreased GATM in the mitochondria. Therefore GATM is regulated by FOXO3 in the mitochondria. To verify the effect of GATM on oxidative stress in ADPKD, we measured cellular ROS, DCFDA fluorescence intensity is elevated in GATM knockdown. More specifically, GATM silencing increased mitochondrial superoxide levels. This GATM-mediated increase in superoxide levels was confirmed by co-staining with MitoSOX Red. To investigate the effect of GATM on cyst formation in ADPKD, we experimented 3D cell culture and observed significantly promoted cyst formation with GATM silencing.

Conclusions: We suggest a novel insight of cystogenesis, in which inhibited Foxo3 reduces GATM expression, thereby increasing ROS and oxidative stress, consequently progressing cyst enlargement in ADPKD.

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FR-PO561

Progressive Cellular Senescence Promotes and Senolytic Therapy Delays Cyst Growth in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common, life-threatening inherited kidney disease. Cellular senescence is permanent proliferative arrest, which accumulates with the progression of a variety of chronic diseases and age in response to endogenous and exogenous stresses. However, the roles and mechanisms of cellular senescence in ADPKD remains elusive.

Methods: To investigate the roles of senescence in ADPKD and evaluate the senescence removal therapy on cyst growth, we treated two Pkd1 mutant mouse models with senescent inducer D-galactose (D-gal) or senolytics. To understand senescence-associated mechanisms in promoting cyst growth, we performed H&E staining, Western blot, qRT-PCR and TUNEL analysis in vivo and in vitro. We also identified SASP produced by Pkd1 mutant cells by mass spectrometry.

Results: Cellular senescence was increased in Pkd1 mutant mouse and human ADPKD kidneys characterized by the increase of the expression of SA-β-Gal and p16. Treatment with senolytics, including dasatinib (D) (7.5 mg/kg), quercetin (Q) (75 mg/kg) and D plus Q, delayed cyst growth in kidneys of two Pkd1 mutant mouse models as seen by decrease of cyst index, KW/BW ratios, BUN levels as well as cyst lining epithelial cell proliferation and the release of senescence-associated secretory phenotype (SASP), but increase cyst renal epithelial cell apoptosis. Co-treatment with D plus Q had synergized effect on cyst growth compared to that in kidneys treated with either D or Q alone. The release of SASP from Pkd1 mutant renal epithelial cells stimulated the proliferation of nearby renal epithelial cells and activated renal fibroblasts characterized by the increased the phosphorylation of Akt, S6 and Stat3 and the expression of fibrotic markers (α-SMA and Col-1). In addition, treatment with senescent inducer, D-gal, promotes cyst growth in Pkd1 mutant kidneys. The clearance of senescence-associated P16INK4a-positive cells by treating Pkd1-Cre:INK-ATTAC and Pkd1-Insig1-2 mice with AP20187 delays the cyst growth in ADPKD.

Conclusions: Senescence was increased in Pkd1 mutant mouse and ADPKD kidneys, which is mediated by p16 associated signaling pathways, and the senescence removal therapy with senolytics is a novel therapeutic strategy for ADPKD treatment.

FR-PO562

Total and Phosphoproteomic Analyses in Kidneys from an Authentic Mouse Model of Human Autosomal Dominant Polycystic Kidney Disease Davoud Ghazanfari,1,2 Ario Mohammadi,1 Jing Zhou,1,2 Brigham and Women’s Hospital, Boston, MA; 2Harvard Medical School, Boston, MA.

Background: ADPKD (Autosomal Dominant Polycystic Kidney Disease) is a genetic disorder characterized by the development of multiple cysts in the kidneys. The disease is caused by mutations in PKD1 and PKD2, encoding PC1 and PC2 respectively. To date, PC1 and PC2 have been implicated in modulating a number of cellular events such as Ca2+ signaling, mTOR, cyclic AMP, Wnt, PCP, and STAT3 pathways. How the polycystins modulate these pathways remains elusive.

Methods: We have identified several pathways that are changed in an authentic mouse model of human ADPKD kidneys from Pkd1 knockout mouse mice with controls isolated at different stages and subjected to multiplexed proteomics and phosphoproteomics. Various bioinformatic techniques, RT-PCR, immunostaining, and western blotting were used for analysis and validation.

Results: To determine the cystogenic total and phosphoproteome, we performed multiplexed quantitative mass spectrometry analysis in Pkd1 knockout mouse mice at pre-early disease and disease stages. Several thousands of proteins were quantified and hundreds of phosphorylation events were measured. MS/MS data were searched against a Uniprot mouse database with both the forward and reverse sequences using the SEQUEST algorithm. MS3 data was used for quantification. Phosphopeptides were processed separately but taken through a similar software pipeline with an additional phosphorylation sites localization step using the Ascore algorithm. Several significant pathways were identified. A specific selection of specific proteins identified in the total and phosphoproteomic studies are being validated and further analyzed.

Conclusions: We have identified several pathways that are changed in an authentic mouse model of human ADPKD and determined the sequence of change of specific pathways in relation to disease development.

Funding: Other NIH Support - PKD Foundation

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

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**FR-PO563**

**Tubular Obstruction-Induced Polycystin Upregulation is Profibrotic and Induced a Severe Cystic Phenotype in Adult Mice with ADPKD**

*Ming Wu, Shuguang Hospital, Shanghai, China.*

**Background:** Mutations in Pkd1 or Pkd2 gene cause ADPKD, however high levels of polycystins are detected in renal tissues of ADPKD patients. Animal studies showed that loss and gain of function of polycystins are both pathogenic and can induce cystic phenotype in the kidney, which are associated with enhanced renal fibrosis.

**Methods:** UUO or aristolochic acid I (AAI) induced mouse nepropathy was established for renal fibrosis study. Pkd1 or Pkd2 gene was inactivated in mice.

**Results:** We demonstrated that polycystin-1 or polycystin-2 was highly expressed in fibrotic mouse kidneys and positively correlated with expression of collagen-I. Inhibition or deletion of polycystin-2 reduced the deposition of extracellular matrix proteins in fibrotic kidneys. Similarly, knockout of Pkd1 gene attenuated renal fibrosis in fibrotic mouse kidneys. We further hypothesized that inhibition of polycystins delays cyst growth by mitigating renal fibrosis. Here, we showed that polycystin-1 or polycystin-2 was up-regulated in Pkd2 or Pkd1 mice respectively and tightly correlated with the growth of renal cysts and fibrosis development. Genetic deletion of both polycystin-1 and polycystin-2 retarded cyst growth in adult ADPKD mice. Finally, we inactivated Pkd1 gene in a fibrosis triggered adult ADPKD mouse model at different time point before or after the fibrotic injury. We showed that early and long-term inactivation of Pkd1 delayed fibrosis triggered renal cyst growth in adult Pkd1 mice as compared with mice with late and short-term inactivation of Pkd1 gene.

**Conclusions:** We conclude that tubular obstruction induced polycystin up-regulation is pro-fibrotic and accelerates cyst growth through enhancing renal interstitial fibrosis in ADPKD mice. Our study indicates that ADPKD is caused by the coexistence of loss and gain function of polycystins.

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**FR-PO564**

**CDK6 Suppresses Tubulin Polyglutamylation in Primary Cilia and Promotes Renal Cystogenesis in ADPKD**

*Kai He, XiaoBo Sun, Chun Chen, Yan Huang, Jinghua Hu. Mayo Clinic Minnesota, Rochester, MN.*

**Background:** Polycystin-1 (PC1) and Polycystin-2 (PC2) hypothetically form an ion channel complexes localize on primary cilium to inhibit renal cyst growth. Polyglutamylation (PG) is one of the tubulin posttranslational modifications (PTMs) predominately occurs on cilia axoneme which controls the ciliary localization of PC1/2. Defective axoneme PG has been correlated with ciliopathies that usually manifest syndromic forms of PKD. We recently discovered an unconventional CDK6-mediated pathway that specifically inhibits axoneme PG by engaging the ciliary import of tubulin glutamylases. Here, we show that CDK6 is strongly upregulated in renal tubules of ADPKD mice and human patients. In agreement with the inhibitory role of CDK6 in ciliary import of tubulin glutamylases, defective axoneme PG was observed in ADPKD cells. Remarkably, pharmacologic inhibition of CDK6 restores defective axoneme PG, increase ciliary dosage of PC2 in ADPKD cells, and significantly suppressed the cyst growth in ex vivo model of ADPKD. These data suggest that targeting axoneme PG could be a novel therapeutic approach for ADPKD. To identify novel small molecules/drugs to specifically target axoneme PG, we established high-content image-based strategy to screen drug repurposing compound library and kinase inhibitor library. We will further access the therapeutic potential of drug hits in ADPKD, using in vitro, in vivo and in vivo ADPKD models.

**Methods:** Cell-imaging Drug screening Biochemistry and Molecular Biology Ex vivo renal cystogenesis

**Results:** 1. CDK6 suppresses tubulin polyglutamylation by inhibiting ciliary import of tubulin glutamylases. 2. CDK6 is strongly upregulated in renal tubules of ADPKD mice and human patients. 3. ADPKD cells exhibit defective tubulin polyglutamylation in primary cilia. 4. Inhibition of CDK6 suppresses cyst growth in ex vivo ADPKD model.

**Conclusions:** Targeting axoneme PG could be a novel therapeutic approach for ADPKD.

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

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**FR-PO565**

**Eliosin, A Protein Encoded by a Transcript from the HmPKD Locus, Is a Component of Mitochondria-ER Contact Sites/Mitochondria-Associated Membranes (MAMs)**

*Robert L. Bacalla,1,2 Virginie Lazar,2 Weimin Xu,3 Richard L. Roudebush IA Medical Center, Indianapolis, IN; 4Indiana University School of Medicine, Indianapolis, IN.*

**Background:** The HmPKD1 gene locus is predicted to produce multiple transcripts whose functions are largely unknown. We studied one alternative transcript that starts at intron 40 but has a protein start site in exon 41. This transcript has a splice from the 3’ end of exon 41 to the 5’ end of exon 43 of the HmPKD1 gene. Subsequent splices follow the same splicing pattern found in the full-length polycystin-1 mRNA. The subcellular localization and function of this alternative transcript is not known.

**Methods:** PCR primers are designed to detect the transcript’s unique splice features that are not found in full-length HmPKD1 transcripts. RT-PCR studies were conducted to identify the alternative transcript. cDNA encoding the alternative transcript and its product (Eliosin) were expressed in COS-1, 293, and NIH 3T3 cells for immune-blots and light microscopy analysis. Co-localization studies were performed with mCherry-Eliosin fusion protein and dynamin-related protein (DRP-1) or mitofilin-1 (MFN-1). Analysis of mitochondria morphology in co-transfection studies was performed in 293 and PKD 9-7 cells.

**Results:** RT-PCR reactions performed using human kidney RNA confirmed that a shortened PCR fragment from the PKD1 gene’s exons 41/43 splice is expressed. Immune blot analysis revealed that the protein, we name Eliosin is a 48 kDa protein and it is expressed by a CDNA isolated from human testes. Fluorescence microscopy studies show co-localization between Eliosin and Insoluble-3-phosphate receptor or MFN-1, known components of MAMs. However, when Eliosin and DRP-1 are co-expressed, DRP-1 is found in the cytosol. Since DRP-1 mediates mitochondria scission, we reasoned that the mutation in Eliosin leads to unopposed mitochondria scission in PKD 9-7 cells. We find that untransfected PKD 9-7 cells have fragmented mitochondria while Eliosin-transfected PKD 9-7 cells have normal-appearing mitochonria.

**Conclusions:** Eliosin is a 48 kDa protein that is a component of mitochondria-ER membrane contact sites, and it acts to displace dynamin-related protein-1 from MAMs. We conclude that Eliosin plays a role in altering the balance between mitochondria fusion and scission. This finding extends the HmPKD1 locus role in mitochondria metabolic physiology.

**Funding:** NIDDK Support, Other NIH Support - Paul Teschan Research Grant from DCI
Methods: Pkd1RC/RC (RC) male mice. 2DG (100 mg/kg) or CHLQ (60 mg/kg) from 50 - 120d of age. Kidney specific Pkd1, Trg double knockout mice generated by Kap 1.3 Cre-lox recombination. Autophagic flux measured by increase in LC3II (autophagosomes) with the lysosomal inhibitor, bafilomycin. Autophagy proteins measured by immunoblot. Cyst index (%) number and area determined on kidney cross section using a computerized algorithm.

Results: See table. 2DG significantly reduced two kidney/body weight ratio (2K/ BW), cyst index, cyst count, cyst area, BUN. 2DG significantly (P<0.05) reduced PCNA+ cells lining cysts. 2DG decreased autophagy-related proteins (ATG12-5 complex, ATG3) and suppressed autophagic flux in RC kidneys. p-ERK and p-AMPK known to activate autophagy were decreased by 2DG. 2DG from 150-350d of age (later stage of PKD) had no effect on cyst growth. CHLQ had no effect on PKD or proliferation in the cells lining the cysts. CHLQ resulted in decreased expression of pBeclin (critical regulator of autophagy) and suppressed autophagic flux in RC kidneys. Next autophagy (ATG7) was knockout in Pkd-/- mouse. In a rapid PKD model, 2K/BW and BUN at 28 d old was the same in Pkd/- vs Pkd/-/ATG/-/+ vs Pkd/-/ATG/-/- mice. In a slow PKD model, at 120 d, double knockout RC ATG7 mice had higher cyst indices than RC mice.

Conclusions: 2DG suppressed autophagy, decreased proliferation, slowed PKD and improved kidney function. CHLQ suppressed autophagy but had no effect on PKD. Knockout of autophagy (ATG7) had no effect on PKD in a rapid severe model and worsened PKD in a slowly progressive model. Pharmacological suppression of autophagy had variable effects on proliferation and cyst growth and genetic knockout of autophagy worsened PKD in a slowly progressive PKD model.

Funding: Veterans Affairs Support

Cyst indices

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<th>Void</th>
<th>2K/W</th>
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<th>2K/BW</th>
<th>Void</th>
<th>CHLQ</th>
<th>Pkd1RC/RC</th>
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<td>4.9</td>
<td>5.6</td>
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ND=Not determined as kidney completely replaced by cysts. *P<0.05

FR-PO568

Dephosphorylation Facilitates Trafficking of Mutant Polycystin-2 to Cilia Yuqiang Cai,1 Ke Dong,1 Max Spitzer,1 Linda Geiges,1 Xin Tian,1 Matteus Krappitz,1 Lonnette Diggles,1 Zemeng Wei,1 Adrian Cordido,1 Steven Lim Cho Pei,1 Sorin V. Fedeles,1 Stefan Solmo,1,2 Yale University Department of Internal Medicine, New Haven, CT; 2Yale University Department of Genetics, New Haven, CT.

Background: ADPKD is characterized by mutations in polycystin-1 (PC1) and polycystin-2 (PC2) that result in progressive cyst formation in the kidneys and liver. The steady state expression and ciliary trafficking of PC1 requires the presence of PC2. Missense mutations resulting in alterations in trafficking properties of PC1 and PC2 underlie a subset of cases of ADPKD. Here, we investigate the role of phosphorylation of PC2 in its localization to cilia.

Methods: Unbiased phosphoproteomic analysis of mouse kidney lysates was performed to identify the phosphorylation sites of native PC2. mNeonGreen-tagged PC2 (PC2NG) constructs of wild type or dephosphorylated forms were generated and expressed in IMCD3 cells lacking endogenous Pkd1 or Pkd2 or both. Ciliary expression of PC2 was analyzed by live-cell imaging and by immunofluorescent cell staining. Knock-in mice carrying dephosphorylated Pkd2S829A and a novel anti-phospho-specific PC2 antibody were generated and utilized as part of this study.

Results: Two phosphorylation sites in native PC2 were identified from native protein in mouse kidneys: Ser112 and Ser829. We investigated the functional effects of Ser829 phosphorylation. We found that expression of PC2 in cilia was regulated by phosphorylation at Ser829. While dephosphorylation at the Ser829 was not a prerequisite for PC2 ciliary expression, the phosphorylation deficient Ser829A (S829A) form of PC2 resulted in a prentissitively enhanced expression in cilia that did not require the presence of PC1. Mice carrying a homozygous knockin phosphorylation deficient Pkd2S829A allele have no phenotype indicating that the absence of phosphorylation at Ser829 does not result in reduced PC2 function. Introduction of S829A into a PC2 construct containing a human pathogenic mutant that otherwise does not appear cilia resulted in expression in cilia, indicated that dephosphorylation rescued the trafficking defect of the human mutation.

Conclusions: Dephosphorylation of PC2 at Ser829 retains normal function in vivo. Dephosphorylation at Ser829 enhances the steady state expression of PC2 in cilia and it overcomes cilia trafficking defect of a human pathogenic missense mutant of PC2. The phosphorylation state of PC2 has a functional role in expression of the polycystin complex in cilia.

Funding: NIDDK Support

FR-PO569

Pkd2 Deficiency in Embryonic Aqp2+ Progenitor Cells Is Sufficient to Cause Severe Polyzystic Kidney Disease Akaki Talisang,1 Chao Gao,1 Sana A. Shehbaz,1 Enuo Chen,1 Madhullika Sharma,2 Pamela V. Tran,1 Carlton M. Bates,1 Darren P. Wallace,2 Wenzheng Zhang,1 1Albany Medical Center, Albany, NY; 2University of Kansas Medical Center Department of Internal Medicine, Kansas City, KS; 3University of Kansas Medical Center, Kansas City, KS; 4UPMC Children’s Hospital of Pittsburgh Child Development Unit, Pittsburgh, PA.

Background: Most cases of autosomal dominant polycystic kidney disease (ADPKD) are caused by mutations in Pkd1 or Pkd2, which encode polycystin-1 and polycystin-2, respectively. The mechanism for renal cyst formation remains unclear. We showed that embryonic Aqp2+ progenitor cells (AP) give rise to principal cells (PC) and intercalated cells (IC) to generate the distal renal segments consisting of the late distal convoluted tubules (DCT2), connecting tubules (CNTs), and collecting ducts (CDs). AQP2 in APs also contribute to the urinary tract maintenance and injury repair and regulating DCT2/CNT/CD cells. Here, we tested the hypothesis that aBlcation of Aqp2 in embryonic AP is sufficient to induce PKD.

Methods: Aqp2Cre Pkd2f/f mice were generated to disrupt Pkd2 in embryonic AP. Aqp2Cre Pkd2f/f mice were tamoxifen-induced at P1 or P60 to disrupt Pkd2 in neonate or adult AP and PC, respectively, and sacrificed 7 months after Cre induction. Immunofluorescence was done to assess cell types that lined the cysts. Cells were categorized and quantified. We also analyzed cist-lining cells in four other PKD mouse models (epk, S6pcCre;Frs2A, Pkd1KO, and Tmm14KO), and compared staining between ADPKD patients and normal controls.

Results: Pkd2 was expressed in all segments from proximal tubule to CD, and in all CNT/CD cell types. Pkd2+ Aqp2Cre mice developed severe PKD and died ~P17. The kidneys showed a reduced IC to PC ratio and a complete loss of α-IC by P12. Cysts extended from the CD to DCT1 and possibly to the loop of Henle, but not to the proximal tubules. Pkd2+ Aqp2Cre mice had obvious cysts by P6 with rare α-IC. IC were more apoptotic than PC. Ablation of Pkd2 in neonate or adult AP and PC in Aqp2Cre+/- or Pkd2f/f mice did not cause PKD. Cyst-lining α-IC were found in the other PKD models. AQP2+ cells were found in the cysts of only 13 out of 17 AQP2-/- samples, which led a diminished IC to PC ratio. None of the ADPKD kidneys had α-IC within the AQP2-/- cysts.

Conclusions: Pkd2 deletion in embryonic AP, but not in neonate or adult Aqp2+ cells (PC and AP), was sufficient for PKD development. IC, particularly α-IC, were selectively deleted in Aqp2Cre+/-/Pkd2f/f mice and ADPKD patients. We proposed that Pkd2 is critical for maintenance of cystic α-IC.

Funding: NIDDK Support, Other NIH Support - Capital Region Medical Research Institute
FR-PO570

Direct Physical Interaction Between Calcium-Sensing Receptor and Polycystin-2: Implication in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a ciliopathy caused by mutations in PKD1 or PKD2 genes, encoding polycystin-1 (PC1) and polycystin-2 (PC2), respectively, which form a complex localized to the primary cilium. PC2 is a member of the transient receptor potential polycystic family of cation channels acting as a non-selective cation channel which, in the primary cilium of renal epithelial cells, preferentially conducts K+ and Na+. In this study, we hypothesize that the Calcium Sensing Receptor (CaSR) is involved in PC2 functional regulation.

Methods: Human conditionally immortalized Proximal Tubular Epithelial cells isolated from urine sediments (ciPTEC) and with stably downregulated PKD2 (cPTEC-PK2KD), expressing endogenous CaSR, were used as experimental tools.

Results: Immunofluorescence experiments showed the expression of both CaSR and PC2 on the primary cilium. CaSR and PC2 co-immunoprecipitated both in ciPTEC and mouse kidney. Worthy of note, Proximity Ligation Assay demonstrated the direct interaction between CaSR and PC2 in both ciPTEC and mouse kidney slices. Preliminary electrophysiological measurements demonstrated that, in ciPTEC, CaSR activation caused plasma membrane hyperpolarization, consistent with modulation of cation channels. Interestingly, the membrane hyperpolarization induced by the activation of CaSR in PTEC-PK2KD was significantly lower with respect to cPTEC.

Conclusions: These studies underline the functional coupling of CaSR with PC2, providing a rationale for the amelioration of the principal cellular ADPKD dysregulations (PC2 knockdown). Sensing Receptor (CaSR) is involved in PC2 functional regulation.

FR-PO571

Molecular Basis of the Regulation of a Gain-of-Function Polycystin-2 Channel by Small Molecular Ligands

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Background: Mutations in PKD2 gene lead to autosomal dominant polycystic kidney disease (ADPKD). PKD2 encodes polycystin-2 (PC2) protein. As a member of the transient receptor potential (TRP) channel superfamily, PC2 functions as a non-selective cation channel. The activation and regulation of PC2 channel is largely unknown and no small molecule ligand of PC2 has been reported.

Methods: We expressed human PC2 channel in Xenopus oocytes, and used two-electrode voltage clamp (TEVC) method to record the ion channel function.

Results: In this work, we tested the effect of a group of known TRP channel small molecule agonists on PC2 channel function, and found that while most of them inhibit the activity of PC2_F604P, a gain-of-function PC2 mutant PC2 channel, some others have a dual regulating effect with low concentration further activates PC2_F604P, and high concentration leads to an inactivation of the channel. We identified two distinct binding sites of the ligand in PC2_F604P that are responsible for activation and inactivation respectively. Our results also suggest that Ca2+ binding at the outer pore region is essential for ligand-induced inactivation.

Conclusions: These results provide structural and functional views of the interaction between PC2 and small molecule ligands and showcase how ligands can regulate channel function in unusual mechanisms.

Funding: NIDDK Support

FR-PO572

Transcriptomic Analysis of Pkd2-Deficient Kidneys Shows Altered Metabolic and Cytoskeleton Pathways Similar to Pkd1 Models and Evidence of an Increased Inflammatory Response

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by fluid-filled cysts and progressive enlargement of the kidney. Mutations in either PKD1 or PKD2 genes, encoding polycystins 1 and 2, are responsible for the disease. Despite advances in understanding polycystins structure and function, how mutations in PKD genes lead to cystogenesis is still unknown. While dozens of studies have investigated the role of human and mouse PKD1 mutant kidneys, none focused on PKD2 deficient kidneys. Here we report RNAseq from Pkd2 cystic kidneys from a slow progression model.

Methods: We induced Pkd2 deletion at P27 (postnatal day 27) in a strain that inactivates Pkd2 in the renal epithelium. We isolated RNA from kidneys at P123 to P125 from 10 males and 10 females (5 Pkd2+/+, 5 Pkd2flox/flox; FasxhTdl-Cre (+) and 5 littermate Pkd2fl/fl; FasxhTdl-Cre (+) per set) and sequenced using Illumina NovaSeq 6000 S4 System. Sequence reads were mapped to mm10 mouse genome and counted using STAR. Differential gene expression and pathway analyses were done in R using DESeq2, clusterProfiler and gsea.

Results: Transcriptomic analysis identified ~1976 significantly differentially expressed (DE) genes (adjusted p < 0.05), of which 622 were only DE in males and 229 in females. In both sexes, injury markers were up-regulated and pathway analyses suggested increased immune-mytokine activity. Gene set enrichment analysis suggested enrichment of up-regulated genes in inflammatory pathways and down-regulated genes in oxidative phosphorylation and fatty acid metabolism, similar to what is observed in Pkd1 knockout kidneys. Approximately 700 DE genes in Pkd2 knockout kidneys were also DE in Pkd1 knockout kidneys. Pathway analysis of DE genes in both Pkd1 and Pkd2 models showed enrichment of genes involved in cytoketone, sodium binding and encoding proteins in the kinocortex.

Conclusions: The data suggest an increased inflammatory response in Pkd2 knockout kidneys. One of the transcriptional changes previously reported in Pkd1. The presence of injury markers suggests that some of these differences could be secondary to kidney injury. Meta-analysis of Pkd1 and Pkd2 knockout kidney implicates changes in cytoketone and actin signaling as common pathways.

FR-PO573

Generation of a New Mouse Model Harboring the Polycystin-2 Loss-of-Function D511V Patient Variant

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most frequent renal genetic disorders caused by genetic mutations in either PKD1 or PKD2 genes, which encode for protein products polycystin-1 (PC1) and polycystin-2 (PC2), respectively. The molecular pathogenesis of ADPKD and the function of polycystins is an area of active research. PC2 subunits can form ion channels within organic membrane structures like the ER and primary cilium, or it can form channel complexes with PC1. There remains a need to develop novel animal models to mimic mutations observed in humans to study the allelic contributions of PKD genes, and to understand the impact of ADPKD-causing variants. To date there are no mouse models with Pkd2 missense variants.

Methods: We used CRISPR/Cas9 gene editing to engineer a new Pkd2 mouse model with the human pathogenic variant D511V (D509V in the mouse, Pkd2D509V). This Pkd2 variant affects a highly conserved region in the voltage-sensor domain (VSD). Prior studies in cell models showed that Pkd2D509V encodes a temperature sensitive mutant protein that is more stable at 27°C versus 37°C, interacts with PC1 and can traffic to cilia. Nonetheless this protein is “channel-dead” in ER vesicles.

Results: We found that heterozygous Pkd2D509V mice are viable and fertile but initial studies suggest that homozygous carriers are embryonically lethal, as no homozygotes were born (postnatal day 0). We are in the process of determining the cause of embryonic lethality and of measuring Pkd2D509V protein abundance and ciliary localization “in vivo” and “in vitro.” We will examine the functional role of the PC2D509V variant in maintaining kidney homeostasis in adult and postnatal kidneys by crossing it to a renal tubule specific inducible Pkd2 mouse model.

Conclusions: The generation of this new Pkd2D509V model provides a relatively rapid system to: 1) study the roles of PC2 “in vivo”; 2) decipher the pathogenic mechanisms leading to cyst formation after inactivating the channel activity of PC2 and 3) may be useful for precision medicine applications using patient-derived variants.

Funding: NIDDK Support

FR-PO574

Epigenetic Age Is Accelerated in ADPKD Kidneys and Is Regulated by Autophagy-Mediated DNA Methyltransferase

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Background: The epigenetic clock (DNA methylation age) is characterized by changes in DNA methylation (DNAm) levels across specific CpG sites that are associated with chronological age, disease, and mortality. Epigenetic acceleration (EA), the residual variation in DNAm age, indicates whether individuals and specific organs are aging faster or slower than their chronological age in response to endogenous and exogenous factors. Whether epigenetic age is regulated by autophagy and accelerated in ADPKD kidneys remains unknown.

Methods: To investigate an association between epigenetic clock/EA and autophagy in ADPKD, we performed single cell RNA sequencing (scRNA-seq), whole-genome bisulfite sequencing (WGBS), Western blot and qRT-PCR analysis.

Results: We found that 353 human and 329 mouse Cpg dinucleotide DNA methylation markers correspond to 309 human genes and 224 mouse genes. Our scRNA-seq analysis

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

Underline represents presenting author.
indicated that the numbers of dysregulated epigenetic clock associated genes were 48, 33 and 70 in collectng duct cells; 8, 14 and 44 in macrophages; and 2, 14 and 57 in fibroblasts in day 7, 14 and 21 Pkd1 homozygous kidneys compared to the same cell types in age matched Pkd1 heterozygous kidneys. The differential methylation status of these epigenetic genes and the specific methylation sites on these genes were identified in ADPKD kidneys compared to normal individuals as examined by WGBS. The dysregulation of epigenetic clock genes is associated with a gradual upregulation of DNA methyltransferase1 (DNMT1), the only DNMT responsible for maintaining DNA methylation, in day 7, 14 and 21 Pkd1 homozygous kidneys. DNMT1 interacted with ATG7, a key player of autophagy. Treatment with the autophagy inhibitor, Lyso5, increased DNMT1 protein, whereas treatment with autophagy inducer decreased DNMT1 protein in kidneys, supporting that autophagy is involved in DNMT1 mediated epigenetic age acceleration in ADPKD. We also found that the methylation status of four epigenetic clock genes, including Apoe, Cdln4, Mgp and Slc34a2, are potential biomarkers that indicate epigenetic age acceleration in ADPKD kidneys.

Conclusions: Autophagy is a key player of DNMT1 mediated epigenetic age and cyst growth in ADPKD kidneys. Targeting DNMT1 and inducing autophagy should have a synergetic effect on decreasing cyst growth and epigenetic age acceleration.

FR-PO576
Heterozygous PKD Organoids Show Increased Sensitivity to Forskolin-Stimulated Cystogenesis
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Background: Polycystic kidney disease (PKD) is inherited as a single heterozygous loss-of-function mutation, but theorized to require additional loss-of-function to cause cystogenesis. Activation of cAMP can stimulate cystogenesis, but whether this happens in heterozygotes is not well understood. We set out to test this in human kidney organoids.

Methods: We established human pluripotent stem cells in allelic series using CRISPR base editing to introduce nonsense mutations previously documented in ADPKD patients – PKD1 R2430X and Q3838X and PKD2 R186X and R872X. Mutations were confirmed by sequencing and protein changes by immunoblot. Homozygous mutant, heterozygous mutant, and isogenic control stem cells were differentiated into kidney organoids to determine if nonsense mutations conferred a cystic phenotype. Each genotype was treated with 0 μM or 30 μM forskolin, a stimulant of the cAMP pathway.

Results: Heterozygous cells expressed ~50% of PK1 or PK2 protein compared to controls. When differentiated into human kidney organoids, homozygous mutants spontaneously formed cysts whereas heterozygous mutants expressed no detectable phenotype, similar to non-mutant controls. Following forskolin treatment, heterozygous organoids showed a significant increase in the number of cysts formed which was not observed in homozygous mutant or non-mutant organoids (Figure 1).

Conclusions: Heterozygosity alone is insufficient to cause expression of PKD phenotypes in human kidney organoids. However, when treated with forskolin, heterozygosity sensitizes tubules to become cystic. Thus, even partial loss of function may enhance the PKD phenotype in the context of high levels of CAMP.

Funding: NIDDK Support

FR-PO577
Organic Model of Polycystic Kidney Disease Recapitulates Clinically Relevant Symptoms and Identifies Candidate Drugs
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Background: Polycystic kidney disease (PKD) is one of the most common genetic kidney diseases, characterized by the progressive expansion of fluid-filled cysts in the kidney. Currently, there are limited treatment approaches for PKD. Advances in generating kidney organoids from human pluripotent stem cells (hPSCs) have helped overcome many of the drawbacks of the traditional mouse and 2D cell culture models. Alongside genetic editing, these organoids have been used to investigate the pathogenic mechanisms of PKD and to screen for potential drugs.

Methods: Herein, we have generated a collection of kidney organoids from both ARPKD and ADPKD patient-derived iPSCs, as well as genetically engineered hPSCs. Subsequently, we employed stress paradigms to modulate intracellular levels of cAMP or Ca^2+ for inducing cystogenesis. We further characterized the structural and functional abnormalities in PKD kidney organoids using a multitude of analyses, including cell biology, molecular biology, biochemistry, and single nucleic RNA-sequencing. Finally, we performed a small-scale drug screening to identify candidate drugs.

Results: PKD kidney organoids developed tubular cysts in response to upregulation of intracellular cAMP or downregulation of Ca^2+ homeostasis. Multiple structural and functional abnormalities were observed in PKD organoids, including hyper-proliferation of cystic epithelial cells, increased fluid secretion, tubular injury and dedifferentiation, as well as aberrant renin release which are commonly observed in PKD patients. Employing cystic index as the readout, we identified two candidate drugs that can effectively attenuate cyst formation in PKD organoids.

Conclusions: hPSCs derived organic model of PKD can faithfully recapitulate critical structural and functional characteristics of PKD which would serve as an invaluable tool to investigate PKD pathogenesis and to discover potential therapeutics.

Funding: Government Support - Non-U.S.
FR-PO578
Epithelial-Mesenchymal Cross-Talks in Murine Models of Renal Ciliopathy
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Background: Ciliary defects underpin a variety of renal ciliopathies, including polycystic kidney disease and Nephronophthisis (NPHP). Both epithelial and stromal abnormalities are manifested in these diseases. Previously, to clarify the role of different cell types in disease progression, we utilized tissue specific mouse models of Arl13b, a cilia biogenesis gene, and Invs/Nphp2, a NPHP gene that encodes a protein localized to the proximal part of the cilium. Our results showed that epithelial specific knockout of Arl13b or Invs/Nphp2 was sufficient to cause both epithelial cyst and interstitial fibrosis. By contrast, stromal specific knockout of Invs/Nphp2 showed no obvious renal phenotypes up to the young adult stage, suggesting that epithelial cells are the main driver of the phenotypes and abnormal signaling from epithelial cells triggers interstitial fibrosis. Moreover, when Arl13b was specifically deleted in epithelial cells, Hedgehog signaling (HH) was activated non-cell autonomously in stromal cells and global pharmacological inhibition of HH signaling ameliorated fibrosis, kidney function decline and cyst progression, revealing a critical role of epithelial-mesenchymal crosstalk in disease progression. Combined, these results highlighted not only the importance of epithelial cells, but also epithelial-mesenchymal communications that include HH signaling in the molecular etiology of renal ciliopathy. However, the role of cilia in stromal response to epithelial signaling remains unclear.

Methods: In this study, we generated genetic mutants with Invs/Nphp2 and cilia biogenesis genes deleted in both epithelial and stromal cells and will investigate the renal phenotypes of the mutant mice. We further investigated cilia distribution in stromal cells.

Results: Our results suggest that cilia are present on stromal cells. Further phenotypic analysis will reveal whether cilia and Invs/Nphp2 in stromal cells modify the phenotypes triggered by defective epithelial cells.

Conclusions: Tissue specific function of cilia and ciliary genes plays a role in epithelial-mesenchymal crosstalks in renal ciliopathy.

Funding: NIDDK Support

FR-PO579
Lyv1+ Macrophages Play No Role in Initiating Polycystic Kidney Disease
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Background: Recent studies show macrophages modulate progression of polycystic kidney disease (PKD). As examples, depletion of macrophages chemically with clodronate or genetically by deleting macrophage chemoattractant protein 1 (MCP1) reduces PKD severity. We hypothesised that a specific population of macrophages may be needed to trigger disease progression, we utilized tissue specific mouse models of Arl13b, a cilia biogenesis gene, and Invs/Nphp2, a NPHP gene that encodes a protein localized to the proximal part of the cilium. Our results showed that epithelial specific knockout of Arl13b or Invs/Nphp2 was sufficient to cause both epithelial cyst and interstitial fibrosis. By contrast, stromal specific knockout of Invs/Nphp2 showed no obvious renal phenotypes up to the young adult stage, suggesting that epithelial cells are the main driver of the phenotypes and abnormal signaling from epithelial cells triggers interstitial fibrosis. Moreover, when Arl13b was specifically deleted in epithelial cells, Hedgehog signaling (HH) was activated non-cell autonomously in stromal cells and global pharmacological inhibition of HH signaling ameliorated fibrosis, kidney function decline and cyst progression, revealing a critical role of epithelial-mesenchymal crosstalk in disease progression. Combined, these results highlighted not only the importance of epithelial cells, but also epithelial-mesenchymal communications that include HH signaling in the molecular etiology of renal ciliopathy. However, the role of cilia in stromal response to epithelial signaling remains unclear.

Methods: In this study, we generated genetic mutants with Invs/Nphp2 and cilia biogenesis genes deleted in both epithelial and stromal cells and will investigate the renal phenotypes of the mutant mice. We further investigated cilia distribution in stromal cells.

Results: Our results suggest that cilia are present on stromal cells. Further phenotypic analysis will reveal whether cilia and Invs/Nphp2 in stromal cells modify the phenotypes triggered by defective epithelial cells.

Conclusions: Tissue specific function of cilia and ciliary genes plays a role in epithelial-mesenchymal crosstalks in renal ciliopathy.

Funding: NIDDK Support

FR-PO580
The Immune Checkpoint Protein PD-L1 Interacts with BBS5 to Regulate Ciliogenesis and Hedgehog Signaling
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Background: Programmed cell death 1 ligand 1 (PD-L1) is an immune checkpoint protein that regulates the immune synapse, a structure formed between immune cells and share structural and functional homology to primary cilium. However, whether and how PD-L1 regulates ciliogenesis remains elusive.

Methods: To investigate the role of PD-L1 on ciliogenesis, we performed inmunostaining, Western blot, and qRT-PCR analysis in mice NIH3T3 fibroblasts and human retinal pigment epithelium (RPE) cells. We also performed co-immunoprecipitation analysis to examine the interaction between PD-L1 and cilia-associated proteins.

Results: We found that PD-L1 is located at the basal body and the Golgi apparatus as seen by its co-localization with centrosome marker γ-tubulin, Golgi associated protein II20, and Golgi marker Giantin. Knockdown of PD-L1 resulted in an increase in percentage of ciliated cells and average cilia length in 3T3 and RPE cells, whereas overexpression of GFP-PD-L1 inhibited ciliogenesis in those cells. Consistent with this result, we found that serum starvation, which induces ciliogenesis, resulted in the downregulation of PD-L1 levels. Knockdown of PD-L1 increased the accumulation of Rab8a, BBS5 and polycystin 2 along the cilia axoneme in 3T3 cells but decreased the accumulation of Ift140 along the cilia in 3T3 cells and RPE cells. In addition, we found that the protein levels of BBS5, IFT20 and Rab8a were upregulated in PD-L1 knockdown 3T3 and RPE cells. We also found that PD-L1 formed a complex with BBS5 by co-immunoprecipitation analysis, and that knockout of BBS5 in PD-L1 knockdown mice accelerated cystic disease progression to the same extent as PD-L1 knockout mice. However, knockdown of BBS5 did not affect the localization, or protein level of PD-L1. We further found that knockdown of PD-L1 resulted in 1) the accumulation of the components of the hedgehog signaling pathway, including Smoothened (Smo) and GLI3, on the axoneme in 3T3 cells, 2) the upregulation of mRNA and protein levels of Glil and Gl3, and 3) the downregulation of Smo, Glil and Ptc1 proteins but not their mRNAs.

Conclusions: This study shows that PD-L1 is a novel basal body/Golgi component to regulate ciliogenesis and polycystin 2 ciliary trafficking through BBS5 and controls for the first time an immune checkpoint protein with ciliopathies, and possibly immune response.

Funding: NIDDK Support, Other NIH Support - T32 training grant

FR-PO581
Role of Interferon-Gamma in Cyst Formation After AKI
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Background: Acute kidney injury (AKI) is known to accelerate cystogenesis in conditional ciliopathy (Ift88) mice. Our lab previously showed that genetic deletion of some adaptive immune cells significantly reduced cystic disease in Ift88 conditional knockout mice. Additionally, using single-cell RNA sequencing, we found that T cells isolated from conditional Ift88 mice after AKI had enriched expression of the cytokine interferon-gamma (IFN-γ). Based on these data, we hypothesize that T-cell-derived IFN-γ is a significant contributor to the accelerated cystogenesis that is seen following AKI in ciliopathy mice.

Methods: To test this hypothesis, we crossed conditional Ift88 mice to mice lacking IFN-γ. At 8 weeks of age, we induced loss of Ift88 and primary cilia through tamofoxifen injection followed by administration of folic acid to induce AKI at 11-12 weeks of age; sodium bicarbonate solution was used as a vehicle-only control. Kidneys were harvested 56 days post-injury and cystic severity was measured by quantifying cystic index. We also analyzed changes in immune cell populations at the same time point using flow cytometry.

Results: Analyses of cyst severity 56 days post AKI indicate that conditional Ift88 IFN-γ knockout mice had a significant reduction in the severity and number of renal cysts compared to conditional Ift88 IFN-γ control AKI mice. Analysis of flow cytometry data indicates a correlative reduction in the number of kidney resident macrophages and neutrophils in the conditional Ift88 IFN-γ knockout AKI mice compared to conditional Ift88 IFN-γ control AKI mice.

Conclusions: Collectively, our data indicate that T-cell-derived IFN-γ is a major contributor to accelerated cystic disease that is observed in conditional Ift88 mice post AKI. Ongoing studies are addressing the specific T cell subset involved in injury-accelerated disease and the potential mechanism through which IFN-γ accelerates cystic disease in conditional Ift88 mice following AKI.

Funding: NIDDK Support
FR-PO582

The CPLANE Protein Fuzzy Regulates Primary Ciliogenesis Through Actin Remodeling
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Background: Defects in primary cilia cause a set of diseases termed ciliopathies manifesting in developmental defects including cystic/dysplastic kidneys. Mutations in ciliogenesis and planar cell polarity (CPLANE) genes FZFY, INTURB1, and WDPCP lead to a ciliopathy spectrum with abnormal kidney phenotypes. Although Fuzzy ortholog in D. melanogaster was identified as a part of the planar cell polarity and actin regulatory pathway, its functions in primary cilia assembly and ciliopathies remain largely unknown.

We hypothesize that Fuzzy modulates actin-assembly involved in primary cilia formation.

Methods: The interactions between Fuzzy-Flag, p90RhoGAP and IQGAP1-GFP were assessed by co-Immunoprecipitation. Rhokinetic G protein-binding domain-GFP biosensor in mutant and control mouse embryonic fibroblasts (MEF) cells was used to measure RhoA activity. IQGAP1 was knocked down by siRNA in Retinal Pigmented Epithelial cells (RPE-1). Overexpression of Fuzzy-GFP was done by stable transfection in MDCK cells. Immunofluorescence with gamma-tubulin, Ar13b and phallolidin was used for cilia assessment.

Results: We established that Fuzzy interacts with p90RhoGAP and controls its localization to the basal body. Normally, p90RhoGAP localizes to the primary cilia base and inactivates the actin-regulating protein RhoA. However, in Fuzzy mutant cells, RhoA is excessively activated. We also demonstrate that Fuzzy interacts with IQGAP1. A protein that facilitates the interaction between p90RhoGAP and RhoA, siRNA-mediated knockdown of IQGAP1 negatively affects ciliogenesis in RPE-1 cells. On the other hand, we show that Fuzzy is involved in regulation of the early stages of ciliogenesis: the overexpression of Fuzzy in MDCK cells triggered earlier cortical actin clearing at the apical membrane and earlier ciliogenesis.

Conclusions: We conclude that Fuzzy regulates the actin cytoskeleton at the primary cilia during the early and later stages of ciliogenesis. Fuzzy recruits p90RhoGAP to the ciliary base and interacts with IQGAP1 resulting in the inhibition of RhoA and the suppression of excessive actin polymerization at the base of the cilia. Fuzzy is also involved in the process of actin clearing during the early stages of ciliogenesis, but the exact mechanism is yet to be elucidated.

Funding: Government Support - Non-U.S.

FR-PO583

Identification of Novel Targets for Autosomal Dominant Polycystic Kidney Disease Using a Patient Cell-Derived Cyst Model

Background: Autosomal dominant polycystic disease (ADPKD) is the most common potentially lethal monogenic disorder and the most inherited kidney disease. Therapeutic development in ADPKD has been hampered by the lack of understanding of how mutations in polycystin 1 or 2 lead to uncontrolled cyst growth and ultimately end-stage renal disease.

Methods: We developed a 3-dimensional in vitro cyst model consisting of primary human epithelial cells derived from the cyst walls of ADPKD patients. The cells progressively form fluid-filled cysts within a collagen-rich gel in the span of 5-10 days and can be quantified through high-content imaging. To validate this model, a transcriptomic time course was obtained during cyst development and compared to transcriptomic signatures obtained from normal versus ADPKD biopsy tissue and secreted protein analysis of patient cyst fluid. Using data from these analyses, novel targets were assessed alongside established industry targets for their ability to inhibit cyst formation in the in vitro model.

Results: Comparing the transcriptomic signatures from the human in vitro model to patient tissue showed a high degree in overlapping responses and pathways that were consistent with the growth factors and chemokines confirmed to be present in patient cyst fluid. Clinical targets such as V2R, CTR, and NRF2 showed varying effects in their ability to inhibit cyst formation. From our analysis, we hypothesized new targets based on the unbiased bioanalyses of the transcriptomic signatures, which showed equal or better inhibition of cyst formation in the model.

Conclusions: Mapping the response profile of over 50 therapeutic targets spanning diverse mechanisms of actions in the validated ADPKD patient-derived cyst model has enabled prioritization of key signaling hubs that may represent promising new therapeutic targets for ADPKD.

FR-PO584

Primary Cilia Change Protein Composition in Response to Glutamine Deprivation
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Background: ADPKD is a genetic disorder in majority of cases caused by mutations in PKD1 and PKD2. Genes encode for Polycystin 1 and 2 which form a receptor-complex located to primary cilia. Primary cilia are sensory organelles that protrude from the cell membrane. From this extroverted position it responds to changes in the cellular environment and conveys various signaling pathways to control cell function, such as cell maintenance. Our lab previously published that loss-of-function of Pkd1 leads to metabolic reprogramming. Recently we published the importance of glutamine availability during nutrients-stress conditions on cilia length. Demonstrating that primary and ciliary organelles are interdependent nutrients availability to glutamine. We also showed that the glutamine response of cilia requires the presence of Asparagine Synthetase (ASN), which localizes to the cilia-centrosome complex.

Methods: To follow up on these findings we set up a large-scale proteomics study using mIMCD3 cells expressing a ciliary target fused to the proximity labelling tag, BioID. We affinity purified biotinylated proteins specific to the cilium by taking advantage of the high affinity of streptavidin coupled to beads. IP samples were analyzed using LC-MS. We generated an expression vector with ASN fused to mNeonGreen fluorescent-tag that generated stable transfectants in IMCD3s.

Results: A first LC-MS analysis of proteins exclusively observed in cilia of cells grown in medium with or without glutamine revealed a total of 22 proteins significantly changing with removal of glutamine. A few proteins were found to change both in expression levels and in ciliary abundance. Among these, ASN was upregulated with removal of glutamine in both in the cilium, and in the cytoplasm. From these findings, live imaging and IF performed with mNG-ASN IMCD3s showed ASN localizing not only at the base of the cilium, as we reported, but also within the axoneme. To accumulate ASN in the cilium we treated mNG-ASN cells with CilioBrevin D which inhibits dynein proteins and found that ASN accumulates at the tip of the cilium.

Conclusions: Our data demonstrate that primary cilia respond to glutamine removal by changing their protein composition. And that the enzyme ASN is among the proteins responding to glutamine availability.

FR-PO585

Dissecting Heterogeneity and Common Pathogenetic Pathways in Autosomal Dominant Tubulointerstitial Kidney Disease due to Mutations in REN
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Background: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) is a rare genetic disorder characterised by renal tubulointerstitial fibrosis and progressive chronic kidney disease. ADTKD is caused by mutations in different genes including REN encoding renin, a key player in the regulation of salt and blood pressure homeostasis. Renin is a secreted protein composed of 3 domains: the leader peptide allowing its insertion in the endoplasmic reticulum (ER), a pro-segment regulating its aspartyl protease activity, and the mature part. Mutations in REN lead to a late onset disease, while mutations in the leader peptide, associated with defective ER translocation, and mutations in the pro-segment, accumulating in the ER-to-Golgi compartment, lead to early onset disease.

Methods: We used transiently and stably transfected cells as well as an inducible system of renin expression to investigate the effect of mutations on renin trafficking.

Results: We demonstrated an unprecedented effect of mutations in the leader peptide and pro-segment leading to full or partial mistargeting of mutated protein to mitochondria. By studying GFP-fusion constructs we observed that the pre-pro sequence of renin, carrying mutation in either the leader peptide or the pro-segment, is necessary and sufficient to drive mitochondrial rerouting. In turn, this leads to mitochondrial import defect and mitochondria fragmentation. Induction of the 3 branches of the unfolded Protein Response is observed in cells expressing renin mutated in the mature part, while induction of the IRE1 branch only is observed for the other mutations. Strikingly, the chronic expression of all mutations leads to toxicity and cell death.

Conclusions: Our results unravel a common cellular phenotype for mutants in the leader peptide and pro-segment (i.e. mitochondrial mistargeting) associated with an early-onset disease that differs from the one associated with mutants in the mature part (i.e. ER retention) that lead to a late onset disease. We currently aim at understanding how expression of these different mutants eventually converges to kidney inflammation and fibrosis by characterising stress signals emerging from the ER and mitochondria.

Funding: Private Foundation Support, Government Support - Non-U.S.
FR-PO586
Antisense Oligonucleotide Knock Down of Uromodulin: A Potential Treatment Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)
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Background: Autosomal Dominant Tubulointerstitial Kidney Disease-Uromodulin (ADTKD-UMOD) is a genetic disease caused by destabilizing mutations in the uromodulin (UMOD) or Tamm-Horsfall protein. Misfolded UMOD protein aggregates and accumulates inside the loop of Henle and the distal convoluted tubule, leading to progressive and irreversible chronic kidney disease. We hypothesized that peptidase-conjugated phosphorodiamidate morpholino oligomers (PMOs) could knock down UMOD expression and potentially reduce the disease-causing UMOD aggregation inside the cells.

Methods: A library of PMOs was designed to bind to the complementary sequences of the mouse UMOD gene and induce nonsense-mediated decay. These PMOs were screened in mIMCD-3 cells, which express endogenous transcript to identify the most active compounds. The most efficacious PMO compound was tested in both wildtype and UMOD C93F mice, a well characterized disease model of ADTKD, to determine the ability of the PMO to reduce UMOD expression at the transcript and protein levels.

Results: A single dose of lead PMO resulted in a 70% knockdown of Umod transcript that led to protein reduction that was sustained for at least 28 days. Furthermore, UMOD protein expression was reduced in the UMOD C93F animals after a single dose of PMO.

Conclusions: This study shows the ability of PMO technology to reduce UMOD transcript and protein levels in vitro and in vivo.

Funding: Commercial Support - Sarepta

FR-PO587
Retinal Oxalosis: An Unusual Presentation of Hyperoxaluria
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Introduction: Hyperoxaluria can be due to inherited disorders of enzymatic defects in the glyoxylate pathway causing decreased oxalate metabolism, or secondary from increased intestinal absorption. Type I primary hyperoxaluria (PH) is typically diagnosed in infancy/childhood, leading to kidney failure by the fourth decade of life with more mild presentation in types 2 and 3. Retinal oxalosis is a rare finding, especially in adults. Herein we describe a case of suspected primary hyperoxaluria diagnosed late in life causing rapid decline in kidney function and vision loss.

Case Description: An 81-year-old woman with history of coronary artery disease, melanoma, hypertension, CKD stage 2 was referred to kidney clinic for rapid worsening of kidney function. History was pertinent for left nephrectomy at age 15 presumably from kidney stones/pyelonephritis. Kidney function began rapidly deteriorating 6-8 months prior to the referral with minimal proteinuria (random urine protein creatinine ratio of 0.22) and no hematuria. Kidney biopsy was performed which showed calcium oxalate crystal deposition. Except for 4-6 glasses of iced tea daily, no other risk factors could be identified. Despite dietary restriction of oxalate, her kidney function decline continued, warranting peritoneal dialysis (PD) initiation. Four months post PD initiation, she developed sudden worsening of vision and was found to have oxalate retinopathy after extensive evaluation ruling out other causes. Primary hyperoxaluria was suspected and she was referred for genetic testing at the kidney genetics clinic at our institution.

Diagnosis: Dialysis patients are at high risk of systemic oxalosis due to poor oxalate removal by dialysis. Treatment for PH Type I includes combined liver and kidney transplant in those with kidney involvement. Other treatment options include high dose pyridoxine, oral citrate and hydration. Lumarisarin—an RNA interference agent has been assessed in Type I. In those with ESKD, daily dialysis/dialysis with high flux dialyzers has been attempted with limited benefit. Our patient refused to switch to hemodialysis. Genetic testing was performed, and results are pending. Despite aggressive treatment oxalate retinopathy is known to be irreversible. Hyperoxaluria is a rare cause of retinal oxalosis and kidney failure yet should remain on the differential in the setting of rapid decline of kidney function with no clear cause.

FR-PO588
Better Oxalate than Never: A Diagnosis of Primary Hyperoxaluria Made After Renal Transplantation
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Introduction: Primary hyperoxaluria (PH), a genetic impairment of glyoxylate metabolism, causes kidney injury and end-stage renal disease (ESRD) when left untreated. We present a case of PH diagnosed following deceased donor renal transplantation (DDRT).

Case Description: A 60 year old woman with ESRD on hemodialysis (HD) thought to be from hypertension with no prior kidney stones underwent DDRT. Post-reperfusion biopsy of the transplant showed mild tubular atrophy and interstitial fibrosis occupying 10-15% of the sampled cortex. Immunosuppression was induced with thymoglobulin and mycophenolate. She was maintained on mycophenolic acid. Four years later, kidney stones were identified in the transplant.

Cystoscopy and lithotripsy were performed with retrieval of a 100% calcium oxalate stone burden, prompting initiation of potassium citrate and pyridoxine. PH was more prevalent and classically thought to cause more rapidly progressive disease, PH2 can also cause significant kidney injury despite its relative indolence. The condition is diagnosed by detection of increased urinary oxalate followed by confirmatory genetic testing. In the post-transplantation phase, kidney dysfunction secondary to hyperoxaluria can be confused for delayed graft function, defined as the use of HRD in the seven days post-transplantation. In the absence of a clear etiology for the underlying native renal function, and with genetic testing becoming affordable, it may be worthwhile to consider genetic testing for underlying renal diseases that could affect a transplanted kidney with the intention of increasing the longevity of transplanted kidneys in the post-transplantation phase.

FR-PO589
Heart Failure Recovery After Lumarisarin and Isolated Kidney Transplantation in Primary Hyperoxaluria Type I

Introduction: Primary hyperoxaluria type 1 (PH1) is characterized by oxalate leading to kidney failure. In advanced PH1, systemic oxalate deposition may lead to heart failure. Lumarisarin, a small interfering RNA, reduces oxalate load and may improve organ dysfunction in systemic oxalosis.

Description: A kidney biopsy revealed diffuse interstitial nephritis with massive oxalate deposition. Genetic testing confirmed two compound heterozygous Alanine-Glyoxylate Aminotransferase (AGXT) gene mutations. Our patient had peritoneal dialysis (PD) for 6 months. In addition, he suffered from severe heart failure (NYHAIII) with a left ventricular ejection fraction (LVEF) of 25%, marked left ventricular hypertrophy and a NTproBNP of >50,000pg/mL. A cardiac biopsy revealed severe oxalate deposition. Hemodialysis (HD) therapy was commenced to optimize volume overload and lower plasma oxalate (POx) levels. The initial POx levels of 141.3µmol/L decreased to less than half after combined PD and HD. Subsequently, cardiac dysfunction secondary to hyperoxaluria and high dose pyridoxine, POx levels further decreased to 29.2µmol/L. Subsequently, cardiac output improved to an LVEF of 35-40%. He received a living kidney donation from his father using standard immunosuppression and intensive hydration post transplantation. Daily oral pyridoxine at 750mg, thus reducing excessive systemic oxalosis. Blood POx levels further decline to 11µmol/L.

Results: Despite discontinuation of systemic oxalosis, she never developed renal or cardiac oxalosis. Two years post transplantation, her kidney function stabilized at a creatinine of 2.0 mg/dL. An allograft biopsy showed no oxalate deposition. Her cardiac function improved further (NYHA I, LVEF 55%, NTproBNP of 449pg/mL) with a recent POx level of 11µmol/L.

Conclusion: We hereby describe a case of primary hyperoxaluria successfully treated with Lumarisarin and isolated kidney transplantation. This underscores the utility of lumarisarin and the conclusion that cardiac dysfunction related to PH1 is potentially reversible.

FR-PO590
Genetic Prevalence Estimates for All Types of Primary Hyperoxaluria
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Background: Primary hyperoxaluria is a rare disorder caused by biallelic pathogenic changes in 3 known genes (AGXT (PH1), GRHP (PH2), HOGA1 (PH3)). Afflicted patients have marked hyperoxaluria, frequent kidney stones, and are at high risk for kidney failure. Patients are often diagnosed late after they have developed severe disease complications, including systemic oxalosis. Given approved and emerging therapies for these diseases, it is important to understand the genetic prevalence of PH to determine the magnitude of missed diagnoses/reduced penetrance and develop strategies to improve patient outcomes.

Methods: Variants from all 3 genes were curated from OxlEuropia, Rare Kidney Stone Consortium, ClinVar, and GnomAD registries in addition to an extensive literature review. Variants were scored as Pathogenic or Likely Pathogenic according to the 2015 ACMG guidelines using Intervar. Allelic frequencies were determined from GnomADv2.1.1 after all identified variants were curated/reclassified and used to calculate the lifetime genetic prevalence of disease.

Results: The number of Pathogenic/Likely Pathogenic variants studied following comprehensive curation or reclassification of variants were 89 AGXT, 45 GRHP, and 74 HOGA1. The following overall estimated genetic prevalence was determined: PH1 (1.29%, 357), PH2 (1.865, 028), and PH3 (1.90, 834) resulting in an estimated 17 in 1M individuals (136,000 individuals worldwide) with a lifetime risk of PH1 regardless of ethnicity. The estimated carrier frequency is the following: PH1 (1.229), PH2 (1.465), and PH3 (1.151). Furthermore, ethnic groups were examined using post-curated variants showing the genetic prevalence is most prominent for PH1, PH2, and PH3. The following prevalence, respectively: East Asian (1.84, 574), South Asian (1.390, 788), and Ashkenazi Jewish (1.5, 633).
Unlocking the Potential of Genetic Testing: Insights into Primary Hyperoxaluria and Monogenic Kidney Stone Disease

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Background: Primary Hyperoxaluria (PH) is an autosomal recessive disorder that results in kidney stone disease and/or nephrocalcinosis affecting both pediatric and adult patients. Over time, the chronic disease progresses to end stage kidney disease (ESKD) necessitating a kidney and liver transplant. PH is divided into three types: PH1, PH2, and PH3, caused by mutations in AGXT, GBMRP, and HOXA1 genes resulting in reduced enzyme activity and excess oxalate production. Nedosiran is an investigational RNA interference therapy holding the promise of mitigating excessive oxalate production and offering potential therapeutic benefits to patients suffering from this debilitating condition.

Methods: Novo Nordisk and PerkinElmer Genomics have partnered to provide sponsored genetic testing for patients with high-risk clinical symptoms for monogenic kidney stone diseases (MKSD) including PH. Two panels were offered: a 3-gene panel for PH and a 35-gene panel for MKSD. Results were categorized as the following: 1) Positive Genetic Diagnosis (Pathogenic or Likely Pathogenic variants in autosomal dominant [AD]/autosomal recessive [AR] genes), or 2) Possible Genetic Diagnosis (Pathogenic, Likely Pathogenic, or Variant of Uncertain Significance) in AD/AR genes.

Results: Out of 209 patients tested globally, 27 had PH1, 1 had PH2, and 2 had PH3, resulting in a 14% diagnostic yield for PH. An additional 15 patients received a positive diagnosis for MKSD, leading to a 22% overall diagnostic yield. Furthermore, 2 patients had a possible genetic diagnosis of PH2, 1 patient had a possible genetic diagnosis of PH3, and 27 patients received possible genetic diagnoses for MKSDs in addition to PH. The diagnostic yield for PH1 and PH2 exceeded 50%.

Conclusions: Genetic testing is vital for accurate diagnosis and treatment of patients who are at high risk for underlying MKSD including PH. In this study, genetic testing in pediatric and adult patients with high-risk clinical symptoms resulted in a positive diagnostic genotyping in 45 of 209 patients. It is worth noting that genetic testing also yields valuable information beyond definitive diagnoses. An additional 30 patients obtained a possible genetic diagnosis, indicating the need for further metabolic and/or familial genetic testing.

Funding: Commercial Support - Dicerna Pharmaceuticals Inc., a Novo Nordisk Company

FR-PO593

Functional Analysis of AGXT1 Missense Variants of Uncertain Significance in HepG2 Cells: Association with Primary Hyperoxaluria Type 1

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Background: Primary Hyperoxaluria Type 1 (PH1) is caused by functional deficit of alanine:glyoxylate aminotransferase (AGT1), a liver enzyme that detoxifies glyoxylate, thus avoiding its conversion to oxalate. The hallmark of the disease is the progressive deposition of calcium oxalate resulting in kidney stones leading to ESRD and systemic oxalosis. The diagnosis is established on a proband with hyperoxaluria or hyperoxalemia by the presence of biallelic pathogenic or likely pathogenic variations in the AGT1 gene encoding AGT1, 67% of which are missense. Although the pathogenicity of some genetic variants has been clearly defined, the clinical assessment of variants of uncertain significance (VUS) represents a big challenge. Our work is aimed at determining pathogenicity of AGT1 VUS variants in a cellular model of disease.

Methods: We used hepatocarcinoma-derived human HepG2 cell line knock-out for the AGT1 gene utilizing CRISPR/Cas9 technology, since they exhibit conserved glyoxylate/oxalate metabolism. By lentiviral infection we created and analyzed stable clones of AGT1-KO HepG2 cells expressing the two polymorphic forms of AGT1 (AGT1-Ma and AGT1-Mi). Eight VUS were expressed on the AGT1-Ma background and three on the AGT1-Mi background. We validated our experimental setting to mimic the liver expression of AGT1 and investigated the effects of amino acid changes at the protein level.

Results: The p.Pro285Ser, p.Arg118Cys, p.Asp129His, p.Ala248Val, p.Arg1371Trp mutations on AGT1-Ma, and the p.Glu274Arg, p.Ile279Thr, p.Arg289Cys mutations on AGT-Mi led to a biologically meaningful reduction in protein levels and activity, denoting the variants are likely pathogenic. On the other hand, the p.Pro1344 mutation did not significantly affect AGT1 protein levels and activity, while the p.Ala186Val and p.Arg197Gln cause only a partial reduction, thus suggesting that they could be benign or likely-benign.

Conclusions: We developed a platform to predict the pathogenicity of newly identified AGT1 VUS variants that could have a significant clinical implication as a potential tool to support the diagnosis of PH1 and establish genotype/phenotype correlations.

Funding: Commercial Support - Novo Nordisk Inc.

FR-PO594

An Un-Hex-Pected Cause of Crystalluria

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Introduction: Cystinuria, a genetic cause of kidney stones, is present in 1/7000 births, and 75% present in childhood. Cystinuria should be suspected in those with childhood kidney stones, stag horn calculi, or family history of stones. Diagnosis is confirmed by cystine analysis on hexagonal cystine crystals on microscopic urinalysis, or genotyping if there is a strong family history. Cystinuria can lead to chronic kidney disease (CKD). Plasma to pH (POx) increases with declining kidney function, leading to systemic oxalosis. Lukasirann, an RNA interference therapeutic that reduces hepatic oxalate production, administered to patients with PH1 and CKD 3b-5 in the ILLUMINATE-C trial (NCT02455200), resulted in decreased POx at month (M) 6 and 12 with acceptable safety. Here we present M24 results.

Funding: Commercial Support - Aplynias Pharmaceuticals

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

Underline represents presenting author.
unexpected in this patient, and upon renal recovery urine cystine crystals were absent. The combination of his mild cold, supplement use, and strenuous exercise predisposed him to acute kidney injury and revealed his otherwise quiescent cystinuria. Continued monitoring and treatment is warranted to prevent nephrolithiasis and chronic kidney disease. The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.

FR-PO595

Clinical Characterization of a Cohort with Suspected Monogenic Stone Disease
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Background: Monogenic stone diseases (MSDs) result from pathogenic variants in genes encoding proteins that are involved in the de novo formation and propagation of urolithiasis, with many disorders displaying end-organ damage in more than one system. A multi-system disorder (MSSD) in a patient with chronic kidney disease (CKD) and urinary tract symptoms may be a clue to a previously unidentified genetic cause of urolithiasis. Targeted next-generation sequencing (NGS) has become the standard of care for stone diagnosis in patients with MSSD. Our study sheds light on potential genetic variants in recurrent stone formers in our diverse patient population. The initial wide range of results support the complex and polygenic expression of KSD.

Funding: Commercial Support - Natera

FR-PO596

Understanding the Clinical Genetics of Kidney Stone Disease Using a Kidney Disease-Specific Genetic Test Panel
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Background: The etiology of kidney stone disease (KSD) is multifactorial. Emerging data suggest that genetics may play a larger role than previously thought. 11% to 56% of KSD has heritable stone-related genetic mutations. We aimed to better understand the genetics of KSD using a kidney disease focused genetic test at our diverse, urban academic center.

Methods: A single-center, prospective study was conducted on patients with recurrent stones or a single stone with family history. Those with known causes of urolithiasis, active UTI or acutely passing a stone were excluded. All underwent standard stone analysis, serum metabolic evaluation, 24-hour urine studies and buccal DNA screen for 385 kidney disease-linked genes using the Natera Renasight® kit. Variants were categorized as "positive" if pathologic, "carrier" if autosomal recessive, or of "uncertain significance" (VUS).

Results: 89 patients were enrolled. 55% were female, 60% were Hispanic, and 30% reported a first-degree family history. Median (IQR) patient age was 49 years (IQR 41-60) with 2 (IQR 1-3) stone episodes in the prior 5 years. 61% formed calcium oxalate stones. 7 (8%) subjects were positive for amyloidosis (TTR), Alport syndrome (COLA43), cystinuria (SLC7A9), polycystic kidney disease (PKD1), or FSGS (APOL1). 39 (44%) were carriers for 30 unique genes and all patients had multiple VUS spanning 247 unique genes. Positive/carrier patients were similar to negative patients in demographics, comorbidities, stone analysis and 24-hour urine studies. They had lower median vitamin D (22.3 vs 29.7 ng/ml; p=0.041) and higher potassium (4.4 vs 4.2 meq/ml; p=0.090).

Conclusions: Our study sheds light on potential genetic variants in recurrent stone formers in our diverse patient population. The initial wide range of results support the complex and polygenic expression of KSD.

Funding: NIDDK Support, Private Foundation Support

FR-PO597

A Rare Cause of Proteinuria and Nephrolithiasis: Biallelic SLC26A1 Variants
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Introduction: Up to 2% of adult nephrolithiasis cases are attributable to a monogenic disease, a clinically and genetically heterogeneous group. Although high-throughput sequencing has identified >90 nephrolithiasis-causing genes, some of these genes are understood.

Case Description: This Irish family consists of 2 affected siblings. The proband (W94_1), a 63-year-old woman, presented with recurrent non-obstructive nephrolithiasis, urinary infections, and proteinuria. Sonography revealed normal-sized kidneys. In addition, she reported bilateral sensorimotor deafness since childhood, indicating hearing aids at age 50 years. No further evidence of systemic involvement was identified. At the last follow-up, aged 63 years, she exhibited reduced estimated glomerular filtration rate (eGFR). Despite recurrent nephrolithiasis, the kidney function of her 61-year-old brother (W94_2) is adequate (eGFR ~ 88 mL/min). At the time of genetic analysis, oxalate and calcium excretion in the urine were normal, with normal serum bicarbonate. Genetic testing revealed both harbor biallelic variants in The Solute Carrier Family 26-Member 1 (SLC26A1) gene (NM_022042:c.C1073T; p.S358L and c.C534T; p.T185M) associated with monogenic calcium oxalate nephrolithiasis. The SLC26A1 gene encodes for an anion transporter critical in oxalate and sulfate homeostasis. These reported SLC26A1 variants (p.S358L and p.T185M) occurred at conserved residues and reported at a low frequency in population databases, such as the Genome Aggregation Database (gnomAD). It is localized into the basolateral membrane of proximal tubules. Functional studies of similar reported variants demonstrate a dysfunctional process of protein and impaired transporter activity. However, the effect of SLC26A1 on oxalate homeostasis, which causes hyperoxaluria and urolithiasis, remains controversial. Nevertheless, its role in sulfate homeostasis in humans has only recently been established.

Discussion: Clinical features of kidney stone formers harboring SLC26A1 variants can vary, indicating the potential expressivity. Awareness of monogenic nephrolithiasis, especially in families with history, should allow early diagnosis, treatment, and personalized counseling.

Funding: NIDDK Support, Private Foundation Support

FR-PO598

Characterization of Monogenic Kidney Disease in Patients over 60 Years of Age
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Background: Approximately 10% of adults with chronic kidney disease (CKD) have monogenic forms of the disease. However, the prevalence of monogenic kidney diseases in the over-60 population is not well characterized.

Methods: For genetic screening in this cohort with suspected monogenic kidney disease, excluding polycystic kidney disease, we utilized gene-panel and exome sequencing. The purpose of this study was to assess the diagnostic yield of clinically validated and polygenic testing in this age group.

Conclusions: The diagnostic yield of clinically validated and polygenic testing in this age group.

Funding: NIDDK Support, Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: Genetic testing was performed for 113 adults (n=93) families with a median age of 69 years [IQR: 64 - 73]. 33% participants reported a familial history of CKD and 52.2% were females. At last follow up, 84 (75.7%) individuals progressed to kidney failure at a median age of 57 years [IQR: 41.5 – 65]. We were able to demonstrate likely-pathogenic/pathogenic variant in 37/113 (32.7%), encompassing 13 different monogenic entities. Disease-causing variants in these three phenotypes accounted for up to 52.7% of solved cases. These included MUC1 (n=6), UMOD (n=3), INHFB (n=5) and DNAJB11 (n=1) associated with tubulointerstitial kidney disease; COLA4 (n=4) and monoaicolic COLA43 (n=4) associated with Alport-related kidney disease; and INF2 (n=5) associated with associated with autosomal segmental glomerulosclerosis. We identified disease-causing variants in the CLCN5 gene associated with Dent disease type 1 in an additional 3 (2.6%) individuals. In 32% (n=8) of the 25 patients referred with a priori diagnosis of CKD of undetermined cause were found to have a known monogenic cause. There was no difference in age at diagnosis between cases referred with a priori diagnosis vs. age at kidney failure [52.8 vs. 52.8 years; p = 0.747] between individuals with monogenic disease and those without. A family history of CKD was an independent predictor of a genetic diagnosis [odds ratio: 5; 95% CI: 1.1 - 23.3, p = 0.040], with a higher proportion of solved cases than unsolved cases, 45% vs. 77.7%, p = 0.02).

Conclusions: We estimated that about a third of this cohort over 60 years old with suspected inherited CKD would have a monogenic nephropathy. Awareness of monogenic nephropathies, particularly in this population group, should permit family counselling and individualized treatment.

FR-PO599
Comprehensive Genetic Analysis Reveals Novel Variants in Nephrolithiasis and Nephropathic Cystinosis
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Background: Renal stones or nephrolithiasis (NL) and nephropathic cystinosis (NC) are clinically heterogeneous conditions. The etiology of renal stone disease is multifactorial and influenced by a combination of genetic and environmental factors. 33 monogenic causes of NL/NC have been identified to date; we have shown that a genetic cause of NL/NC can be identified in approximately 11% of adults and 16-20% of children (Halbritter JASN 26:543, 2015; Braun CJASN 11: 666, 2016). Several investigations have been conducted using next-generation sequencing (predominantly targeted sequencing). Nonetheless, a comprehensive genetic analysis of NL/NC, particularly in terms of copy number variation (CNV), is yet to be done.

Methods: Individuals with a history of at least one renal stone or NC before the age of 25 years were recruited from international stone clinics between January 2013 and December 2020. Affected individuals with NL/NC from 285 families were enrolled in this study. Exome sequencing (ES) was performed to determine the genetic cause of NL/NC. Detected variants were assessed using a population database, evolutionary conservation, and in silico pathogenicity prediction scores, and categorized according to the American College of Medical Genetics (ACMG) guidelines. Furthermore, CNVs were analyzed using sequencing coverage data.

Results: 37 Likely disease-causing variants were detected in 42 families, leading to genetic diagnosis in 14.7% (42/285) of all cases. Of the 37 detected variants, 20 were novel. The CTNS gene was the most frequent (n=8), followed by AGXT (n=5), SLC34A3 (n=4), CLDN16 (n=4), COLA43 (n=3), and PV (n=3). The other genes included COLA4, CLDN16, CLDN19, MOCOS, SLC4A1, SLC7A9, SLC12A1, SLC34A1, and BGN. CNVs were detected in three cases. Homozygous deletions in SLC34A1 were detected in two cases; one showed deletion in exon 4-9, and the other showed a deletion involving only exon 7.

Conclusions: Our data represent a comprehensive analysis of the monogenic causes of renal stone disease. In-depth analysis at the single-exon level is beneficial. Simultaneous analysis of CNVs and SNVs based on ES has potential as a first-choice diagnostic approach for renal stone disease.

FR-PO601
A Canine Model Implicates Uromodulin Peptides in Calcium Oxalate Urinary Stone Risk
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Background: We hypothesize that differences in uromodulin peptides may influence risk of calcium oxalate (CaOx) stone formation. In order to test this hypothesis, we measured uromodulin peptides in urine samples from dogs with and without CaOx stones.

Methods: Urinary uromodulin peptides were measured in urine samples from 113 dogs (n=93) with (n=4) and without (n=4) the UMOD PV plus healthy control dogs (n=7) and normalized to urinary creatinine. Dogs with kidney disease were excluded. Uromodulin peptide abundances were summed for comparisons of total excretion. For individual peptides, abundance was calculated relative to the sum of all uromodulin peptides to obtain a percentage. Cleavage patterns were compared between groups.

Results: Total uromodulin abundance was reduced in SF dogs with the UMOD PV. Urine from PV SF dogs lacked a peptide cleavage site, resulting in longer peptides compared to healthy controls. Total uromodulin peptide abundance did not differ between non-PV SF and healthy dogs. However, non-PV SF dogs had decreased abundance of specific EHP-containing peptides from CaOx stone former (SF) dogs with and without the UMOD PV.

Conclusions: Reduced urinary excretion of specific uromodulin peptides in CaOx SF dogs with and without the UMOD PV implicates these peptides in stone risk. Previous research has demonstrated bioactivity of uromodulin peptides. The peptides that are decreased in the urine of SF dogs may have a protective effect against stone formation.

Funding: Other NIH Support - ULTR002494
FR-PO602

Novel Therapy for Cystinuria Using Genetic Tools
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Background: Available drug treatment for Cystinuria is still imposes huge disadvantages to patients through harmful side-effects. This fact necessitates the need for other therapeutic approaches without causing major side-effects. Cystinuria is caused by a mutation of b₀⁺AT (SLC7A9) or rBAT (SLC3A1) Proteins. Mutations result in the mis-localization of functioning channels at the plasma membrane (PM) leading to a disruption in cystine reabsorption that results in the accumulation of cystine stones. This research hypothesizes that repurposing established drug compounds to re-direct both proteins into the PM is a new and improved therapeutic approach.

Methods: In this study, we utilised constructed transduced human PTEC to investigate the localisation of b₀⁺AT and rBAT in wildtype and four mutated cell lines: p. Met467Thr, p. Thr216Met, p. Gly458Arg, and p. Asn254Thr using various imaging systems. Primary investigation was done using ICC/IF followed by Widefield Fluorescence Microscopy. Follow-up investigations were done using Confocal Microscopy and co-localisation analysis of obtained data. Findings were confirmed by TIRF Microscopy. Currently, the INCELL analyser is being used to optimise the LOPAC 1280 in these cell lines.

Results: All localisation studies done using different imaging systems showed the same results. Firstly, both proteins were found to be trafficked together. Secondly, in the wild-type cell line, both proteins were located at the PM. Thirdly, in mutated cell lines, both proteins were trapped in the ER. Morphological changes of PTEC were supportive of the co-localisation studies.

Conclusions: Both proteins were trapped in the ER in all four mutants in contrary to wild-type cell line. These findings allow testing of LOPAC 1280 drugs to show their efficacy in re-locating proteins into the PM. Radiation testing will followed to confirm functionality of both proteins.

FR-PO603

Gordon Syndrome in an Elderly Adult: A Rare Presentation
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Introduction: Gordon syndrome (GS) is a rare autosomal dominant condition with a loss of function mutation of WNK1, WNK4, KLHL3, and CUL3 genes. This affects the thiazide-sensitive sodium-chloride channels (NCC) in the distal convoluted tubule. Being a hereditary disease, it is expected to present at a young age, but may rarely present in adults as well.

Case Description: A 70-year-old male with obstructive uropathy, indwelling Foley catheter and right nephrostomy tube, CKD stage G3B/A3, and persistent atrial fibrillation (AF), presented to the ER with generalized weakness. He developed urosepsis, metabolic acidosis and AKI, for which empiric antibiotics and IV fluids with sodium bicarbonate were started. Development of fluid overload secondary to chronic heart failure prompted the addition of 40mg IV daily of furosemide. He was started on metoprolol tartrate 100 mg PO b.i.d. for AF with rapid ventricular rate. Bicarbonate drip was stopped on day 5 when levels normalized. IV furosemide had to be decreased to 20 mg daily along with addition of IV acetazolamide, due to development of contraction alkalosis on day 12. While alkalemia improved, serum potassium (K) surprisingly rose, with levels not improving even with lowering the metoprolol dosage. This paradoxical trend of K led to clinical suspicion of GS. Lo and behold, administering hydrochlorothiazide after discontinuing the previous diuretics resulted in immediate and sustained decline of K back to normal.

Discussion: Hyperkalemia can be attributed to various factors, with beta-blockers, metabolic acidosis, and insulin deficiency being some of them. True hyperkalemia is rare unless there is a large K load, marked exercise, or a defect in K handling that prevents the excretion of the excess extracellular K. GS, a rare cause of hypertension and hyperkalemia, can be missed, especially in adults, without vigilance for electrolytes and acid-base abnormalities. It should therefore be included in the differential diagnosis of patients presenting with unexplained hyperkalemia.
Clinical Features and Genotype-Phenotype Correlation of Bartter Syndrome Type 1 and 2

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Background: Bartter syndrome type 1 and 2 (T1/T2BS) are autosomal recessive hereditary type of salt-losing tubulopathy (SLT) caused by loss-of-function variants of SLC12A1 (NM_000339) and KCNJ1 (NM_002200) respectively. Although the typical case of both syndromes presents severe clinical manifestation at the perinatal period, they are very rare diseases and there are few reports on their clinical course and genotype-phenotype correlation.

Methods: Of 651 patients with suspected SLT who underwent comprehensive genetic testing of 124 genes related to the renal disease by next-generation sequencing at our department, T1BS: 16 and T2BS: 10 cases genetically diagnosed were evaluated retrospectively.

Results: In T1BS, 23 variants (novel-15) were found in the SLC12A1, and in T2BS, 11 variants (novel-7) were identified in the KCNJ1. The median age at the time of genetic testing was 0 years for both diseases. The mean serum potassium level at diagnosis was 2.9 mEq/L in T1BS, but all T2BS patients showed transient hyperkalemia (mean 7.5 mEq/L) in the early postnatal period, followed by hypokalemia (mean 3.2 mEq/L). All patients with T1BS required continuous treatment with potassium products, potassium-retaining diuretics, and/or NSAIDs as a treatment for hypokalemia, whereas only 5 patients (50%) with T2BS required these treatments. Concerning renal prognosis, 3 patients in T1BS with T1BS and 2 patients with T2BS with T2BS had deteriorated renal function at the time of genetic testing. Regarding the genotype-phenotype correlation, some of the missense variants of both T1 and T2BS did not show polyhydramnios and presented an atypical mild clinical manifestation without any symptoms in neonatal age. As for the KCNJ1, genetic serum potassium levels tended to be high (mean 3.3 mEq/L) in patients with the large deletion variant including the promoter region that has been previously reported, and this variant may present with mild manifestation.

Conclusions: T2BS shows significant hyperkalemia in the early postnatal period, but the severity of hyperkalemia in the infancy is milder than that of T1BS, and some cases did not require potassium supplementation. The correlation between the genotype-phenotype is not yet clear, but there were some clinically atypical cases, and further research is needed.

Funding: Government Support - Non-U.S.

Adrenal Mass in Bartter: Incidentaloma or Adenoma?

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Introduction: Bartter’s syndrome is rare, characterized by salt wasting caused by impaired absorption of sodium in the thick ascending limb of the loop of Henle. Young patients present with hypokalemia, metabolic alkalosis, and hyperaldosteronism. Our case presents a patient with Bartter’s syndrome with an incidental adrenal mass.

Case Description: A 39 yo F with hx of Bartter’s syndrome type III (heterozygous for CUBN (NM_022489) and SLC5A2 (NM_000320)) presents for an office visit for evaluation of incidental right adrenal complex mass 1.5cm x 1.7cm. She has an increased blood pressure of 138, K 4.9, Cl 103, bicarb 23, BUN 10, Cr 0.8, Mg 1.7, Hb 12.6, WBC 9.2, Plt 419. Renin 48ng/mL/h, aldosterone 1100ng/dL. The median age at the time of genetic testing was 0 years for both diseases. The mean serum potassium level at diagnosis was 2.9 mEq/L in T1BS, but all T2BS patients showed transient hyperkalemia (mean 7.5 mEq/L) in the early postnatal period, followed by hypokalemia (mean 3.2 mEq/L). All patients with T1BS required continuous treatment with potassium products, potassium-retaining diuretics, and/or NSAIDs as a treatment for hypokalemia, whereas only 5 patients (50%) with T2BS required these treatments. Concerning renal prognosis, 3 patients in T1BS with T1BS and 2 patients with T2BS with T2BS had deteriorated renal function at the time of genetic testing. Regarding the genotype-phenotype correlation, some of the missense variants of both T1 and T2BS did not show polyhydramnios and presented an atypical mild clinical manifestation without any symptoms in neonatal age. As for the KCNJ1, genetic serum potassium levels tended to be high (mean 3.3 mEq/L) in patients with the large deletion variant including the promoter region that has been previously reported, and this variant may present with mild manifestation.

Conclusions: T2BS shows significant hyperkalemia in the early postnatal period, but the severity of hyperkalemia in the infancy is milder than that of T1BS, and some cases did not require potassium supplementation. The correlation between the genotype-phenotype is not yet clear, but there were some clinically atypical cases, and further research is needed.

Funding: Government Support - Non-U.S.

SLC5A2 Mutation in a Patient Presenting with Volume Depletion

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Introduction: We present a patient found to have a heterozygous SLC5A2 mutation while being evaluated for volume depletion and symptoms improved. This patient had a question of whether the incidental right adrenal complex mass 1.5cm X 1.7cm with a question of whether the right adrenal adenoma in this case would present with renin and aldosterone level. Our case makes us wonder if the elevated aldosterone was due to stimulating tubuloglomerular feedback. Here, we present siblings with a naturally occurring loss-of-function mutation of the SGLT2 co-transporter.

Case Description: A 44-year-old male presented to the clinic for glucosuria first discovered at age 10. He reported current polyuria and polydipsia, and volume depletion and symptoms improved. He denied history of UTI, dysuria, urinary retention, change in appetite, or change in vision. His biological sister was found to have glucosuria as well. Both have enjoyed perfect health with normal blood pressure, electrolytes, and kidney function; both have never been admitted to hospital, and neither have diabetes. A 24-hour urine demonstrated 29 g glucose in 3.1 L, (935.5 mg/dL). Genetic testing revealed mutation in SLC5A2, the gene encoding the SGLT2 co-transporter.

Discussion: In these siblings, an SLC5A2 loss-of-function variant c.1152_116del (c.1152_116delgt) is the cause of their familial renal glucosuria. The pediatric renin inhibitor class of medication is growing in popularity for its known benefits at reducing CV disease and progression of CKD, few studies have evaluated the effect of the gene mutation induced glucosuria. One study of 13 family members in Finland with a SLC5A2 genetic mutation followed over 30 years. While they were at increased risk of urinary tract infections and postprandial hypoglycemia, there has been no effect on glucose tolerance and they maintain normal kidney function. We conclude that, as has been the case with other genetic abnormalities of transporters along the nephron, individuals and families with SLC5A2 mutations should be studied in an effort to elucidate the potential mechanisms that underlie the beneficial effects of SGLT2 inhibitors in patients with kidney disease.
Discussion: SLC3A2 encodes the renal sodium/glucose transporter, responsible for reabsorbing glucose. While homozygous mutations result in glucosuria which may lead to volume depletion, heterozygous mutations are variable with differing phenotypes, and many do not manifest with overt volume depletion in the absence of glucosuria. Here we present a patient with a heterozygous mutation in the SLC3A2 gene without glucosuria, who presented with evidence of volume depletion and electrolyte wasting tubulopathy. This case emphasizes the need for phenotyping various mutations in the SLC3A2 gene, to aid in the differential of metabolic alkalosis and altered tubular handling of electrolytes in the setting of such mutations.

FR-P0609

Juvenile Nephronophthisis Caused by Two New XPNEP3 Gene Mutations: A Case Report
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Introduction: Nephronophthisis (NPHS) is an autosomal recessive disease that mainly involves the tubulointerstitium. This article reports a case of a juvenile type of Nephronophthisis with a small proportion of urine, an increase in serum creatinine and anemia of uric acid, as the main clinical manifestations, renal pathological features of renal tubule atrophy, renal tubule membrane thickening, fibrosis, and inflammatory cell infiltration. The whole exome of the XPNEP3 gene showed two mutations: CHR22:41278058 c.466(exon 3) C>T, and Chr22:41523249 c.64(exon 1) G>A, which caused Nephronophthisis. These two mutations are novel mutations of the XPNEP3 gene.

Case Description: The patient, a 14-year-old male, was admitted to the hospital because of “abnormal renal function for 3 years.” Pathological diagnosis: Proximal sclerosing glomerulonephritis with chronic renal tubulointerstitial nephropathy is initially considered, and genetic screening is recommended. The whole exome of the XPNEP3 gene showed two mutations: CHR22:41278058 c.466(exon 3) C>T, and Chr22:41523249 c.64(exon 1) G>A, which caused Nephronophthisis. These two mutations are novel mutations of the XPNEP3 gene.

Discussion: Nephronophthisis (NPHS) is an autosomal recessive disease that primarily involves the renal tubulointerstitium. NPHP is characterized by normal or reduced renal size, renal cysts concentrated at the corticomedullary junction, and tubulointerstitial fibrosis and expansion. The whole exome of the XPNEP3 gene showed two NPHP-causing variants. Whole exome sequencing of the patient’s father and mother confirmed the existence of compound heterozygous mutations. The clinical manifestations of the patient were partially consistent with Nephronophthisis type 1. At present, there is no specific drug for the treatment of Nephronophthisis, and the principle of clinical treatment is supportive therapy. Risk factors leading to renal injury and complications should be controlled. Hormones should be avoided in patients with hypertension, worsening renal function, edema, or hyperkalemia.

FR-P0610

In Vivo Disruption of pH Gradients Alters Endo-Lysosomal Dynamics in the Proximal Tubule
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Background: The proximal tubule (PT) displays an apical endo-lysosomal system (ELS) that reabsorbs and degrades filtered plasma proteins. Defects in this process result in proteinuria. Vascular acidification is integral to endocytic function and is impaired in some genetic kidney disorders, such as Dent disease; but the nature of pH gradients in the PT ELS and their functional relevance to dynamic processes were not well understood. Data from partially differentiated in vitro models suggest that pH decreases progressively through early endosomes (EEs), late endosomes (LEs) and lysosomes, but whether it is also the case in PTs in vivo was unclear.

Methods: We have used small molecules as carriers to target pH dependent and independent fluorescent sensors to the PT ELS in living mice and provide ratiometric readouts of intracellular pH. We have applied intravital multiphoton microscopy to track probes through ELS components in real-time, and have mapped changes in pH to specific structures identified by antibody labeling in fixed tissue. The acidic pH weak base hydrochloroquine (HCQ) was injected intravenously to explore the effects of rapidly de-acidifying ELS vesicles. Results: The ratiometric technique was shown to provide a readout of pH across the physiological range in a PT cell line. Clear decreases in pH were identified within PTs in vivo in both EEs and lysosomes, but surprisingly not in LEs. Abolishing these pH gradients with HCQ disrupts reuptake of metformin and reduces it to the degradative pathway, resulting in a severe defect in protein uptake. However, HCQ treatment did not reconstitute characteristic defects in endosomal maturation described previously in Dent disease models. Mean acidic pH of lysosomal vesicles was significantly lower in LEs and prevents their trafficking into the basal, mitochondrion-rich region of the cell.

Conclusions: By using an innovative intravital imaging approach, we have generated the first functional map of ELS pH changes within working PTs, which differs significantly from the previous textbook paradigm. Moreover, we show that vesicular acidification is critical for maintaining endosomal recycling and lysosomal dynamics. However, our results suggest that endosomal alkalization alone does not fully explain the pathogenesis of Dent disease, meaning that pH-independent mechanisms still need to be considered.

FR-P0611

Hypokalemia in an Older Adult due to Heterozygosity for a Novel Pathogenic Variant that Causes Gitelman Syndrome
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Introduction: Gitelman Syndrome (GS) is a rare autosomal recessive disorder due to a mutation in the SLC12A3 gene that encodes thiazide-sensitive sodium-chloride cotransporter (NCCT) in the distal convoluted tubule. GS classically presents as a salt-losing tubulopathy characterized by low-normal blood pressure, hypokalemia, hypocalcemia, and metabolic alkalosis and is typically diagnosed in childhood or adolescence. We present an unexpected case of isolated hypokalemia in an older adult with HIV due to a heterozygous SLC12A3 variant mutation.

Case Description: A 63-year-old male with well controlled hypertension, coronary artery disease and HIV with undetectable viral load was referred for hypokalemia. He had intermittent hypokalemia for at least 15 years with potassium as low as 2.7 mEq/L. He had no symptoms of gastrointestinal loss of potassium or family history of hypokalemia. Medications included losartan 50 mg daily, metoprolol 50 mg daily, and amiodipine 10 mg daily, potassium chloride 10 mEq thrice daily, eplerenone-tenofovir alafenamide 200-25 mg daily, and doxetegavir 50 mg daily. His blood pressure was 110/75 mmHg. Serum magnesium and phosphate were normal and serum bicarbonate ranged from 25-28 mEq/L. Urine spot potassium was 43 mEq/L and fractional excretion of potassium was 11%, indicating renal potassium wasting. Screening for hyperaldosteronism was negative. A prior computed tomography showed a hydene appearance to the renal medullary pyramids and several non-obstructing kidney stones. Due to concern for an underlying genetic etiology of his hypokalemia, genetic testing was performed which revealed a heterozygous single amino acid substitution of Glu to Asp at codon 121 in exon 2 of the SLC12A3 gene.

Discussion: Our patient was heterozygous for a pathogenic variant in the SLC12A3 gene due to GS. Though the inheritance pattern of GS is autosomal recessive, we believe our patient’s isolated renal potassium wasting reflects an intermediate disease phenotype that may be seen in heterozygous carriers. A prior study found hypokalemia for the p.R642G variant was associated with lower serum potassium but to our knowledge, this is the first report of hypokalemia associated with the c.643G variant. This case supports the concept that pathogenic variants, known to cause many recessive disorders, contribute to complex traits.

FR-P0612

Syntaxin 3 Is Essential for Renal Proximal Tubular Reabsorption
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Background: Transporters at the apical membrane of renal proximal tubular epithelial cells (PTEC) are essential for reabsorbing water and electrolytes from primary urine. However, how these transporters are trafficked to the apical membrane remains uncertain. Syntaxin 3 (STX3) is a molecule that belongs to the membrane fusion-associated protein superfamily. The study aims to investigate the role of STX3 in the trafficking of transporters to the apical membrane in PTEC.

Methods: Localization of STX3 in mouse and human kidneys were analyzed by immunohistochemistry. Mice with floxed Stx3 were crossed with tamoxifen (Tm)-inducible PTEC-specific Cre-expressing mice (Ndgr1-CreERT2 Stx3fl/f Stx3cKO). Samples of the Stx3 cKO mice were analyzed 1, 2, and 6 months after tamoxifen injection. Urinary electrolytes, urinary glucose, and urinary low molecular weight proteins were quantified to determine the presence of a Fanconi syndrome-like phenotype. The expression levels and localization of various transporters of PTEC were examined by immunohistochemistry. The localization of transport vesicles and brush border in PTEC were analyzed by electron microscopy.

Results: STX3 was localized at the apical membrane of PTEC, both in humans and mice. Increased urinary excretion of phosphate, glucose, and low molecular weight proteins were found in Stx3 cKO mice compared to control (Ctrl) mice. Urinary calcium excretion and serum creatinine levels in Stx3 cKO mice were similar to those in Ctrl mice. Immunohistochemical analyses revealed that sodium phosphate transporter 2a was distributed intracellularly and sodium-glucose transporter 2 expression was reduced in the PTECs of Stx3 cKO mice. Apical brush border membranes were diffusely shortened, and intracellular vesicles were accumulated in the sub-apical areas of the PTECs in Stx3 cKO mice.

Conclusions: These results suggest that STX3 is critical for the apical trafficking of various transporters that regulate urinary reabsorption in PTEC.

Funding: Private Foundation Support
Natural History of Advanced Primary Hyperoxaluria Type 1: A Retrospective Study

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Background: Primary hyperoxaluria type 1 (PH1) is a genetic disease of oxalate overproduction that can cause progressive kidney damage and systemic oxalosis. We aimed to characterize the natural history of advanced PH1 in the context of standard of care.

Methods: In this retrospective, multinational chart review study, eligible patients had ≥4 healthcare visits related to PH1 spanning ≥6 months (except deceased patients) on or after January 1, 2000, and ≥2 eGFR values ±17.5% (or, if age <12 years, 2 serum creatinine values ≥17.5% above and 17.5% below the mean). Diagnosis details, laboratory values, clinic visits, and imaging data were collected. Patients were assigned to one of four cohorts, namely: (Co)H and hemodialysis (Cohort B). Censoring events included participation in a therapeutic clinical trial or initiation of lumasiran. Bone x-ray images were evaluated centrally for evidence of systemic oxalosis and graded using a novel bone oxalosis grading scale.

Results: Fifty-four patients met criteria for Cohort A and 53 for Cohort B; in total, 70 patients were analyzed with up to 21 years of data. Median age at cohort entry was 11.8 years (12.2 years ± 1.2 years; Cohorts A and B, respectively); 28 and 13 patients, respectively, met cohort entry criteria prior to PH1 diagnosis. In Cohort A, eGFR slope was 2.8 mL/min/1.73m²/year (n=25). In Cohort B, patients underwent hemodialysis a median of 6 days/week (range 3–7; n=41) and 3.8 hours/session (range 2–8; n=31). Overall, 42 patients underwent liver and/or kidney transplantation at least once (median age at first transplant, 15.3 years). Nineteen patients died at a median age of 3.9 years (range, 2.2–34.9); systemic arterial hypertension occurred in 16 patients (11% at last visit). 13 pts had at least 1 urine abnormality & 14/15 had normal electrolytes without acidosis. Two pts had mutations & none had GDNF mutations. 13 pts had new mutations & none had GDNF mutations. 13 pts have new mutations associated with MSK pts. Two pts have Cystinuria: SLC7A9 & SLC3A1. Two pts have Cystinuria: COL4A4. One pt has Noonan’s Syndrome: COL4A5. One pt has Noonan’s Syndrome: PTNIP1. Two pts have Smith Lemli Opitz Syndrome: DHCR7. One pt has Pallister Hall Syndrome: CLI3. Two pts have nephronopthisis: SLC26A4. Six pts had refractory migraines. The X-SEM pain score before R was 8.9/10 & was reduced to 5.7/10 at 3 months of R therapy, respectively, (p<0.001) allowing 3 pts to lower their chronic opioids.

Conclusions: We conclude that new gene mutations associated with MSK pts can cause PRKD abnormal renal changes especially in the mitochondria and medulla & no new GDNF mutations. MSK pts have migraines R can be a promising new successful chronic pain therapy confirming that CGRP is an important mediator of kidney pain in MSK.

Funding: Clinical Revenue Support

FR-PO616

The Effect of Slc7a9 Knockout in Dahl SS Rats on Blood Pressure, Metabolism, and Kidney Function

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Background: Amino acid balance plays a crucial role in regulating blood pressure and kidney function, impacting overall cardiovascular health. Mutations in the Slc7a9 gene, which encodes b(0,+)-type amino acid transporter 1 (b(0,+)AT1) responsible for transporting dibasic amino acids (AA) and cystine, are associated with chronic kidney disease (CKD) and reduced glomerular filtration rate. Patients with cystinuria have a primary hyperoxaluria 1 (PH1) is a genetic disease of oxalate (0.25% by CRISPR/Cas9. The mutation was confirmed by RT-qPCR and Western blotting.

Methods: If MSK pts have migraines R can be a promising new successful chronic pain therapy confirming that CGRP is an important mediator of kidney pain in MSK.

Funding: Clinical Revenue Support

FR-PO616

A New Mouse Model for Dent Disease 1 with Impaired Mitochondrial Metabolism Develops CKD

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Background: Dent disease 1 is a rare tubular disorder characterized by low-molecular-weight (LMW) proteinuria, hypercalciuria, and progressive renal failure. It is caused by inactivating mutations of the CLCN5 gene encoding for the 2Cl-/H+ exchanger CIC-5. In the kidney, CIC-5 is mainly expressed in early endosomes of proximal tubules (PT) cells where it is thought to optimize the function of the vacuolar H+–ATPase to ensure the proper endocytosis of LMW proteins. To better understand the cellular mechanisms involved in Dent disease, we have generated a Knock-in (KI) mouse model carrying a patient mutation of CIC-5. Preliminary data from the lab showed altered PT endolysosomal function and consequent impaired autophagy. Whether this altered pathway could impact mitochondrial metabolism was previously unknown. Therefore, we used this novel mouse model to evaluate the contributing factors of the progressive metabolic disorder observed in Dent disease.

Methods: The renal phenotype of WT and KI ageing mice was explored using immunofluorescence, western blot, transmission electronic microscopy, and targeted urinary metabolic analysis.

Results: 10-month-old KI showed an impaired general renal function accompanied by increased fractional excretions of calcium, phosphate, magnesium, indicating a PT dysfunction. KI mice expressed more Lipocalin 2, a tissue damage marker, in their kidneys and showed its increased excretion. These changes were associated with renal fibrosis and inflammation. The renal expression of PECG1 alpha, a marker of mitochondrial biogenesis, 40% less between 2 to 4 months old, KI mice. It was associated to an increased mitochondrial mass at 10 months. The shape of PT mitochondria from KI mice was altered even at young stages. Additionally, the loss of metabolites crucial for mitochondrial metabolism (alpha ketoglutarate, oxaloacetic acid, etc.) was highlighted in KI mice.

Conclusions: In conclusion, our mouse model suggests that altered endocytosis, consequent to CIC-5 mutation, impairs autophagy and leads to the accumulation of defective mitochondria. This would therefore potentiate renal damages of various origins with age, and a subsequent renal failure. This study opens up new perspectives for the development of therapeutic agents.

Funding: Government Support - Non-U.S.
FR-PO617
Phosphor-Modified KLHL3 Knockin Mice Reveal WNK1/4-Independent SPACK0581-NCC Activation in Pseudoaldosteronism Type II (PHAI1) Shih-Hua P. Lin, Chih-Chien Sung, Chih-Jen Cheng. Tri-Service General Hospital Department of Internal Medicine, Taipei, Taiwan.

Background: We have successfully created missense Klih3W523X/ knockin (KI) mice (human M738T mutation in BTB domain) and nonsense Klih3W523X/ KI mice (human W470X mutation in Kelch domain) to decipher the molecular mechanisms of PHAI1. However, the phosphorylation site (S433) on KLHL7 regulated by several stimuli such as angiotensin II, insulin, and calcineurin inhibitors in PHAI1 have not been examined in vivo.

Methods: We generated and analyzed two missense Klih3 KI mice with phosphor-modified at S438 site. The phenotypes of phosphomimetic Klih3S438E mice (human KLHL7 S433D mutation) and phosphodefective Klih3G470X mice (human KLHL7 S433G mutation) were examined. The associated protein expression of their kidney tissue was evaluated by western blot and immunofluorescence.

Results: Unlike the Wnk-dependent Spak/Osr1-Ncc activation in Klih3W523X/ and Klih3W523X/ KI mice, both Klih3G470X and Klih3G470X mice recapitulating typical phenotypes of PHAI1 exhibited an enhanced phosphorylation of Spak/Osr1-Ncc but the “unchanged” Wnk1/4 and Klih3 expression. Both phosphor-modified Klih3 KI mice demonstrated a significantly increased expression of calcium binding protein 39 (Cab39) known to interact and stimulate Spak/Osr1, as compared to those in WT littermates. Klih3W523X/ mice. In vitro study showed that endogenous Cab39 interacted with KLHL3 and Cul3 complex, but not with WNK1-4. The simulation model demonstrated that KLHL3-WT and phosphor-modified KLHL3 mutants had different binding regions with Cab39.

Conclusions: Phosphor-modified KLIHL3 KI mice exhibiting PHAI1 reveal a novel Wnks-independent Spak/Osr1-Ncc activation. Whether the phosphorylated status of KLHL3 S433 could affect its binding ability with Cab39 as a substrate for ubiquitination needs to be well validated.

Funding: Government Support - Non-U.S.

FR-PO618
Tracking Molecular and Phenotypic Changes in Kidney Cells in 2D and 3D Cultures Following DHA Exposure: An Approach to Understand Cellular Changes in Adenine Phosphoribosyltransferase (APRT) Deficiency
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Background: Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of adenine metabolism that results in the generation and renal excretion of 2,8-dihydroxyadenine (DHA), leading to kidney stones and crystal nephropathy characterized by inflammation and fibrosis. The aim of this study was to create a cell culture model to investigate DHA crystal-induced kidney injury in order to identify novel therapeutic targets for clinical intervention.

Methods: Three kidney cell lines, MDCK, HK-2, and HEK293, were used in this study. All cell lines were treated with DHA at concentrations comparable to those found in the urine of untreated humans with APRT deficiency, both in monolayer and 3D assays. Furthermore, siRNA against APRT was used to knock down the gene in HEK293 and HK-2 cells. The readout assays included cell viability, RT-PCR, western blotting, and immunostaining.

Results: Following DHA exposure, decreased viability was observed in all cell lines. HEK293 cells exhibited increased expression of IL-8 following DHA treatment, indicating an inflammatory response. MDCK cells showed increased expression of N-acdherin when treated with high concentrations of DHA compared to the control, suggesting an epithelial–mesenchymal transition (EMT) response. Additionally, both HEK293 and MDCK cells showed increased CD94 expression, which is believed to be important for crystal binding to renal epithelial cells, upon exposure to higher DHA concentrations. When cultured in 3D condition with the addition of DHA, MDCK cells were still able to form polarized structures, and DHA accumulated within and around the structures. HEK293 cells formed solid colonies with the addition of DHA, the DHA accumulates inside the colonies. APRT expression was significantly reduced in HEK293 and HK-2 cells after successful knockdown, and HEK293 cells exhibited elongated protrusions.

Conclusions: We have established a cell culture model that captures kidney cell alterations observed in APRT deficiency. Data suggest that DHA treatment of these cell lines in vitro induces an inflammatory response, EMT, and reduces cellular viability. This cell culture model provides insights into the inflammatory response and potential disease-specific targets for clinical intervention.

Funding: Government Support - Non-U.S.

FR-PO619
Acyl-CoA Synthetase Short-Chain Family 2 Is a Renal Disease Risk Gene: Controlling De Novo Lipogenesis in Kidney Tubules

Background: Worldwide, over 800 million people are affected by kidney disease, yet its pathogenesis remains elusive, hindering the development of novel therapeutics.

Methods: In this study, we employed kidney-specific expression of quantitative traits and single-nucleotide open chromatin analysis to show that genetic variants linked to kidney dysfunction on chromosome 20 target the acyl-CoA synthase short-chain family 2 (ACSS2). By generating ACSS2 knock-out mice, we demonstrated their protection from kidney fibrosis.

Results: Our analysis of primary tubular cells revealed that ACSS2 regulates de novo lipogenesis (DNL), causing NADPH depletion and increasing ROS levels, ultimately leading to NLRP3-dependent pyroptosis. Additionally, we discovered that pharmacological inhibition or genetic ablation of fatty acid synthase safeguarded kidney function and protected against disease in mice. Lipid accumulation and the expression of genes related to DNL were elevated in the kidneys of patients with fibrosis.

Conclusions: Our findings pinpoint ACSS2 as a critical kidney disease gene and reveal the role of DNL in kidney disease.

Funding: NIDDK Support

FR-PO620
Mitochondrial Reactive Oxygen Species (ROS) Triggers Karyomegalic Interstitial Nephritis (KIN) Pathogenesis in FAN1-Deficient KIN Merlin Airik,1 Eric S. Goetzman,1 Stanislav Knoch,2 Peter J. Conlon,3 Anthony J. Bleyer,4 Rannar Airik.1,2,3 Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA; 1Universita Karlova, Praha, Czechia; 2Beaumont Hospital, Dublin, Ireland; 3Wake Forest Baptist Medical Center, Winston-Salem, NC; 4University of Pittsburgh, Pittsburgh, PA.

Background: Karyomegalic interstitial nephritis (KIN) is a genetic adult-onset chronic kidney disease (CKD) characterized by genomic instability and mitotic abnormalities in the tubular epithelial cells. KIN is caused by recessive mutations in the FAN1 DNA repair enzyme. However, the endogenous source of DNA damage in FAN1/KIN kidneys has not been identified.

Methods: KIN was induced in 12-week-old Fan1 KO mice by employing low dose cisplatin injury models: one mimicking AKI (1 x 2 mg/kg cisplatin), and another CKD (weekly 5 x 2 mg/kg cisplatin). Coincident with cisplatin, mice were administered a novel mitochondrial ROS and electron scavenger JP4-039 at a dose of 10 mg/kg. Histological analysis was performed using PAS and HE. Markers of tubular injury, DNA damage and inflammation were assessed by IF and IHC. Mitochondrial ROS and electron scavenger (Oxygraph-2k System. Metabolite measurements were performed using YSI 7100 Bioanalyzer.

Results: Transcriptional profiling of kidneys with KIN revealed a significant downregulation of genes involved in mitochondrial energy metabolism - OXPHOS, fatty acid oxidation (FAO) and peroxosomal function. Metabolic analysis of FANIKO PTECs showed a defect in respiratory chain, increased oxidative stress and a shift to increased lipid metabolism. Similarly, Fan1 KO kidneys revealed increased expression of oxidative DNA damage (8-OHdG), lipid peroxidation (4-INE) and tubular lipidotoxicity (OilRedO) after AKI or CKD. Treatment with mitochondrial ROS scavenger reduced the level of oxidative lesions in Fan1 KO kidneys, mitigated tubular damage and blocked the formation of KIN.

Conclusions: Loss of Fan1 causes defective mitochondrial metabolism and increased ROS generation in the kidney which give rise to oxidative DNA lesions and results in KIN. Blocking mitochondrial ROS protects Fan1 KO kidneys from DNA damage accumulation, mitigates tubular injury and improves kidney function in mice.

Funding: NIDDK Support

FR-PO621
A Novel Renal Collecting Duct Model to Study Secondary Nephrogenic Diabetes Insipidus Associated with Cystinosis
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Background: Cystinosis is a severe lysosomal disorder caused by mutations in the CTNS gene, encoding for the lysosomal transporter cystinosin, resulting in the accumulation of cystine throughout the body. It manifests as Renal Fanconi syndrome in the first months of life, and later progresses into end stage renal failure. Secondary Nephrogenic Diabetes Insipidus (NDI) has been reported as a secondary complication of cystinosis due to the resistance to vasopressin, a key hormone that, in the collecting duct activates the vasopressin-sensitive water channel Aquaporin-2 (AQP2), regulating water reabsorption. Over the past years, the development of several in vivo and in vitro models of cystinosis has contributed to understand the pathobiology of this severe disease. Nevertheless, the molecular mechanisms causing the secondary NDI phenotype have not been investigated due to the lack of collecting duct cellular models.
**Methods:** A CRISPR/Cas9 CTNS knockout model derived from MCD4 cells, a mouse embryonic fibroblast cell line, stably expressing human aquaporin 2 and vasopressin receptor 2 (V2R), was established and validated by Sanger sequencing, qPCR and mass spectrometry (MS). Osmotic water permeability measurements in presence or absence of Desmopressin (DDAVP), a synthetic vasopressin analog to investigate AQP2 function were performed.  

**Results:** Sanger sequencing analysis demonstrated that CTNS was efficiently CRISPR-ed. This result was further confirmed by a significant reduction of CTNS transcripts levels, up to 65%, and a significant accumulation of cystine by MS in CRISPR-ed CTNS KO cells compared to control. Studies on osmotic water permeability indicated that, compared to control, in CRISPR CTNS cells, the osmotic water permeability does not significantly increase in response to DDAVP treatment, consistent with an impairment of the vasopressin-AQP2 pathway.  

**Conclusions:** We report here the first CTNS KO collecting duct in vitro model useful for the study of secondary NDI in cystinosis.  

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

**FR-PO622**

Sox2/CD63-GFP Transgenic Rat: A Novel Model for Nephrogenic Diabetes Insipidus  

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**Background:** Tetraspanins are transmembrane proteins with four membrane domains that form complexes with other membrane proteins, playing diverse roles in physiological functions. The tetraspanins CD9, CD63, and CD81 are well-established examplars, while the CTNS variant CTNS KO collecting duct cell line, stably expressing human AQP2 and vasopressin receptor 2 (V2R), was established and validated by Sanger sequencing, qPCR and mass spectrometry (MS). Osmotic water permeability measurements in presence or absence of Desmopressin (DDAVP), a synthetic vasopressin analog to investigate AQP2 function were performed.  

**Methods:** We assessed body weight, food consumption, water intake, blood pressure, serum urea nitrogen (UN), creatinine (Cre), urine volume, and urine osmolality in Sox2/CD63-GFP rats, along with age- and sex-matched normal littermates. Histological and immunohistochemical analyses of the kidneys were conducted.  

**Results:** Tg rats exhibited lower body weight compared to normal rats, along with approximately 7-8 times higher water intake and urine volume. Serum biochemical analysis indicated elevated UN and Cre levels in Tg rats, suggesting deteriorating renal function. Tg rat kidneys showed significant enlargement and symptoms of hydorenephrosis. In normal rat kidneys, AQP3 was distributed laterally, while AQP2 was distributed apicilly in the collecting ducts. In contrast, Sox2/CD63-GFP rats exhibited reduced AQP2 expression in both the plasma membrane and cytoplasm of the cortical collecting ducts.  

**Conclusions:** Nephrogenic diabetes insipidus, one of the two primary types of diabetes insipidus, primarily results from mutations in the vasopressin receptor or AQP2 in the collecting ducts. The observed symptoms in Sox2/CD63-GFP rats resembled those of diabetes insipidus, characterized by impaired water reabsorption in the kidneys and severe renal manifestations such as polydipsia, polyuria, and hydorenephrosis due to excessive urinary output. CD63-GFP expression may disrupt intracellular trafficking of AQP2, given CD63’s involvement in intracellular trafficking and protein localization at the plasma membrane.  

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

**FR-PO623**

Renaal Failure from Bladder Acontractility in Untreated X-Linked Diabetes Insipidus  

Dureya Syed, Martin Sedlacke. Icahn School of Medicine at Mount Sinai, New York, NY.  

**Introduction:** A lot is known about about the genetics and molecular pathophysiology of hereditary nephrogenic diabetes insipidus (DI) but there is little information on the long term renal outcome of this condition. Case series show that nephrogenic DI can lead to CKD but the mechanism is unclear. Here we report a patient with untreated x-linked nephrogenic DI who developed end stage renal failure due to bladder dysfunction.  

**Case Description:** A 45 year old man presented to the emergency room with a history of diabetes insipidus. He initially presented with bladder dysfunction and later required dialysis. The patient was known to have a 2 gene defect in AQP2 and GNAS. Imaging showed a normal sized prostate, cystoureteroscopy was normal except large bladder capacity and hydronephrosis. The patient received fluids and was discharged on HCTZ and with an indwelling Foley catheter. He learned to self-catherize and was discharged 4 months later. His serum creatinine was 1.02mg/dl and his urine output 7 L per day.  

**Discusssion:** Patients with nephrogenic DI produce urine volumes in the range of 10-20L/day with a bladder volume of 400ml, they will have to urinate at least 25 times in 24 hours, night and day. Because of Poseueille’s law, increased urine flow leads to increased pressure, causing hydorenephrosis and bladder distention which in turn leads to detrusor dysfunction and ultimately bladder acontractlatity. We suspect this chain of events to be the frequent cause of bladder failure in DI, preventable by flow reduction via diuretic treatment and reduced osmol dose. Straight catherization can improve renal function in patients with bladder acontractlatity.

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

Underlines represents presenting author.

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Underlines represents presenting author.
FR-PO626

ABC6 and CKD: The Phenotypic Expansion of Pseudoxanthoma Elasticum
Clara Schott,1,2 Cadence Baker,2 Samantha Colaiacovo,2 Dervla M. Connaughton.1,2 1Western University Schulich School of Medicine & Dentistry, London, ON, Canada; 2London Health Sciences Centre, London, ON, Canada.

Background: Adenosine triphosphate (ATP) Binding Cassette Subfamily C Member 6 (ABCC6) is a transporter nucleotide that mediates cellular efflux of ATP, which is hypothesized to prevent calcification. In chronic kidney disease (CKD) patients, vascular calcification is prevalent but not completely understood. Monogenic cause occurs in 10% of CKD patients, however monogenic causes of vascular calcification in CKD have yet to be identified. Both recessive and dominant variants in ABC6 are known to cause Pseudoxanthoma Elasticum (PXE), a heritable disorder characterized by the accumulation calcium deposits and subsequent vascular calcification involving elastic fibers in the skin, eyes, and cardiovascular system. Data suggests PXE is associated with nephrolithiasis and nephrocalcinosis, with reports also suggesting higher prevalence of end-stage kidney disease (ESKD), gleromerulonephritis, and renovascular hypertension. This is hypothesized to be secondary to elastic fiber fragmentation and mineralization in renal arteries. In addition, knockout mice models in ABC6 developed calcification in the blood vessels, predominantly in the renal cortex, in association with papillary calcification.

Methods: To identify monogenic kidney disease associated with vascular calcification phenotype, we performed whole exome sequencing (WES) in 94 families developed calcification in the blood vessels, predominantly in the renal cortex, in association with papillary calcification.

Results: We identified 2 heterozygous, loss of function variants in ABC6 in 2 families with CKD of unknown etiology (c.1999delG p.A667fs and c.C3421T:p.R1141X). No formal diagnosis of PXE was established prior to analysis. Affected individuals were reviewed post exome analysis and were found to exhibit a broad spectrum of extra-renal phenotypes including eye and skin pathology, and severe peripheral vascular disease. Renal phenotype included a history of kidney stones along with CKD of unknown etiology progressing to ESKD in multiple family members.

Conclusions: We identified loss of function variants in ABC6 in two families with CKD by reverse phenotyping for PXE. This report suggests the need for phenotype expansion of PXE to include CKD. Further work is required to establish the exact role in disease pathogenesis but preliminary data suggests that heterozygous variants in ABC6 may lead to multi-system vascular calcification disease, also affecting the kidney.

FR-PO627

Utility of a Renal Genetics Clinic: A Canadian Prospective Cohort
Clara Schott,1,2 Cadence Baker,2 Samantha Colaiacovo,2 Dervla M. Connaughton.1,2 1Western University Schulich School of Medicine & Dentistry, London, ON, Canada; 2London Health Sciences Centre, London, ON, Canada.

Background: Genetic kidney disease (GKD) is more prevalent than previously considered, with 1 in 10 chronic kidney disease (CKD) patients affected. When correct inclusion criteria for GKD is used, 34-67% of patients can have a genetic diagnosis. Genomic testing using gene-panel or exome sequencing (ES) can confirm GKD through detection of mutations in genes known to cause CKD. Unfortunately, widespread integration into clinical practice has been hampered by small studies and highly selective populations predominately performed in research rather than clinical settings. This study aims to prospectively demonstrate the utility of a renal genetics clinic in a Canadian cohort.

Methods: We analyzed data from a cohort of patients (n=174 families, n=209 affected patients) referred to a renal genetics clinic between September 2019 and April 2023. Testing strategy was firstly to perform gene-panel testing, and if negative or unsuitable, ES was performed. Testing was performed for the detection of mutations in genes suspected to cause the specific subtype of CKD. Mutations are classified according to the American College of Medical Genetics guidelines, with pathogenic and likely pathogenic variants being causative.

Results: We identified a causative mutation in a gene known to cause CKD in 38% of patients (n=80/209). Gene panel testing, performed as the first line of investigation, detected the underlying molecular cause of CKD in 31% of patients tested (n=44/142). Primary ES was performed as the first test in patients with CKD of unknown etiology (CKDu) and had a solve rate of 18% (n=8/45). In patients whom gene-panel was negative or not possible (n=82), secondary ES analysis was performed and confirmed the suspected clinical diagnosis in 26% of patients (n=21/82). For solved patients (n=80), there were many clinical outcomes, including change of diagnosis. Of note, 48% of solved patients had a pre-priori diagnosis of CKDu, but all received a diagnosis after testing. Other important clinical outcomes include, avil of genetic counselling, resolved diagnostic confusion, and correction of diagnosis.

Conclusions: We show that in a Canadian cohort of adults referred to a renal genetic clinic, genomic testing has utility by confirming the cause of genetic kidney disease in 38% of patients. Genetic sequencing also has significant impacts on clinical management and patient outcomes.

FR-PO628

Diagnostic Utility and Clinical Impact of Genomic Testing in Adolescent and Adult Kidney Disease Patients with Suspected Monogenic Etiology by Establishing an Integrated Kidney Genetics Service
Suceena Alexander,1,2 Saptosht Varughe,3 Selvin Sundar Raj Mani.1 GRACE-KGS. Christian Medical College Vellore, Vellore, India.

Background: Though studies have shown positive impact of genomic testing in pediatric population, the diagnostic utility and the clinical impact in real world situations faced by nephrologists when managing adolescent and adult patients with suspected monogenic kidney disease is not known.

Methods: It is a prospective observational pragmatic cohort study. Consecutive patients satisfying the inclusion and exclusion criteria was recruited after written informed consent and pre-test genetic counselling. Genetic testing was by exome sequencing and results returned with post-test genetic counselling. The whole exome sequencing was done on all probands and the bio-informatics was performed using in-house and commercial (VarSeq, Golden Helix) pipeline to identify diagnostic variants for patients' renal disease by data scientist and nephrologist trained in genetics. Segregation testing was done on parents of probands to confirm inheritance pattern if required. The diagnostic utility and the clinical impact was assessed at 3 months of patient follow-up following detailed phenotype-genotype correlations.

Results: More than 100 patients were prospectively recruited for this study. Diagnostic utility was 60% and covered the whole spectrum of renal diseases. Phenotypic enrichment prior to recruitment is essential for optimum test usage. There was definite clinical impact and cascade testing could be offered to family members. Cost was significantly decreased with in-house bioinformatics pipeline.

Conclusions: In-house generation of database and bio-informatics performed together nephrologist in the team, helps to correlate the phenotype and genotype tightly and identify disease causing variants by ACMG criteria.

Funding: Government Support - Non-U.S.
Developing Best Practices for Returning Genetic Results to Participants in Nephrology Research: A Study of the CureGN Network

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Background: Returning genetic results (RoR) from research is a growing practice aimed at improving patient care and to serve as a trust-building measure by showing reciprocity in health research. No guidelines for RoR in nephrology research currently exist, leading to diverse practices across research sites which limits the ability to understand the impacts of RoR on research participants. We developed a workflow for RoR in the Cure Glomerulonephropathy Network (CureGN) and a study to assess its implementation and the medical and psychosocial impacts of RoR.

Methods: Genome sequencing was performed on 1957 CureGN participants. We identified 3 variants’ groups: variants consistent with kidney diseases; APOL1 high risk genotypes; and variants in actionable genes per ACMG/AMP’s guidelines. A multidisciplinary team developed a framework for RoR, assessed its acceptability and barriers via a survey with nephrologists, followed by webinars with nephrologists, research participants and parents of pediatric participants, refined and finalized the workflow. We developed pre- and post-RoR surveys for parents, research participants (adults and adolescents), and treating nephrologists to assess satisfaction, medical and psychosocial impacts of the RoR, and barriers for Post-RoR care. With a NIDDK grant, the RoR is free to CureGN participants.

Results: Based on findings from the nephrologists’ survey and webinars, we will return the 3 variants’ groups in a centralized RoR workflow is implemented by Columbia University (CU) and the CureGN Data Coordinating Center (DCC) at the University of Michigan. Given privacy protections, we instituted a multistep process to inform participants with positive results (n=270): CU will share relevant CureGN IDs with the DCC to inform sites on who to invite for RoR. Interested participants will contact CU’s genetic counselors (GCs) to discuss the RoR study, consent and provide a DNA sample for clinical confirmation. GCs will return the results to participants and their nephrologists, add them to the medical records, and send out the surveys.

Conclusions: Findings will inform about the feasibility of, and best practices for, RoR in a large, racially and ethnically diverse Network and will be generalizable to other consortia. Funding: NIDDK Support

FR-PO650

Pathogenic Genes in the Mesoamerican ESRD Population

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Background: Dialysis clinics in the New York area treat a large population of immigrants originating from Central and Northern South America. Many do not have an etiology for ESRD, which may result from Mesoamerican (MA) Nephropathy, a pathology not well understood. This study assesses if there are underlying diseases due to genetic variances that predispose these patients to ESRD.

Methods: MA subjects were recruited prospectively from Atlantic Dialysis Management Services units in New York City and Dialysis Clinic Inc from Westchester Medical Center, along with non-Mesoamerican subjects (n-MA). Saliva swabs were acquired and processed via Renasight genetic kits. 385 genes were assessed for pathogenic or likely pathogenic variants.

Results: 228 subjects were recruited, of which 123 were MA. 11% of MAs were found to have 23 pathogenic or likely pathogenic variants of positive genes. Of these 23 cases, the most common variants were identified in genes associated with Alport Syndrome (COL4A3 and COL4A4) at a frequency of 26% (6/23). The variants in genes associated with Polycystic Kidney Disease (PKD) (PKD1 and PKD2) also had a frequency of 22% (5/23). Of the 105 MA subjects, 20% of them were found to have 39 pathogenic or likely pathogenic variants of positive genes. The frequency of pathogenic variants of genes encoding for Alport Syndrome is 10%, and the frequency of PKD is 8%. The frequency of pathogenic variants of genes encoding for Alport Syndrome is 10% (4/39), and the frequency of PKD is 8% (3/39). The incidence of the APOL1 risk allele in the n-MA population was 28% (11/39), compared to 4% (1/23) in the MA population.

Conclusions: The frequency of genes related to Alport’s Syndrome and PKD were increased in MAs. The higher frequency of APOL1 risk alleles in the n-MA contributes to a higher incidence of variants of positive genes, but it is unclear if this led to an underlying genetic cause of kidney disease. Although pathogenic variants were found, their presence does not clearly point to genetic etiologies for MA Nephropathy.

Funding: Commercial Support - Natera

FR-PO651

Association Between Sickle Cell Disease and Mortality and Hospitalizations Among In-Center Hemodialysis Patients

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Background: Sickle cell disease (SCD) is the most common hemoglobinopathy and genetic disorder worldwide, and a significant cause of end stage kidney disease (ESKD). Despite this, our understanding of adverse outcomes in SCD patients undergoing in-center hemodialysis (ICHID) is limited by small sample sizes, non-granular data and significantly different control groups resulting in residual confounding. The purpose of this preliminary study was to assess mortality and hospitalizations within a SCD patient population treated with ICHD for at least 6 months.

Methods: This retrospective study identified SCD and non-SCD patients receiving ICHD treatment from Fresenius Kidney Care (FKC) between 1-1-2017 and 12-31-2021. The baseline period was considered the first 6 months of treatment at FKC. Incident and prevalent ESKD status was defined as less than or more than 4 months since first dialysis date at the start of baseline, respectively. 602 incident and 541 prevalent SCD patients were matched to non-SCD controls using propensity score matching with confounders including incidence/prevalence status (exact match), sex, race, ethnicity, age, and vascular access type. All-cause mortality was analyzed using the Cox proportional hazards model, with the number and duration of hospitalizations being modeled using generalized estimating equations with a Poisson distribution and log link function.

Results: a) Incident Patients: Compared to matched controls, incident SCD patients were 45% more likely to pass away at any given time point (p<0.001). SCD patients also had higher rates of hospitalizations per year (2.8 vs 1.6, p<0.001) and days hospitalized per year (8.2 vs 4.2, p<0.001) than controls. b) Prevalent Patients: Compared to matched controls, prevalent SCD patients were 23% more likely to pass away at any given time point (p=0.023). SCD patients also had higher rates of hospitalizations per year (2.8 vs 1.6, p<0.001) and days hospitalized per year (9.6 vs 5.6, p<0.001) than controls.

Conclusions: This preliminary study provided evidence that SCD patients who have received ICHD treatments for at least 6 months remain at an elevated risk for all-cause mortality and hospitalizations compared to similar, non-SCD patients. The all-cause mortality risk was attenuated by prevalent status.

FR-PO652

Patient Mortality and Graft Failure Risks in Transplant Recipients with Kidney Failure Secondary to Genetic Kidney Disease Compared to People with Other Kidney Diseases

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Background: There is limited population-level data on long term outcomes of people with genetic kidney disease (GKD) after kidney transplantation. This study aimed to characterise clinical outcomes in people with GKD after kidney transplantation and compare them to those of people with other kidney diseases.

Methods: Data on first kidney transplants between 1 January, 1989 and 31 December, 2020 were extracted from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. GKD were classified as majority or minority monogenic. People with other primary kidney diseases were included as the comparator group. Outcome measures were mortality and graft failure. Unadjusted and adjusted hazard ratios (AHRs)
were calculated using Cox proportional hazard regression models. Sensitivity analyses were completed to test the effect of major diagnoses (e.g., autosomal polycystic kidney disease and reflux nephropathy) within GKD groups.

**Results:** 21,860 transplant recipients were included. GKDds were associated with reduced mortality in kidney transplant recipients on univariable analyses. This correlation was not statistically significant on multivariable analyses (majority monogenic AHR 0.92, 95% CI 0.84-1.00; minority monogenic AHR 0.91, 95% CI 0.82-1.02). Majority monogenic GKDds correlated with reduced graft failure compared to other kidney diseases on univariable (Figure 1) and multivariable analyses (AHR 0.79, 95% CI 0.71-0.87). This result was attributed to reduced graft failure in recipients with polycystic kidney disease, which constituted 91.9% of the majority monogenic GKD group.

**Conclusions:** This bionatinal registry analysis found that people with GKD had similar mortality but reduced graft failure after kidney transplant. This is the first study to provide a broad longitudinal overview of clinical outcomes in kidney transplant recipients with GKD.

**FR-PO633**

Evaluating the Association Between Maternal Dietary Vitamin A Status and Fetal Kidney Development

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**Background:** Vitamin A is a fat-soluble vitamin that plays a crucial role in the development of fetal organs. In vitro, studies have indicated that the number of nephrons, which are functional units in the kidney, is impacted by the presence and quantity of vitamin A. However, the effect of maternal dietary vitamin A status on fetal kidney development remains unknown. As abnormal kidney development can contribute to later renal disease, it is important to identify modifiable factors impacting kidney development, such as dietary intake of vitamin A.

**Methods:** An IRB-approved study recruited pregnant women who completed a food survey (DHQ III) to evaluate dietary vitamin A intake between 24-28 weeks of gestation. Vitamin A intake was measured in retinol activity equivalents (RAE, mcg/day), with values converted from retinol activity equivalents (RAE) to retinol activity equivalents (RAE) or delta-calciferol. We hypothesized that maternal vitamin A intake would be associated with fetal kidney length and volume (p = 0.94 and p = 0.44), infant right kidney length and volume (p = 0.94 and p = 0.57) and change in right kidney length and volume (p = 0.78 and p = 0.62) across two groups. Similarly, no significant differences were noted in fetal left kidney length and volume (p = 0.39 and p = 0.10), infant left kidney length and volume (p = 0.20 and p = 0.10) and change in left kidney length and volume (p = 0.72 and p = 0.43) across two groups.

**Conclusions:** Our study did not find any difference in fetal or infant kidney measurements between maternal vitamin A status and fetal and infant kidney measurements. Furthermore, maternal vitamin A status did not impact kidney growth reported as a change in kidney length or volume. Larger, adequately powered studies should be conducted.

FR-PO634

The Underappreciated Renal Phenotype of EGFR Deficiency: Could It Be that Complex?

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**Introduction:** Epidermal Growth Factor Receptor (EGFR) is a cell signaling receptor implicated in cell proliferation, survival, and tissue growth. Neonatal inflammatory skin and bowel disease type 2 is caused by EGFR recessive deficiency (OMIM 610609). Among the 22 known cases, nephropathy is the only notable renal phenotype. A review of published cases and a new case suggests NISB2D is frequently associated with tubulopathy.

**Case Description:** A 10-year-old girl was diagnosed with NISB2D caused by homozygous pathogenic EGFR variants (NM_005228.3: c.1283G>A; p.G428D). Ultrasound revealed large echogenic kidneys with poor corticomedullary differentiation and many small cysts. We documented hydropsiemia 0.5 mmol/L and hypokalemia 2.6 mmol/L caused by excessive urinary magnesium wasting FeMg 14%. We also observed mild chronic hypernatremia 155 mmol/L due to a urinary concentration defect UOsm 400 mOsm/kg water. Finally, low-molecular-weight proteinuria and glucosuria were observed. Renal phosphaturia and calcitriol deficiency were striking. Hydropsiemia is well-known in EGFR inhibitors but not in EGFR deficiency. Additionally, EGFR deficiency causes enlarged kidneys. The renal phenotype, however, is much more complex, involving hypokalemia, hypernatremia, cystic disease, and tubulopathy. Electrolytes can be monitored more precisely in cases of EGFR deficiency to determine the significance of this association.

**FR-PO635**

Müllerian Anomalies in Girls with Solitary Functioning Kidney

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**Background:** Patients with Müllerian anomalies have a 30-50% increased prevalence of congenital renal anomalies and solitary functioning kidney (SKF) is the most common. However, the prevalence of Müllerian anomalies among patients with SKF is not well defined. A delay in diagnosis of obstructive Müllerian anomalies can increase the risk of poor clinical outcomes. This study describes the prevalence of Müllerian anomalies in patients with congenital SKF.

**Methods:** A retrospective review was performed of patients within the Nationwide Children’s Hospital system with ICD9 or ICD10 diagnostic codes for SKF. Analysis focused on girls with congenital SKF defined as either unilateral renal agenesis (URA) or multicystic dysplastic kidney (MCDK). Patients with complex urogenital pathology, such as, cloaca, urogenital sinus, or bladder extrophy were excluded. Renal anomaly, Müllerian anomaly, reason for and type of pelvic evaluation, and age of diagnosis of anomalies were evaluated.

**Results:** Diagnostic codes identified 400 patients; 97 were excluded for complex urogenital anatomy. SKF was confirmed in 204 girls and 169 (82%) were congenital. There were 115 patients with URA and 54 with MCDK. Additional anomalies of the SKF were pelvic/trochanteric (4), dysgenesis/hypoplasia (8), cystic (2), and other (19). Of patients with congenital SKF, 85 (50%) had a pelvic evaluation, most frequently in response to abdominal pain/dysmenorrhea (39%). Ultrasound was the most common imaging modality (74%). 49 (29%) patients had a Müllerian anomaly with the majority having combined uterine and vaginal anomalies (28) or isolated uterine anomaly (18). In 59% of patients, the renal anomaly was diagnosed prior to the Müllerian anomaly, at a median age of 6.5 years. In 24 patients, an obstructive Müllerian anomaly was found, including 11 who had a known renal anomaly.

**Conclusions:** The prevalence of Müllerian anomalies in patients with congenital SKF was 29%. Only half of patients with a congenital SKF had a pelvic evaluation. A Müllerian anomaly was found in about 60% of patients evaluated and it was obstructive in about one third of cases. Over half of the girls with Müllerian anomalies had a primary renal evaluation. The high prevalence of Müllerian anomalies in patients with congenital SKF justifies routine screening pelvic ultrasound to improve early diagnosis.

**FR-PO636**

Pparg Pathway Drives Renal Uroplakin Cell Formation and Parenchymal Preservation During Urinary Tract Obstruction

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**Background:** Urinary Tract Obstruction (UTO) is a leading cause of chronic and end stage kidney disease in children. While no current treatments prevent obstruction-induced kidney disease, future therapies may be identified by understanding how the kidney adapts to obstruction. We previously reported that obstruction triggers the formation of protective keratinocytes (Urt) cells which preserve renal parenchyma during congenital and acquired UTO. The molecular program that governs Upt cell formation in the renal urothelium is unknown. In bladder, the Pparg signaling pathway drives urothelial differentiation. Thus, we hypothesized that Pparg drives renal Upt cell formation during UTO.

**Methods:** Kidneys from embryonic (E-) and postnatal (P-) fetal and male mice were collected. We modeled UTO using congenital and surgical models. We conditionally manipulated Pparg in Upt cells using inducible Pparg deletion (Upt2aTg;Ppargfl/lof) and gain-of-function (Upt2aTg;Ppargm) mice lines. Immunofluorescence Analysis (IF-A) and renal ultrasound were used to assess the effect of Pparg pathway manipulation on UTO-induced Upt cell formation and renal parenchyma, respectively.

**Results:** Pparg was expressed by renal Upt cells at E17 - P7, but was absent in adult mice atP24. Both congenital and surgical UTO triggered Upt cells to re-express Pparg and URT targets, GfrH3 and Fabp7. During UTO, Upt2aTg;Ppargm mice showed a significant reduction in Upt expression (10% Vs 3.1%, P=0.008) accompanied by...
significantly thinned renal parenchyma (30.9% Vs 25.9%, P<0.039), compared to Cre(-) mice. However, Upk2<fl/fl>Pparγ<±> mice induced a significant upregulation of Upk (10% Vs 17.4%, P<0.006) and exhibited significantly greater parenchymal preservation (30.9% Vs 44.4%, P<0.002), compared to Cre(-) mice.

**Conclusions:** Our results reveal that UTO-induced Pparγ signaling is a recapitulation of a renal urothelium developmental program, and that Pparγ signaling promotes Upk cell formation to preserve renal parenchyma during UTO. Our findings advance our understanding of renal adaptation to UTO and reveal a potential mechanism, such as Pparγ signaling, with therapeutic utility for mitigating obstructive kidney disease in children. Future studies will investigate the utility of synthetic Pparγ agonists during UTO.

**Funding:** NIDDK Support

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**FR-PO637**

**Selected Renal Cells Exhibit Renal Tubule Formation Associated with Transforming Growth Factor B2 Expression**

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**Background:** TGFB2 mediates interactions between the ureteric bud and the metanephric mesenchyme resulting in renal tubule formation. Selected renal cells (SRCs) express ureteric bud markers RET and FGf8, and cap mesenchyme markers, LHX1, OSR1 and SIX2, their administration is therapeutic in models of chronic kidney disease. We tested the hypothesis that SRCs express tgfb2 and assemble into renal tubules.

**Methods:** Human SRCs (sourced from NDRI kidneys) were submitted to miRNASeq and mRNASeq, differentially expressed nodes identified and seeded into miRNet for interactome visualization. SRCs were submitted to scRNAseq to map gene expression. SRCs were placed in culture, and secreted TGFB2 measured using ELISA, and evidence of renal tubule formation confirmed by antibody staining for epithelial markers GGT1 and SLC12A1.

**Results:** Compared to the source biopsy hsam-ir1-145-5p (logFC=–6.9) and hsa-miR-199a-5p (logFC=–5.7) were downregulated in SRCs (p=0.01). Gene ontology revealed that these miRNAs regulate expression of tgfb2 together with renal epithelial markers (A). SRCs overexpressed tgfb2 (logFC=2.5, p<0.001). scRNA-seq confirmed tgfb2 expression (B) and SRC secreted TGFB2 exhibited 12-fold increase vs. control; p=0.01. Gene ontology revealed that tgfb2 forms an interactome with ret, fgf8, lhx1, osr1 and stc2, ureteric bud and cap mesenchyme markers expressed by SRCs (C). Placed in culture, SRCs assembled into GGT1+ and SLC12A1+ positive renal tubules (D).

**Conclusions:** These data suggest that therapeutic activity of SRCs may be mediated in part via formation of renal tubules and maintenance of electrolyte balance, fluid homeostasis, reabsorption of essential nutrients, urine concentration and Cystatin C clearance.

**Funding:** Commercial Support - ProKidney

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**FR-PO638**

**Notch Signaling Regulates Renal Urothelium Differentiation**

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**Background:** Children with congenital urinary tract obstruction (UTO) face limited treatment options and experience high rates of ESKD. The renal urothelium undergoes a protective adaptation during UTO by forming differentiated Uropak (Upk) cells. However, little is known about signaling pathways that govern Upk expression and urothelial differentiation within the kidney. The Notch signaling pathway regulates bladder urothelial differentiation and single cell RNAseq data suggest a role in renal urothelium development. The objective of this study was to test the hypothesis that Notch signaling regulates Upk expression and urothelial differentiation in the kidney.

**Methods:** We generated Hsa-miR-145-5p and Hsa-miR-199a-5p knockdown (Dicer<±>) mice and Hsa-miR-199a-5p control (Dicer<±>), to conditionally disrupt Notch signaling. We collected kidneys and bladders from Dicer<±> mice and Dicer<±> controls and controls at embryonic, neonatal, juvenile, and adult time points. We confirmed tissue-specific depletion of RBPF and Notch abrogation using immunofluorescent analysis (IF) and RNAseq, respectively. We used IF to evaluate markers of urothelial differentiation.

**Results:** IF: A confirmed efficient RBPF depletion in renal urothelium and collecting ducts, but not bladder urothelium at all time points in RBPF<±>±> mice. RNAseq confirmed that Notch targets, Hes1 and Hes6, were significantly decreased in RBPF<±>±> renal urothelium compared to controls. IF-A showed that RBPF<±>±> kidneys had significant decreases in Upk at each stage. Pparγ - a transcription factor that regulates Upk expression - and its targets were also significantly decreased in RBPF<±>±> kidneys compared to controls.

**Conclusions:** We have demonstrated that Notch signaling is key to the formation and maintenance of Upk cells in the renal urothelium. Our data also suggest that Pparγ signaling in the renal urothelium may be regulated by Notch. Future studies will investigate whether the Notch signaling directly regulates Upk expression or whether Upk expression is regulated by a Notch-dependent Pparγ signaling axis.

**Funding:** NIDDK Support

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**FR-PO639**

**Dotl/H3K79 Pathway Mediates Defective Ureteric Bud (UB) Branching Leading to Renal Hypoplasia (RHD) in Prorenin Receptor (PRR) RPRUB--/ Mice**

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**Background:** Dot1 is histone methyltransferase specific for Histone 3 lysine 79 (H3K79) that is important for differentiation of collecting duct (CD) cells. Targeted deletion of the Dot1 in the CD principal cells (PCs) in mice represses the acquisition of PCs phenotype resulting in polycystia (Yu, JASN, 2013). We tested the hypothesis that RHD and polycystia observed in mice that lack the PRR in the UB lineage (PRR<±>±>–) (Song, PLOS ONE, 2013) is due to reduced Dot1/H3 dimethyl K79 (H3K27Me2) expression.

**Methods:** Mutant [Het/Het<±>±>±>(PRR<±>±>–)], n=3 and control (PRR<±>±>±>, n=3) mice were studied on embryonic (E) day 13.5. Dot1 mRNA and protein expression in the kidney was studied by real-time qRT-PCR and immunohistochemistry, respectively. H3K27Me2 protein expression was determined by immunohistochemistry and Western blot analysis. The intensity of H3K27Me2 and Dot1 immunoreactivity, normalized for surface area of the kidney section, was examined by Slidebook 4.1 software.

**Results:** Kidney section surface area was smaller in the mutant compared to control mice (220600±20120 vs.33800±72170 pixels, p<0.05). Dot1 mRNA levels were decreased in mutant compared to control mice (0.8±0.06 vs. 1.0±0.01, p<0.01). Dot1 and H3K27Me2 immunostaining was reduced in the mutant vs. control kidneys (Dot1: 0.6±0.03 vs. 1.0±0.01, p<0.05; H3M27K9: 0.6±0.04 vs. 1.1±0.01, p<0.05). Western blot analysis revealed decreased H3K27Me2 protein levels in mutant compared to control kidneys (1.0±0.06 vs. 1.5±0.02, p<0.05).

**Conclusions:** We conclude that reduced H3K27Me2 methylation by Dot1 in the UB of PRR<±>±>– mice contributes, in part, to RHD and polycystia observed in these mice.

**Funding:** NIDDK Support

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**FR-PO640**

**Roles of microRNA in Development and Maintenance of Urothelium**

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**Background:** MicroRNA (miRNA) serve essential roles in epithelial cell development, maintenance, and response to injury by modulating mRNA and protein expression, but their function in urothelium remains largely unexplored. To address this knowledge gap, we engineered mice with urothelium-specific constitutive and inducible inactivation of Dicer, an exonuclease required for miRNA biogenesis.

**Methods:** We generated renal Dicer conditional knockout mice by crossing Dicer<±>±> and Upk2Cre or Upk2CreERT, animals. A tdTomato (tdT) fluorescent protein was expressed in a Cre/LoxP dependent manner from the Rosa26 locus to identify cells in which Dicer inactivation had occurred. Urothelial lineage markers were evaluated by immunofluorescence microscopy, Western blotting and QRT-PCR.

**Results:** Bladders from control animals displayed the expected urothelial morphology with sequential layers of Ker5+ basal (B) cells, Upk+ intermediate (I) cells, and Upk+; Fabp4<±> superficial (S) cells. In contrast, bladders from 3-week-old mice with biallelic inactivation of Dicer exhibited rounded S cells appearance with patchy/discontinuous Fabp4 expression and frequent exfoliation into the bladder lumen. This was increasingly evident at 6 and 9 weeks of life and associated with expansion of Ker5+ progenitor cell population in the B and I cell layers. Conditional inactivation of Dicer in the urothelium of 3-week-old mice recapitulated the phenotype of S cell loss and expansion of the remaining urothelial cell layers.

**Conclusions:** Dicer is dispensable for urothelial formation but serves an essential role toward its structural integrity. Ongoing efforts will identify the specific microRNAs responsible for S cell maintenance.

**Funding:** NIDDK Support
FR-PO641
Defining the Expression and Functions of SLPI, an Antibacterial Peptide Produced by Kidney Intercalated Cells
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Background: Mounting evidence suggests intercalated cells (IC) in the kidney collecting duct have antibacterial defenses that prevent pyelonephritis. In part, ICs prevent uropathogenic E. coli (UPEC) infections by expressing antimicrobial peptides and secreting them into the urine. The goal of this project is to define the expression, regulation, and antibacterial capacity of secretory leukocyte protease inhibitor (SLPI), a peptide that prevents infections in other organ systems by killing Gram-positive and negative bacteria. SLPI expression in the kidney has not been tested and its antibacterial activity against UPEC is unclear.

Methods: To evaluate SLPI expression, human kidney samples were obtained from people with and without a history of pyelonephritis. Mouse kidney samples were collected before and after mice were transurethrally infected with UPEC. ICs were enriched from mouse kidneys using FACS, cultured to confluency, and challenged with UPEC. SLPI expression was defined using qRT-PCR and Western blot. To test if SLPI is transcriptionally regulated, chromatin immunoprecipitation was performed. The antibacterial activity of SLPI was defined by performing UPEC bactericidal assays.

Results: qRT-PCR and Western blot identify SLPI expression in human and mouse kidneys and show SLPI expression increases with pyelonephritis. Within ICs, SLpi transcript expression increases 1.7-fold following UPEC infection. With UPEC infection, we observed increased NF-κB binding to the SLPI promoter. Reconstituent human and mouse SLPI exhibit dose-dependent killing of UPEC, including multi-drug resistant UPEC. Urothelial STAT3 overexpression directly impacts its viability in infected renal urothelium. With STAT3C urothelium showing persistent activation at 7 dpi. TUNEL staining pathway can alter susceptibility to chronic UTI.

Conclusions: These findings are the first to demonstrate that SLPI is expressed in human and mouse kidneys and ICs. Its expression is augmented during pyelonephritis, perhaps via NF-κB activation. They also show that SLPI has antibacterial activity against UPEC and multi-drug resistant UPEC. Future studies are needed to assess the utility of SLPI as a pyelonephritis biomarker and define its IC antimicrobial activity in model systems.

Funding: NIDDK Support

FR-PO642
Stat3-Driven Urothelial Programming Prevents Urinary Tract Infection (UTI) Chronicity
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Background: Uropathogenic E. coli (UPEC) can evade host immunity resulting in urinary tract infection (UTI) chronicity. We have previously demonstrated that STAT3 limits chronic UTI at 7 days. STAT3 controls several cellular processes by regulating gene transcription. Persistent activation of STAT3 has been shown to be oncogenic however not much is known about its impact in UTI. We hypothesize that constitutive STAT3 activation has direct effects on urothelial integrity and epithelial immunity.

Methods: 6-8 weeks old female FVB/N wild type controls (WT) and constitutively active Stat3 (Stat3c) mice underwent experimental UPEC UTI. Serial bladder tissue and urine were collected up to 7 days post infection (dpi). Cytosins were performed on urine. Immunohistochemical staining was performed on bladders for Keratin 5, pStat3, Ly6G, and Iba-1. TUNEL staining was also performed. A Quagen RT2 profiler PCR microarray for the IL/6-STAT3 signaling pathway was also performed on bladders. Results were evaluated by Mann-Whitney U test with p <0.05 being significant.

Results: Stat3c and WT urothelium demonstrated induction of pStat3 after infection, with Stat3c urothelium showing persistent activation at 7 dpi. TUNEL staining demonstrated more severe cellular apoptosis in the WT compared to Stat3c bladders at 24hpi and 7dpi, with cellular shedding on WT cytosins at corresponding time points. There was an earlier infiltration of neutrophils in the urothelium of WT mice with a later infiltration of macrophages in Stat3c mice. RT2 profile PCR arrays showed altered expression of genes involved in cell cycle regulation, immune cell recruitment, cytokine expression at 24hpi and 7dpi.

Conclusions: Urothelial STAT3 overexpression directly impacts its viability in response to UTI and the recruited inflammatory milieu. Manipulation of this signaling pathway can alter susceptibility to chronic UTI.

Funding: NIDDK Support

FR-PO643
The Renal Urothelium Serves Essential Roles in Host Defense and Pathogenesis of Pyelonephritis
Birong Li, Rishi H. Patel, Hanna H. Cortado, Sudipti Gupta, Christina B. Ching, Juan de Dios Ruiz-Rosado, Xin Wang, Ashley R. Jackson, Brian Becknell. Kidney and Urinary Tract Center. Abigail Wexner Research Institute at Nationwide Children’s Hospital, Columbus, OH.

Background: Uropathogenic Escherichia coli (UPEC) causes over 90% of acute pyelonephritis cases in humans. The urothelial lining of the pelvicalyceal system serves a proposed gatekeeper role in limiting renal parenchymal invasion by UPEC, but the exact mechanisms that account for this function are unclear. In this study we utilized spatial transcriptomics to map host-pathogen interactions within renal urothelium during pyelonephritis.

Methods: We established acute pyelonephritis in female C3H/HeOuJ mice by transurethral inoculation of UPEC strain CFT073. We profiled transcriptional changes in renal pelvic urothelium through spatial transcriptomics at baseline and 7 days post infection (dpi). We validated these changes by qRT-PCR and immunofluorescence microscopy. Upklb deletion mice were used to investigate the role of the urothelial plaque in the initiation of pyelonephritis.

Results: Spatial transcriptomics identified induction of transcripts with roles in barrier function, leukocyte recruitment, and bactericidal activity in infected renal urothelium. Conversely, transcripts encoding Uroplakin subunits that comprise the urothelial plaque were decreased following infection. Upklb deletion results in absent urothelial plaque formation. Following transurethral UPEC inoculation, Upklb+/− mice exhibited reduced renal bacterial burden and decreased neutrophil infiltration, when compared to Upklb+/+ mice.

Conclusions: The renal pelvis engages multiple antimicrobial mechanisms in response to E. coli pyelonephritis – including the downregulation of urothelial plaque formation, which serves to limit parenchymal invasion by UPEC. This study identifies a foundational role for the urothelial plaque in Gram-negative pyelonephritis and further strengthens the rationale for the development of antimicrobial agents that disrupt UPEC-plaque interactions in preventing pyelonephritis.

Funding: NIDDK Support

FR-PO644
Gain- and Loss-of-Function Approaches Substantiate Roles for Ribonuclease 6 in Pyelonephritis
Hanna H. Cortado, Macie M. Kercsmar, Birong Li, Ashley R. Jackson, Xin Wang, John D. Spencer, Juan de Dios Ruiz-Rosado, Brian Becknell. Kidney and Urinary Tract Center. Abigail Wexner Research Institute at Nationwide Children’s Hospital, Columbus, OH.

Background: Acute pyelonephritis (APN) episodes can result in urosepsis, acute kidney injury, and renal scarring. Identifying mechanisms of host defense against APN is a priority to mitigate these sequelae, particularly in an era of mounting antibiotic resistance. Ribonuclease 6 (RNase 6) is a cationic protein with potent bactericidal activity toward uropathogenic Escherichia coli (UPEC). We took complementary approaches to examine roles for RNase 6 in experimental APN.

Methods: We utilized a novel Rnase6+/− knockin allele to identify the cellular sources of RNase 6 and the impact of its deficiency on APN susceptibility in mice. As a complementary approach we generated human RNASE6 transgenic mice. Flow cytometry, immunofluorescence microscopy, and scRNAseq identified cellular sources of RNase6 within the kidney. The role of RNase 6 in intracellular UPEC killing was identified in a gentamicin protection assay using bone marrow derived macrophages (BMDM).

Results: Mouse and human RNase 6 are expressed by resident mononuclear phagocytes and circulating monocytes that are recruited to the infected kidney during APN. Rnase6 deficient mice are more susceptible to APN, whereas RNASE6 transgenic mice exhibit reduced renal UPEC burden. Rnase6 deficiency is associated with increased intramacrophage UPEC survival, while human RNASE6 transgenic macrophages are more adept at killing phagocytosed UPEC.

Conclusions: RNase 6 is an essential antimicrobial protein within the renal mononuclear phagocyte system that promotes UPEC clearance during APN.

Funding: NIDDK Support
Table 3 Renal and functional outcomes after augmentation cystoplasty in children with neurogenic bladder.

<table>
<thead>
<tr>
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<th>Patients</th>
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Table 3 Renal and functional outcomes after augmentation cystoplasty
FR-PO648

Incidence and Risk Factors for Obesity and Short Stature in Childhood Nephrolithiasis: A Prospective Cohort Study

Cal Robinson,1 Nowrin F. Aman,1 Rahul Chanchlani,2 Vaneet Dhillon,1 Christoph Licht,1 Damien G. Noone,1 Rachel J. Pearl,1 Seetha Radhakrishnan,1 Chia Wei Teoh,1 Rulan S. Parekh,1,2,3 The Hospital for Sick Children, Toronto, ON, Canada; 4McMaster Children’s Hospital, Hamilton, ON, Canada; 5Women’s College Hospital, Toronto, ON, Canada.

Background: Children with nephrolithiasis are at risk of obesity and short stature from repeated steroid treatment. The incidence, timing, and risk factors for these outcomes remain uncertain.

Methods: We evaluated longitudinal growth and obesity in children (1-18yr) enrolled in Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics (INSIGHT). We included nephrotic syndrome cases diagnosed from 1996-2019 in Greater Toronto. Growth parameters were measured at annual clinic visits. Primary outcomes were de novo obesity (body mass index (BMI) Z-score ≥2) and short stature (height Z-score ≤-2). We calculated hazard ratios (HR) using Cox proportional hazards models.

Results: We included 531 children with nephrotic syndrome (24% frequently relapsing (FRNS) by 1-yr). At their initial clinic visit (within 1-yr of diagnosis), 23.5% of cases were obese, 51.8% were overweight (BMI Z-score >0 ≤+1), and 4.9% had short stature. At the last clinic visit, the prevalence of obesity had decreased (17.3%) and short stature was unchanged (3.8%). During median 4.2-yr follow-up, 69 (17.7%) children developed obesity and 16 (3.3%) developed short stature, among those without obesity or short stature initially. Total relapse count was a significant predictor for de novo obesity (adjusted HR 1.03, 95%CI 1.01-1.06, p=0.01) and short stature (unadjusted HR 1.06, 95%CI 1.02-1.10, p=0.01). Children with ≥6 and >12 total relapses were more likely to develop obesity and short stature, respectively.

Conclusions: Obesity is common among children with nephrotic syndrome early after diagnosis, but prevalence decreases over time. Effective relapse prevention may reduce steroid exposure and the risks of de novo obesity or short stature.

FR-PO650

Clinical and Metabolic Findings in Children with Nephrolithiasis: A Single-Center Experience

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Background: Prevalence of nephrolithiasis in children has increased in recent decades and is associated with high risk of recurrence. Over 50% of children with nephrolithiasis may have a metabolic, genetic, or anatomic cause, making the epidemiology of the disease notable. The epidemiology of stones, including etiology, may better inform future treatment and prevention in at-risk populations. This study aims to describe clinical and metabolic findings in children with nephrolithiasis followed in a multidisciplinary stone clinic within a tertiary children’s hospital.

Methods: This is a retrospective study that included all children (n=330) with nephrolithiasis followed in the stone clinic from 5/2013-5/2023. Demographic, clinical, and metabolic variables were recorded from the patient’s first encounter in the clinic.

Results: A total of 82 patients were reviewed at the time of reporting. Majority of patients were male (59%, n=48). Roughly 37% (n=30) of patients were Hispanic and 48% (n=39) were non-Hispanic White. The median age of presentation with first kidney stone was 11 years (range: 6 months–18 years). Almost half of patients had a family history of stone disease (48%, n=39), with the most common relative being the patient’s mother (33%, n=13). For patients who underwent a 24-hour urine collection (73%, n=60), 78% had metabolic abnormalities (n=47). The most common metabolic abnormalities were hypocitraturia (77%, n=36) and hypercalcuria (40%, n=19). A fifth of patients with hypocitraturia (22%, n=8) had bilateral nephrolithiasis. Almost a third of patients had hypertension (30%, n=25) and required surgical stone removal (36%, n=9). Majority of patients had spontaneous passage of a stone (56%, n=46). For patients that completed stone analysis (38%, n=31), 71% (n=22) contained calcium, with the most common composition being calcium phosphate (73%, n=16). Being wheelchair bound (15%, n=12), having cerebral palsy (1%, n=1), or taking Zonisamide (10%, n=8) were frequent risk factors for stone formation.

Conclusions: Almost half of patients had a family history of stone disease, suggesting a genetic aspect to nephrolithiasis and importance of genetic testing in this subset of patients. Metabolic abnormalities are frequent among children with stone disease, with hypocitraturia being the most common.

FR-PO651

Nephritic Factor-Like Autoantibodies Are Present in Unaffected Children

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Background: We previously reported that C3-convertase targeted autoantibodies (nephritic factor-like antibodies) were highly prevalent in normal young adults (publication pending). In this study, we explore the prevalence of these convertase-directed antibodies in the pediatric population.

Methods: We measured the binding and stabilization of the C3-convertase and its proenzyme by normal human IgG purified from plasma samples. We selected samples for three age cohorts: one, five, and ten-year-olds. Binding was determined using surface polarization resonance with 30b was immobilized as the surface ligand. Each purified antibody was tested in four analyte conditions: IgG alone, IgG with FB (proconvertase), IgG with FD, and IgG with FB and FD (convertase). These conditions were compared to four control conditions: buffer alone, FB alone, FD alone, and FB with FD. Response (in relative units) was recorded at 20 seconds post-injection to measure binding and at 200 seconds post-injection to evaluate stabilization.

Results: Binding and stabilization results were mixed. All three age cohorts (1, 5, 10 years) show a statistically significant increase in binding for IgG+FB (proconvertase) vs FB.
alone at 20 seconds post-injection (two-tailed students t-tests values of 0.002, 0.004, and 0.002 at 200). However, none of the cohorts show statistical significance at 200 seconds (t-tests results of 0.49, 0.13, and 0.41). Significant binding was observed in the IgG+FB+FD samples compared to FB+FD at both 20- and 200-seconds post-injection for all age groups. Review of the data shows strong positive results (increasing reagent response by >20%) in 16 individuals for the convertase and 20 individuals for the proconvertase.

Conclusions: Our data suggests that convertase- and proconvertase-directed antibodies exist in pediatric cohorts. The prevalence is less than what we previously reported in adults (29/30 individuals were positive for both antigens). Whether this indicates the de novo emergence of these antibodies over time or class switching of an IgM to an IgG over time is currently under investigation. Determining an origin for nephritic factors is an important research goal in complement-mediated kidney disease. Identifying non-pathogenic antibodies that share the convertase antigen may provide an origin for nephritic factors.

Funding: NIDDK Support

FR-PO652
Identification of Patients with Potential Undiagnosed Atypical Hemolytic Uremic Syndrome (aHUS) in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry

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Background: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, and impaired kidney function. Diagnosis of aHUS is complicated by its similarity to other forms of thrombotic microangiopathy (TMA). The recognition of aHUS has become more commonplace in the last 10 years due to advancements in laboratory diagnostics and targeted complement inhibition. Although acute presentation with fulminant TMA are readily diagnosed, more indolent presentations may not be recognized as aHUS but may progress if untreated to end-stage kidney disease.

Methods: Potential participants were identified from the 3 NAPRTCS registry arms through a query of underlying diagnoses that could be associated with TMA or unknown etiology and transplant eligibility (defined as eGFR <30 ml/min/1.73m², history of maintenance dialysis or kidney transplant). Identified participants were eligible if they had evidence of TMA (thrombocytopenia, schistocytes, decreased hemoglobin levels, elevated lactate dehydrogenase, and/or decreased haptoglobin levels). Enrollees were evaluated for evidence of thrombocytopenia and severe anemia as a marker of microangiopathic hemolysis. Major organ symptoms and growth factors (height or weight z-score <-2.0), were also reviewed at the time of potential TMA.

Results: Ninety-five participants were identified in the query of diagnosis and transplant eligibility. Thirty-three (35%) participant records from 9 NAPRTCS centers were available for retrospective review and had at least one marker of potential TMA. The most common cause of TMA were AKI (27%), LUS (27%) and unknown (22%). They were 55% biological female and median age at enrollment was 15 years. Thrombocytopenia OR microangiopathic hemolysis were each suspected in 74% of participants, while 42% had evidence of both. Major organ involvement most frequently identified at time of suspected TMA episodes included cardiac (hypertension; 31%) and gastrointestinal (19%), while 44% of participants had evidence of growth failure or were underweight.

Conclusions: This analysis shows that there may be a higher prevalence of aHUS in the NAPRTCS registries than was previously thought.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

FR-PO653
Shiga Toxin-Producing Escherichia coli (STEC) Infection in a Pediatric Uremic Syndrome (aHUS) in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry

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Introduction: Shiga Toxin-Producing Escherichia coli (STEC) infection is a well-known cause of diarrhea and hemolytic uremic syndrome (HUS). STEC infection is characterized by the production of Shiga toxin by certain strains of Escherichia coli, which lead to vascular endothelial damage and subsequent clinical manifestations, including microangiopathic hemolysis, thrombocytopenia, and acute kidney injury (AKI). STEC infection is most common in children under the age of 5 and has been associated with severe outcomes, including acute kidney injury (AKI) and death.

Methods: A retrospective review of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) registry was conducted to identify cases of STEC infection in children with aHUS. The primary outcome of interest was the association between STEC infection and aHUS.

Results: A total of 95 participants were identified who met the inclusion criteria. Of these, 30 participants were diagnosed with STEC infection and 20 participants were diagnosed with aHUS. The prevalence of STEC infection in children with aHUS was 16.3%, which is significantly higher than the prevalence in the general pediatric population (p<0.05).

Conclusions: STEC infection is a significant risk factor for the development of aHUS. Early recognition and treatment of STEC infection may be crucial to prevent the progression to aHUS. Further research is needed to understand the mechanisms underlying this association and to develop effective prevention strategies.

Funding: NIDDK Support
Methods: From July 1976 to December 2018, among 560 children with biopsy-proven IgAN at Kagoshima University and Wakayama Medical University, 58 cases at onset were available in 555. We investigated clinical-pathological differences in 107 (19.3%) patients with eGFR<90 at onset and the other 448 patients.

Results: About 30% of eGFR<90 cases were detected as with gross hematuria. And there are more significant differences in the proportion of boys (69.2 vs. 51.8%, p=0.001), the onset age (9.6 vs. 11.0 years, p<0.001), the prevalence of nephrotic syndrome (10.3 vs. 4.9%, p=0.004), proteinuria (1.2 vs. 0.9 g/gCr, p=0.03), and renal biopsy before 1990 vs. after 1990 (73.8 vs. 33.7%, p=0.0001). There was no significant difference in pathological findings. The renal survival rate in the eGFR<90 group was significantly lower (77.9 vs. 93.3% at 15 years; 95%CI: 53.9-91.6 vs. 83.8-97.0%, p=0.006).

In patients with eGFR<90 at onset, when irreversible eGFR<60 state is defined as kidney failure, the patients who progressed to kidney failure showed lower eGFR at onset (64.7 vs. 78.2 ml/min/1.73m2, p=0.0001), higher proteinuria (2.6 vs. 1.0 g/gCr, p=0.008), and no remission of proteinuria after treatment (0.0 vs. 52.6%, p=0.001).

Conclusions: Cases with eGFR<90 at onset are clinically severe cases with various histopathological features, and some of them do not respond to treatment and have poor renal prognoses.

FR-PO656

DNASE1L3-Associated Nephropathy in Two Siblings Presenting CIC Nephropathy and Membranoproliferative Glomerulonephritis

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Introduction: Deoxyribonuclease is in charge of extracellular DNA degradation, limiting inflammatory response. Deoxyribonuclease 1 like 3 (DNASE1L3) of DNase I family is known to be essential for the prevention of autoimmune disorders by sustaining the immune system. DNASE1L3 of DNase I family has been known to be associated with autoimmune disorders such as chronic glomerulonephritis.

Case Description: An eight-year-old boy presented hematuria with proteinuria and diagnosed as CIC nephropathy after kidney biopsy. Past medical history and family history were unremarkable. Despite treatment with immunosuppressive agents including steroid and tacrolimus, his kidney function deteriorated and lost at his age of 12. After living-donor kidney transplantation (KT), his allograft function has been well maintained until the last follow-up after 2 years of KT without proteinuria or any extra-renal complications. His younger brother also presented hematuria and proteinuria at his age of 6 and was diagnosed with two different chronic glomerulonephritis.

Case: Despite treatment with immunosuppressive agents including steroid and tacrolimus, his kidney function deteriorated and lost at his age of 12. After living-donor kidney transplantation (KT), his allograft function has been well maintained until the last follow-up after 2 years of KT without proteinuria or any extra-renal complications.

Discussion: Interestingly, two siblings with same genetic predisposition showed different spectrum of diseases. In one of these cases, DNASE1L3- associated chronic glomerulonephritis was detected. It is suggested that dysfunction of deoxyribonucleases and predisposition to autoimmune disorders can be one of the pathogenic mechanisms of chronic glomerulonephritis. We propose that DNASE1L3- associated nephropathy should be included in the differential diagnosis of chronic glomerulonephritis.

FR-PO658

Anti-Nephrin Antibodies in Idiopathic Nephrotic Syndrome in Japanese Children

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Background: Many patients with childhood idiopathic nephrotic syndrome are steroid-sensitive, suggesting the involvement of the immune system in the pathogenesis. Several genome-wide association studies have suggested a polygenic contribution, particularly in the HLA DR/DQ region and a locus including NPHS1, but the etiology remains unclear. Anti-nephrin antibodies have recently been reported in both adults and children with biopsy proven minimal change disease (MCD), but the presence of anti-nephrin antibodies in Japanese childhood idiopathic nephrotic syndrome (INS) has not been investigated.

Methods: Anti-nephrin antibodies were measured by ELISA in paired plasma samples obtained from 14 Japanese pediatric patients with INS (male/female: 8/6), at initial disease onset (active disease) and following steroid monotherapy. Clinical characteristics were compared between the anti-nephrin antibodies positive and negative groups.

Results: The median age at the onset was 75.5 months (interquartile range (IQR): 45-113). Steroid sensitivity resulted in complete remission in 13 patients and almost complete remission in one patient after 4 weeks of glucocorticoid monotherapy. Circulating anti-nephrin antibodies were detected in seven of 14 patients during active disease. In all cases, anti-nephrin antibodies were significantly reduced following treatment concordant with clinical response. There were no differences between the positive and negative groups in terms of treatment parameters. Of the 13 patients who achieved complete remission, nine had at least one relapse during a median follow-up of 851 days (IQR: 808-973). There was also no significant difference in the relapse-free period after the onset between the two groups (P=0.658).

Conclusions: We have identified circulating anti-nephrin antibodies at initial presentation in half of Japanese pediatric INS, which is a higher proportion than previously reported for a North American cohort of adults and children with biopsy proven MCD. Further studies are needed to establish the prognostic implications of anti-nephrin antibodies in childhood INS and the relationship with the NPHS1 risk variants in this population.

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

Underline represents presenting author.
Metabolic Acidosis in Pediatric Participants with Glomerular Disease in the NEPTUNE and CureGN Cohorts
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Background: Metabolic acidosis (MA) has been associated with a more rapid decline of kidney function in cohorts of children with chronic kidney disease (CKD) and children with glomerular (vs. non-glomerular) CKD were more likely to have untreated acidosis. To date, no study has systematically examined MA in children with varying types of glomerular disease.

Methods: Children ages 1-17 y/o, enrolled in the NEPTUNE or CureGN studies with at least 1 serum bicarbonate and eGFR measurement were included. MA was defined as serum bicarbonate <22mEq/L whereas resolved acidosis was baseline acidosis that improved to ≥22 mEq/L, unresolved acidosis was acidosis at baseline that remained <22 mEq/L and eGFR measurement were included. MA was defined as serum bicarbonate <22 mEq/L. To date, no study has systematically examined MA in children with varying types of glomerular disease.

Results: In the 786 participants eligible for study inclusion, the mean baseline serum bicarbonate was 24.8±3.15 mEq/L. 12.2% (n=96) of the cohort were acidotic and only 1.4% (n=11) were receiving alkali therapy. In the adjusted longitudinal analysis, patients with unresolved MA had faster eGFR loss when compared to those with resolved acidosis (95%CI: -17.5, -7.4) (Table 2).

Conclusions: Unresolved MA is common in children with glomerular disease. Patients with unresolved MA had faster eGFR loss when compared to those with resolved acidosis from baseline. Future analyses will examine mechanistic pathways by which MA is proposed to contribute to disease progression through gene expression analysis.

Funding: NIDDK Support, Other NIH Support - New York Consortium for Interdisciplinary Training on Kidney, Urological and Hematological Research (NYC Train KU4R). TL1DK136048.

Mitochondrial DNA in Urinary Large Extracellular Vesicles as a Marker of Relapse in Children with Nephrotic Syndrome
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Background: Nephrotic Syndrome (NS) is one of the most common causes of glomerulopathy in children. There has been an increased focus on reactive oxygen species (ROS) and mitochondrial injury in podocytes as drivers of proteinuric disease. We recently showed that podocyte-specific large extracellular vesicles (LEV; 0.1-1.0 um) are increased in the urine of children with NS. The aim of this study was to characterize LEV mitochondrial DNA (mtDNA) content from those same children. We investigated this relationship further using cultured podocytes exposed to toxins in vitro.

Methods: We analyzed urine samples from a prospective cohort enrolling children 1-18y with NS. Podocyte specific LEVs were quantified using flow cytometry and nanoparticle tracking (NTA). Urinary LEV mtDNA was assessed using qPCR. Human immortalized podocytes (hPoD) were used in cell culture experiments. Purmycin aminonucleoside (PAN; 25 ug/mL; 24 hours) and lipopolysaccharide (LPS; 25 ug/mL; 24 hours) were used as podocyte toxins.

Results: We analyzed 28 samples from 14 patients. Podocyte LEVs were significantly lower in remission vs. nephrosis (p<0.01). Urine protein to creatinine ratio correlated with elevated LEVs (p=0.0005). Patient urinary LEV mtDNA was higher in NS relapse compared to remission (p=0.04). In hPoD cells, PAN treatment resulted in a 2.5-fold increase in hPoD LEVs (p=0.03) while LPS caused a 3.5-fold increase (p=0.004). The decreased urine LEV production was abrogated by the antioxidant Mito-Tempol. Following treatment with PAN or LPS in vitro, we observed an ~25-fold increase in LEV mtDNA content (p=0.01).

Conclusions: In summary, LEVs may serve as a biomarker of podocyte injury in nephrotic syndrome in children and their mtDNA content can differentiate remission from relapse. hPoD show similar characteristics when treated with common podocyte toxins, and ongoing studies aim to characterize this further.

Multi-Omic Serum Profiling in Children and Young Adults Affected by Steroid-Dependent Nephrotic Syndrome
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Background: Idiopathic nephrotic syndrome (INS) is the most common cause of proteinuria in children and young adults. The majority of therapy is steroids and based on treatment response, patients can be classified as dependent or resistant. However, there is little ongoing studies aim to characterize this further.

FR-PO660

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Genotype-Phenotype Associations in Patients with Congenital and Infantile Nephrotic Syndrome

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Background: Congenital nephrotic syndrome (CNS) and infantile nephrotic syndrome (INS) are disorders of the slit diaphragm of podocytes in the glomerular basement membrane. CNS manifests during the first three months of life, and INS between 3-12 months. The clinical features of the diseases include nephrotic-range proteinuria, hypoalbuminemia, and edema. The most common causes of CNS and INS are mutations in the NPHS1 and NPHS2 genes encoding nephrin and podocin, respectively. This study aimed to establish specific genetic characteristics of CNS and INS and their clinical presentations in the North American population.

Methods: Nine Pediatric Nephrology Research Consortium (PNRRC) sites retrospectively reviewed charts of 36 patients born between 1998 and 2019 with CNS or INS and underwent genetic testing. ClinVar, SNP, and Human mutation database confirmed the mutation’s pathogenicity.

Results: NPHS1 mutations were more often seen in CNS patients (27/36; 75%), whereas the INS group had more frequent mutations of WT1 (3/11;27.3%) and NPHS2 (4/11;36.3%) genes. Among patients with NPHS1 mutations, the splice site had more mutations than the gene coding region, irrespective of the group. Among these mutations, IVS17-1 G>A splice mutation was found in 4 subjects that showed aggressive features of INS. Interestingly, the mutation’s pathogenicity was confirmed by ClinVar, SNP, and Human mutation database. In patients with CNS, the frequency (9/18,50%) of multiple mutations of the NPHS1 gene was higher than in the INS group (2/5,40%) and significantly associated with hyperproteinemia (p=0.021) and hypoalbuminemia (p=0.03). Albumin infusions were more effective in CNS patients with NPHS2/WT1 mutations than those with NPHS1 mutations. In INS patients with WT1 mutations, albumin infusions were less effective in supporting serum albumin levels.

Conclusions: Variations in splice sites, especially IVS17-1 G>A, and multiple mutations in the NPHS1 gene were associated with a more aggressive course of CNS in infants.

FR-PO665

Nephrotic Syndrome in a Child with R138Q NPHS2 Mutation

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Introduction: Steroid resistant nephrotic syndrome (SRNS) accounts for 30% of all cases of nephrotic syndrome (NS) in children and frequently leads to end stage kidney disease (ESKD). 30% of children with SRNS demonstrate identifiable causative mutations in podocyte-associated genes. Early identification of genetic forms of SRNS is critical to avoid potentially harmful immunosuppressive therapy.

Case Description: A 2-year-old male patient with NS (plasma creatinine of 0.7 mg/dL, serum albumin of 0.6 g/dL, urine protein/creatinine ratio of 18.0 mg/mg) and negative family history of renal disease did not respond to 4-week steroid treatment. Infectious and immune workup for secondary NS was negative. Kidney biopsy showed mesangial proliferative glomerulonephritis, focal membranoproliferative pattern, global glomerulosclerosis (3/50), mild interstitial fibrosis, foot process fusion and basement membrane dysmorphism. Tacrolimus and lisinopril were added to therapy pending results of genetic testing. Genetic panel showed NPHS2 c.413G>A (p.Arg138Gln) homozygous pathogenic variant. A diagnosis of autosomal-recessive form of nonsyndromic SRNS due to NPHS2 causative variant was made. Immunosuppressive therapy was stopped, and the child’s proteinuria decreased and weekly infusions of albumin/furosemide were initiated to manage edema.

Discussion: A diagnosis of SRNS due to NPHS2 causative variant was made. Immunosuppressive therapy was stopped, and lisnoprill dose was increased. Weekly infusions of albumin/furosemide were initiated to manage edema.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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FR-PO666
Improving PPSV23 Vaccination Rates in Children with Nephrotic Syndrome
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Background: Children with nephrotic syndrome (NS) are at high risk for pneumococcal infections and the PPSV23 vaccine is recommended as part of the pneumococcal vaccine series. Barriers such as lack of availability in pediatrician clinics, inability to verify primary series status, and not addressing vaccinations has led to an inadequate rate of PPSV23 vaccination.

Methods: This is a quality improvement (QI) study that aims to increase PPSV23 vaccination rate among eligible NS patients admitted to the renal service to 75% by September 2023. An H&P template was created that includes a smart phrase prompting residents to review eligibility criteria for PPSV23 vaccination and vaccinate if appropriate. Patients older than 2 years of age that have completed primary pneumococcal vaccine series, and had not received Rituximab in the last 6 months were included. Pediatric residents were educated on QI study at the beginning of their renal rotation by fellows and sign placed in workroom to serve as a reminder. Process metrics included resident use of H&P and percent of eligible patients that refused vaccinations.

Results: In 2-month period, 12 patients with NS were admitted to the renal service. 8 patients were up-to-date and 4 were eligible for PPSV23. Of eligible patients, 3 were identified, 2 received PPSV23 prior to discharge and 1 family declined. The H&P template was used for 7/12 (58%) of admissions and at hospital discharge 2/4 (50%) of eligible patients were up-to-date.

Conclusions: Increasing PPSV23 vaccination is important in decreasing serious pneumococcal infections. Our project showed in identifying eligible NS patients with the implementation of the new H&P template. The participation from pediatric residents underscores value of simple interventions woven into work flow and work space.

FR-PO667
Homeostatic Model Assessment (HOMA) in Pediatric Patients with Nephrotic Syndrome Receiving Tacrolimus
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Background: Children with nephrotic syndrome receive diabetogenic drugs like tacrolimus (TAC) and steroids. TAC is toxic to pancreatic β-cells and suppresses insulin production in a time and dose dependent manner. Post transplant diabetes mellitus due to TAC and or steroids is well documented in renal transplant patients. Although overt diabetes is rare in children receiving TAC with or without steroids for nephrotic syndrome (NS), the subclinical effect on β cell function has not been studied.

Methods: We prospectively followed children with NS who received TAC therapy at least for 1 year. We noted patient demographics, clinical and histologic pattern of NS, cumulative steroid dose (mg/kg/day) received 90 days prior and TAC C0 levels. Fasting insulin, blood sugar to calculate HOMA indices for IR (insulin resistance), HOMA % β for beta cell function, HOMA-IS (insulin sensitivity), C-peptide and HbA1C were done once at study inclusion and yearly intervals when required. Statistical analysis included Pearson’s correlation, paired t test and regression analysis.

Results: We performed HOMA indices in 37 patients between September 2021—February 2023. Six patients had 2 measurements during the study period. The mean TAC duration, TAC C0 level and cumulative steroid dose were 27 months (95% CI[22.32, 34.45] mg/ml (95% CI[4.124.97]) and 0.36 mg/kg/d (95% CI[0.28.044]) respectively. In Pearson’s correlation analysis we found positive correlation between TAC Co level, HOMA IR (r=0.4, P=0.008) and TAC Co, HOMA IS (r=0.4, P=0.003) and cumulative steroid dose, fasting blood glucose (r=0.3, P=0.46). There was negative correlation between TAC Co level, HOMA IS (r=-0.4, P=0.007). In regression analysis, only TAC Co level significantly influenced all HOMA indices including insulin resistance, insulin sensitivity and beta cell function. A HbA1C of > 5.7 (pre-diabetes range) was found in 32.4% (12/37) patients which warrants further monitoring. C-peptide levels were significantly higher after 12 months of TAC therapy in 6 patients who had two measurements (p=0.032).

Conclusions: Tacrolimus therapy for nephrotic syndrome in children can affect pancreatic beta cell function as assessed by HOMA indices.

FR-PO668
Using Degree of Foot Process Effacement to Predict Outcome in Paediatric Steroid-Resistant Nephrotic Syndrome: A Multi-Centre Analysis
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Background: Steroid resistant nephrotic syndrome (SRNS) is a common cause of paediatric end-stage renal failure requiring transplantation. Recurrence post-transplantation is high in those with no identified pathogenic variant, but those with pathogenic mutations rarely develop recurrence post-transplantation. Previous work suggests that degree of native renal biopsy podocyte foot process effacement (FPE) may distinguish genetic and non-genetic causes of SRNS, but the studies are limited by small samples and single-centre recruitment. This suggests that degree of native biopsy FPE may detect risk of post-transplant recurrence. We hypothesised that diffuse FPE is a marker of circulating factor disease and predicts post-transplant recurrence, while segmental FPE is a marker of non-recurrent disease.

Methods: We analysed a multi-centre nationwide cohort of paediatric SRNS patients (RADAR) to assess if FPE degree can predict disease recurrence. 138 paediatric Nephrotic Syndrome patients had transplantation between 2007-22. 28 with native biopsy electron microscopy (EM) reports available were included. We quantified FPE as diffuse or segmental from report language.

Results: 9/28 patients developed disease recurrence. 27 patients had genetic testing, of which 11 had a causative genetic mutation. No patients with pathogenic genetic variants developed recurrence (recurrence if pathogenic variant 0/11; recurrence if no pathogenic variant 9/17; p=0.0039). 9/11 patients with pathogenic variants show diffuse FPE on EM while 9/17 without identified genetic mutations show diffuse FPE (p=0.2264). All 7 patients with slit diaphragm protein pathogenic mutations had diffuse FPE. Patients with diffuse FPE (recurrence 4/18) trended towards lower recurrence rates than those with segmental FPE (recurrence 5/10, p=0.0296).

Conclusions: In this multi-centre cohort we show trends between genetic causes of SRNS and FPE, and the direction of the association contrasts with literature. We show that slit diaphragm protein mutations are associated with diffuse FPE. We show a non statistically significant trend towards diffuse FPE and lower recurrence post-transplant. This study is limited by small numbers and its retrospective nature, but the trends justify further investigation in larger groups of patients.

FR-PO669
A Pediatric Patient with Proteinuria and Hepatic Steatosis
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Introduction: Frasier syndrome is a rare but well described disorder arising from a donor splice site mutation in intron 9 of the WILM Tumor 1 (WT1) gene. It is associated with steroid resistant nephrotic syndrome and progression to ESRD. Patients with Frasier syndrome are characteristically phenotypic females with an XY genotype, streak ovaries and a risk for gonadalablastoma. Here we describe an XX pediatric patient with WT1 mutation characteristic of Frasier syndrome and an incidental finding of hepatic steatosis.

Case Description: A six year old obese female was referred to nephrology after two years of progressive isolated proteinuria; dipstick of 3+ and UPC of 2.5 mg/mg at time of referral. She had no overt edema. Her serum albumin and creatinine were normal at 4.0 g/dL and 0.7 mg/dL respectively. Ultrasound of abdomen showed a hyperechoic liver without evidence of a gall stone. Serology revealed cTnI of 0.09. Platelet count was 178,000. Lipid profile was normal. Her OAG was 6/15. Urine Examination revealed protein of 3+/500x, red blood cells 1-2/HPF, 10-15 WBC/HPF. Fetal type proteinuria made us think of Frasier syndrome.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
and 0.48 mg/dL, respectively, and labs were notable for transaminis with AST 56/ALAT 126. Unilateral nephromatous kidneys but incidentally an echogenic liver. On dissection, consistent with FSGS: 1/2 glomeruli had global sclerosis, EM had diffuse podocyte foot process effacement, and IF was unrevealing. Genetic panel testing was then completed and revealed a pathogenic mutation in WT1 (IVS9+4C>T) and a separate pathogenic mutation in HNF1A which portended risk to Monogenic Diabetes of the Young (MODY). In some cases hepatic steatosis. Normal uterine and ovaries as well as XX genotype were confirmed on this patient. She was initiated on ACEI therapy with no improvements in proteinuria over two years (recent UPC of 4.7 mg/mg), but renal function has remained stable. She is followed with regards to proteinuria and progression to ESRD, therapy is mainly limited in pediatrics to ACEI and ARB. In this patient with an HNF1A associated risk of metabolic syndrome, we consider the role of an SGLT-2 inhibitor for its nephroprotective and antiproteinuric effects.

Discussion: This case highlights the value of genetic testing in pediatric patients who present with isolated nephrotic range proteinuria without nephrotic syndrome, and whether rituximab biopsy can be avoided if genetic results are available. Our patient is unique in that she is an XX female with normal ovarian development thus we question the need for gonadal monitoring as the risk for gonadoblastoma is seen in those XY females with streak ovaries. With regards to proteinuria and progression to ESRD, therapy is mainly limited in pediatrics to ACEI and ARB. In this patient with an HNF1A associated risk of metabolic syndrome, we consider the role of an SGLT-2 inhibitor for its nephroprotective and antiproteinuric effects.

FR-PO670
Improving Polygenic Risk Scores for Steroid-Sensitive Nephrotic Syndrome by Integrating Relevant Traits
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Background: Polygenic risk scores (PRS) have been widely applied in research studies to identify associations of a person’s overall genetic profile with diseases/trait. We are in the early stages of developing PRS for steroid sensitive nephrotic syndrome (SSNS). PRSmix and PRSmix+ have been created to incorporate additional PRS for both the same disease and correlated traits to improve PRS prediction accuracy. Here, we tested the hypothesis that the prediction accuracy of an SSNS PRS would be increased using these strategies.

Methods: Using our previously created SSNS PRS (Barry et al., we applied PRSmix and PRSmix+ in a European SSNS cohort. Candidate PRSs were obtained from the Polygenic Score Catalog. Individuals in our European SSNS cohort were randomly assigned to a training/testing cohort. Three models were created to assess the additive benefit of combining multiple PRS and correlated traits: the “best PRS” model only includes our SSNS PRS as a predictor, the “PRSmix” model incorporates all SSNS PRS, and the “PRSmix+” model adds high-power PRS from correlated traits to the PRSmix model. The Likelihood-Ratio test (LRT) was used to compare the goodness of fit when adding a PRS to the model. The Matthews Correlation Coefficient (MCC) was used to evaluate binary classifications; it ranges from −1 to 1, with extreme values 1 reached in case of perfect classification. Comparative predictive accuracy in the testing dataset was assessed using a two-sample z test.

Results: In a 100-fold cross validation study, adding another SSNS PRS (PRSmix) always significantly improved model fit (LRT<0.05) compared to the best PRS. Furthermore, adding high-powered traits (PRSmix+) always significantly improved model fit (LRT<0.05) compared to the PRSmix. The average case prediction accuracy (as measured by MCC) was slightly improved for both the PRS mix (MCC=0.499) over bestPRS (MCC=0.477); p=0.38 and the PRSmix+ (MCC=0.502) over best PRSmix (p=0.01). The PRSmix+ model adds high-power PRS from correlated traits to the PRSmix model. The Likelihood-Ratio test (LRT) was used to compare the goodness of fit when adding a PRS to the model. The Matthews Correlation Coefficient (MCC) was used to evaluate binary classifications; it ranges from −1 to 1, with extreme values 1 reached in case of perfect classification. Comparative predictive accuracy in the testing dataset was assessed using a two-sample z test.

Conclusions: We improved the prediction capability of SSNS PRS using PRSmix and PRS mix+. PRS of other diseases/trait can increase the accuracy of predictive models, may ultimately improve clinical inference, and could provide a better understanding of SSNS disease etiology.

FR-PO671
Trends from 2010 to 2022 in the Utilization of Anti-CD20 Antibodies to Treat Childhood Nephrotic Syndrome
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Background: A growing body of evidence supports the efficacy of the type I anti-CD20 monoclonal antibody, rituximab, in the management of children with frequently relapsing or steroid dependent nephrotic syndrome (NS). We examined trends in the use of anti-CD20 antibodies in a multi-institutional population of children with NS.

Methods: Data came from PEDSnet, a clinical research network that aggregates electronic health record (EHR) data at several children’s healthcare organizations (database version 4.8). Patients were aged 2-21.99 years, had ≥2 outpatient visits in 1 year apart, and met our published EHR-based computable phenotype algorithm for nephrotic conditions between January 2010-November 2022. Children with systemic lupus erythematosus (SLE) or congenital or genetic nephrotic diagnoses were excluded. Treatments were measured from NS diagnosis to kidney transplant or most recent in-person encounter. We stratified the cohort by presence of native kidney biopsy.

Results: Among 6,880,824 patients across 6 centers, 3,021 met criteria for nephrotic conditions. At year 10, 32% (95% CI 30.9-33.3) had at least one kidney biopsy. Rituximab utilization increased over time, with a sustained increase since 2019 from 5.9% to 7.8%. Similar trends were observed for mycophenolate and tacrolimus. Concurrently, use of cyclosporine and cyclophosphamide decreased. Tacrolimus was most frequently used.

Conclusions: Use of rituximab to manage NS has steadily increased. PEDSnet provides the ability to collect real-world data and enhance our understanding of long-term efficacy and trends in steroid-sparing medication use for rare diseases such as NS.

Funding: NIDDK Support, Other U.S. Government Support

FR-PO672
Efficacy and Safety of Single-Dose Rituximab Biosimilar in the Initial Episode of Paediatric Steroid-Sensitive Nephrotic Syndrome
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Background: The 12-month relapse-free survival rate is less than 30% in steroid-sensitive nephrotic syndrome (SSNS) children after the standard corticosteroid therapy. Rituximab is effective in reducing the relapse in children with frequent relapse or steroid dependent NS. Accordingly, we hypothesize rituximab added to guideline-recommended corticosteroid therapy is effective for maintaining remission for the first year of onset.

Methods: An open-label, single-arm, multicentre trial was performed at eight centers in China with a 12-month follow-up (NCT04783675). The first episode of SSNS children treated with standard corticosteroids was eligible for inclusion. Eligible patients received a single dose of 375 mg/m² rituximab biosimilar within one week after achieving remission. The primary outcome was the 12-month relapse-free survival rate after rituximab was added to corticosteroid therapy, was compared with historical controls treated without rituximab on NCT03878914.

Results: Totally, 44 children were treated with rituximab and all but one patient completed one year of follow-up. Rituximab therapy was associated with a significantly higher 12-month relapse-free survival rate than the historical control [32.7% vs 10.30%] children; P <0.001; hazard ratio, 1.89; 95%CI, 1.15-3.11). The median time to first relapse was 123 days (95%CI, 73 to 201 days). The treatment was well tolerated. During infusion, three participants reported throat irritation. Besides two patients with a decreased neutrophil count, all other adverse events were resolved.

Conclusions: In children with the initial episode of SSNS, rituximab appears to be an effective and safe treatment for maintaining disease remission. It provides evidence for the initial treatment strategy of SSNS in children to prevent the recurrence.

Drug exposure trends in NS patients; counts <11 not shown
FR-PO673

The Genetic Background of Persistent Hypogammaglobulinemia After Rituximab Treatment in Refractory Nephrotic Syndrome

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Background: Rituximab (RTX) has been proven to be effective for refractory nephrotic syndrome(NS); however, persistent severe hypogammaglobulinemia (HGG) is occasionally observed and causes health problems in some patients. We suspected the coexistence of common variable immunodeficiency (CVID) in these patients, and we proved that they had either genetic mutations associated with CVID or FCGR3 F176V polymorphism, that is, a missense variant, c.526T>G (p.Phe176Val) in FCGR3A gene (NM_000569.8).

Methods: We performed whole genome sequence analysis on patients who developed persistent HGG (<400 mg/dL, more than two years) after the last RTX therapy.

Results: Five patients were recruited (table). All of them developed RNs and were treated with repeated RTX <18 years old. Their HGG was persistent for more than five years after the last RTX therapy. Among the five patients, three (No.1-3) showed severe (<200 mg/dL) HGG, pan hypogammaglobulinemia, and susceptibility to infection. The other two (No.4 and 5) showed relatively mild HGG, normal to high levels of other types of immunoglobulin, and no clinical symptoms. Genetic analysis revealed that No.1 had a novel heterozygous mutation in NFKB1, and No.3 had a heterozygous mutation in TNFSF12. Both genes were associated with CVID. FCGR3A F176V polymorphisms were found in No.2 and 3. Thus, patients who developed severe and symptomatic pan hypogammaglobulinemia had either a genetic mutation associated with CVID or FCGR3 F176V polymorphism.

Conclusions: Severe and symptomatic pan hypogammaglobulinemia after RTX treatment was accompanied by genetic alterations in CVID-associated genes or in FCGR3A genes. Advanced analysis of these genes before RTX administration could prevent, or at least delay, the development of symptomatic pan hypogammaglobulinemia.

FR-PO674

Genetic Insights into Pediatric Polycystic Kidney Disease

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Background: Pediatric polycystic kidney disease (PKD) exhibits genetic heterogeneity, including autosomal dominant and recessive PKD, as well as ciliopathies with syndromic involvement. Relying solely on gene-specific analyses may lead to missed diagnoses. Our objective was to summarize genetic findings in pediatric patients (pts) with bilateral kidney cysts seen at our clinic, emphasizing unique cases.

Methods: We reviewed resolved cases from Jan 2020 to Apr 2023 involving clinical or research genetic testing. Targeted next-generation sequencing, encompassing known and candidate PKD/ciliopathy genes, was performed at our research lab. Variants were assessed using disease-specific and population databases, along with in silico variant assessment tools. Categorization followed ACMG guidelines.

Results: Genetic screening identified pathogenic changes in 9 genes, accounting for 49 pts (45 families): 40 with monoallelic and 9 with biallelic variants. Monoallelic genes included PKD1 (n=18), HNF1B (n=9), PKD2 (n=5), PKHD1 (n=2), IFT20 (n=2), NEK8 (n=1), GANAB (n=1), TSC2 (n=1), and TSC2/PKD1 deletion. Biallelic variants were PKHD1 (n=6) and NPHP1 (n=1). Among PKD1 pts, 83% (15/18) had a positive family history, while 60% (3/5) of PKD2 pts did. Incident discovery or family screening diagnosed 67% (12/18) of PKD1 pts, 28% (5/18) had prenatal presentation, and one case involved an early onset intracranial aneurysm rupture. PKD2 pts were all clearly diagnosed. Children with monoallelic variants in IFT20, GANAB, or PKD1 exhibited mild PKD phenotypes and were incidentally diagnosed through abdominal imaging. The NEK8 variant pt presented with severe neonatal PKD and kidney failure requiring dialysis at 6 months old, representing a novel manifestation for this gene. Nearly all HNF1B variant/ deletion pts (8/9) presented in utero with kidney cysts and/or hyperchoeic kidneys.

Conclusions: Comprehensive analysis of clinical and research-related genetic screening reveals the complexity of monogenic causes of PKD. This study reports the first pathogenic variant in IFT20 found in pediatric pts, an additional case involving GANAB, and a new monoallelic NEK8 disorder. Genetic screening in pediatric PKD pts, irrespective of family history, offers a definitive diagnosis, informs prognosis and therapy discussions, and facilitates enrollment in clinical trials.

Funding: NIDDK Support

FR-PO675

Kidney Survival in Pediatric Patients with Pathogenic Hepatocyte Nuclear Factor 1β Variants

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Background: Hepatocyte nuclear factor 1β (HNF1B) gene variants represent the most common monogenic cause of developmental kidney disease. Identification of specific genotype-phenotype associations in HNF1B disease would inform genetic counselling. The objective of this study was to determine whether the HNF1B mutation type is associated with kidney survival.

Methods: This was a retrospective observational study involving 521 patients from 14 European countries using the European ERKNet-ERN network. Mean follow-up time was 7.7 years with 6.2 visits per patient. The primary end point was progression to chronic kidney disease (CKD) stage 3 (eGFR<60 mL/min/1.73m2). Secondary endpoints were the development of extra renal abnormalities including hypomagnesemia, hyperuricemia and hyperglycemia.

Results: Progression towards CKD-stage 3 was significantly delayed in patients with the 17q112 deletion compared to patients with other pathogenic HNF1B variants (HR 0.31 (95%CI: 0.20-0.47), p=0.001). Presence of only one functional kidney due to a contralateral multicystic dysplastic kidney or agenesis was associated with accelerated CKD progression (p=0.028). Interestingly, the 17q12 deletion conferred a significant better kidney function than the other HNF1B variants already in the neonatal period. Finally, the 17q12 deletion was associated with hypomagnesemia (HR 2.49, 95%CI:1.57-4.03, p=0.001), but not with hyperuricemia or hyperglycemia.

Conclusions: Pediatric patients with the 17q12 deletion and two functional kidneys displayed survival better than healthy children and than patients with other pathogenic HNF1B variants. We identified the first clinically relevant HNF1B genotype-phenotype correlation that informs genetic counselling of pediatric patients.

FR-PO676

Characteristics of Kidney Resident IgA Antibody-Secreting Cells in IgA Nephropathy

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Background: The trigger and sources of pathogenic IgA in IgAN are not established. Prevailing theories suggest that circulating polymeric nephritogenic IgA is produced by antibody secreting cells located within the mucosa-associated lymphoid tissue or the bone marrow. Our recent work demonstrated that in experimental IgAN mice (BAFF-Tg), mucosal pathobiont-directed IgA antibody secreting cells (APC) are identified within the kidney. In the current study we aimed to characterize kidney IgA APC in experimental IgAN Tg, mucosal pathobiont-directed IgA antibody secreting cells (APC) are identified within the kidney. Characteristic features of kidney resident IgA APC in IgA nephropathy.

Methods: We used intraperitoneal BAFF-Tg mice, an experimental model of IgAN, to generate IgA antibody secreting cells (APC) in the kidney.

Results: We found that the number of kidney resident IgA APC was significantly increased in BAFF-Tg mice compared to control mice. The proportion of IgA APC expressing the costimulatory molecules CD80 and CD86 was also increased in BAFF-Tg mice.

Conclusions: Our study provides new insights into the pathogenesis of IgA nephropathy by identifying kidney resident IgA APC as a potential target for therapeutic intervention.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Dihydroartemisinin Inhibits Mesangial Cell Proliferation in IgA Nephropathy by Regulating PGC1α-Mediated Glycolmetabolism

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Background: Mesangial cell proliferation is the basic pathological feature of IgA nephropathy (IgAN), but the mechanism of glucose metabolism in mesangial cell proliferation has not been studied. It has been reported that artemisinin analogs can effectively regulate cellular glycometabolic enzymes and improve autoimmune diseases, but their efficacy on IgAN remains unclear. The aim of this study was to clarify the changes of glucose metabolism in IgAN, and to explore the therapeutic effect of dihydroartemisinin (DHA) on IgAN.

Methods: The expression of glycometabolic enzymes, and the relationship between enzymes and clinicopathology in IgAN patients were analyzed using GEO datasets and renal biopsy specimens. The expression of glucometabolic enzymes, energy metabolic enzymes and clinicopathology in IgAN patients were analyzed using GEO datasets and renal biopsy specimens. The expression of glucometabolic enzymes, energy metabolic enzymes and clinicopathology in IgAN patients were analyzed using GEO datasets and renal biopsy specimens. The expression of glucometabolic enzymes, energy metabolic enzymes and clinicopathology in IgAN patients were analyzed using GEO datasets and renal biopsy specimens.

Results: The expression of glucometabolic enzymes were significantly correlated with renal clinical indicators. PGC1α was significantly correlated with differentially expressed glucometabolic enzymes, and its expression was lower in IgAN patients with heavy mesangial cell proliferation. DHA upregulated PGC1α expression, inhibited glycolysis and suppressed mesangial cell proliferation. In vivo, DHA reversed the expression of glucometabolic enzymes and alleviated kidney injury in IgAN mice.

Conclusions: This study demonstrated the alteration of glucose metabolism in glomeruli, and the therapeutic effects of DHA in regulation of PGC1α and glucose metabolism in IgAN. These results provide new strategies for renal protection, as well as theoretical basis and intervention targets for DHA therapy of IgAN.

Funding: Other NIH Support - This work was supported by the National Natural Science Foundation of China 82070737, 82270752.
Spatially Resolved Transcriptomic Profiling for Glomerular and Tubulointerstitial Gene Expression in C3 Glomerulonephritis

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**Background:** C3 glomerulonephritis (C3GN) is a rare but clinically significant primary glomerulopathy. However, little is known about its transcriptomic profile. We aimed to investigate the substructure-specific gene expression profile of C3GN using the recently introduced spatial transcriptomics technology.

**Methods:** We performed spatial transcriptomic profiling using GeoMex Digital Spatial Profiler with formalin-fixed paraffin-embedded kidney biopsy specimens of three C3GN cases and eight donor kidney controls. Profiles from other glomerular diseases, including focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease, were included as disease controls. Gene expression levels between C3GN and the controls were compared by DESeq2 method, and differentially expressed genes (DEGs) were identified with a false discovery rate threshold of 0.05. We performed gene ontology (GO) annotation by the TopGene Suite and mapped interaction networks among the DEGs using the STRING database.

**Results:** We identified 229 and 157 highly expressed DEGs in the glomeruli of C3GN compared to those of donor and disease controls, respectively, with consistently highest fold changes seen in POSTN, COL1A2, IFI44L, and TAGLN. Protease binding, structural molecule activity, and extracellular matrix constituent were the top enriched GO terms in the glomeruli of C3GNs, with consistent features seen in the network analysis. In contrast, no significant GO enrichment was found among the 353 and 347 lowly expressed DEGs in the glomeruli of C3GN compared to donor and disease controls. The tubular transcriptome profiles of C3GN were similar to those of the controls.

**Conclusions:** This is the first report of kidney substructure-specific transcriptomic profile of C3GN to date. Significant disease-specific transcriptomic alterations occur in the glomerulus of C3GN, providing potential insights into the pathophysiology.

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

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Single-Cell Spatial Profiling of Glomerular Structures in Alport Syndrome

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**Background:** Many transcriptomics studies have described the molecular mechanisms underlying the progression of glomerular diseases, but very little is known about the gene spatial map of the different cell types, the heterogeneous tissue niche composition, and how each glomerulus is affected during progressive CKD. Here we report the spatial characterization of gene expression at the single-cell level in renal biopsies of Alport Syndrome (AS) patients and from healthy subjects.

**Methods:** Using the Nanostring CosMX Spatial Molecular Imager (SMI) platform, and the human 1000-plex RNA panel we generated spatial maps of gene expression of kidney biopsies from AS patients (n=3) vs healthy subjects. Using H&E images we selected 29 fields of view (FOV) with dimensions of 0.9mm x 0.7mm for analysis. After data QC and normalization steps, we supervised cell typing. Spatial data analysis was achieved using different software and integrated with histopathology.

**Results:** We identified 36 clusters corresponding to different renal cells including glomerular, tubular, interstitial, and immune cell types. A spatial map of cell types in each FOV was reconstructed. Localization of podocytes, glomerular endothelial cells, and mesangial cells could be visualized. Color-coded gene expression maps of each cell type could be visualized at a single-cell resolution. Our analysis indicated the cellular composition varied between the different AS biopsies, revealing the presence of different cell types in the AS glomerulus not previously described including 3 different types of fibroblasts. We could also identify specific “glomerular immune niches.”

**Conclusions:** CosMx SMI analysis revealed significant differences in gene expression between AS and healthy biopsies at a single-cell level. These preliminary data using this technology may allow the discovery of potential new therapeutic targets for patients with AS, and other CKDs.
syngeneic MPO-ANCA B cells. This model could be used to identify specific stem cells for targeted therapy of autoimmune disease.

Methods: As previously described (Xiao H, et al. J Clin Invest 2002; 110:955-963), B6 Mpo knockout (KO) mice were immunized with mouse MPO and used as donors of splenocytes (SC) containing B-cells producing pathogenic MPO-ANCA. All B6 WT or B6 Rag2 KO mice received anti-MPO SC on day 0 (Table G1-G9). G3, 7 and 8 Rag2 KO mice also received normal WT B6 BM or SC Tx on day 0 (G6) or 2-6 weeks before anti-MPO SC Tx. Serum MPO-ANCA was measured on days 0, 4, 7, 11 and 14; and mice were euthanized on day 14 for pathology evaluation.

Results: No male (G1) or female (G2) Rag2 KO mice developed MPO-ANCA or GN 14 d after injection of MPO-ANCA SC. All male (G2) and female (G5) Rag2 KO mice developed MPO-ANCA and GN by day 14. WT BM Tx into Rag2 KO mice 6 wks prior to anti-MPO SC (G3) prevented MPO-ANCA and GN. Similarly, Tx of WT SC 2 or 4 wks prior to anti-MPO SC (G4, G5) prevented MPO-ANCA and GN. However, Tx of WT SC on 0d (G6) did not prevent MPO-ANCA and GN.

Conclusions: Transplanted immune-competent stem cells from B6 WT BM or spleen prevent MPO-ANCA GN in Rag2 KO B6 syngeneic mice. Delay in developing autimmune defense indicates that Tx stem cells require time to proliferate and differentiate to establish autoimmune defense (G6 vs G7 & G8). This model system will be used to identify specific stem cells that are effective in suppressing autoimmunity and effective for targeted immunotherapy.

Funding: NIDDK Support

FR-PO684

Regulatory Function of FcγRIIB Involving the NLRP3 Inflammasome in a Mouse Model of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis and represents a leading cause of end-stage renal disease. Ample evidence confirms the deposition of IgA and IgG and filtration of mononuclear leukocytes in IgAN patients. Previously, we established an experimental IgAN model in B cell-deficient mice, which implicated interactions between Fce receptors (FceRs) in the pathogenesis of IgAN. Although it is generally accepted that FcγRIIB plays a regulatory role in humoral responses, it remains unknown whether this function and the cell type-specificity of FcγRIIB are reno-protective in IgAN.

Methods: We observed a dramatic increase in albuminuria, renal function impairment, and renal injury in FcγRIIB knockout mice with induced IgAN. Utilizing a mouse model of IgAN and three different types of FcγRIIB-deficient mice, including CEBPα+Cre (myeloid cells), CD11c+Cre (dendritic cells) and CD19 Cre (B cells) in flox and WT mice, as well as several specific cell markers.

Results: We demonstrated that macrophage- and dendritic cell-specific FcγRIIB deficiency blunted the activation of the NLRP3 inflammasome and inhibited the development of IgAN. Moreover, activation of the inflammasome was induced by IgA immune complexes dependent on TLR4/MyD88 signaling, associated with crosstalk between TLR4 and Dectin-2.

Conclusions: These results suggest that activation of FcγRIIB and its downstream signaling pathways could moderate progression of IgAN involving the suppression of the NLRP3 inflammasome. A cell type-specific targeting of FcγRIIB may help the establishment of therapeutic strategy for the renal disease.

Funding: NIDDK Support, Other NIH Support - NCATS, Commercial Support - Eli Lilly, Private Foundation Support

FR-PO685

Group 3 Innate Lymphoid Cells (ILC3s) Accelerate Lupus Nephritis Development by Promoting B Cell Activation in Kidney Ectopic Lymphoid Structures

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Background: Group 3 innate lymphoid cells (ILC3s), a novel subset of immune cells with the features of both innate and adaptive immunity, have emerged as important players in many autoimmune diseases. However, whether they participate in lupus nephritis (LN) remains elusive. Here, we investigated the role of ILC3s in the pathogenesis of LN.

Methods: Systemic and renal ILC3s were detected by flow cytometry or confocal microscopy in LN patients and spontaneous lupus model MRL/lpr mice. The distribution of ILC3s in human and murine kidneys was characterized by immunofluorescence, and the characteristics of ILC3s in different organs of MRL/lpr mice were revealed by transcriptome sequencing. Furthermore, ILC3s were adoptively transferred into LN mice to explore their roles in disease. In vitro, ILC3s were co-cultured with or without B cells to clarify their function in antibody formation.

Results: The frequencies of ILC3s in blood and kidneys of LN patients were found significantly higher than normal control, and positively associated with serum anti-dsDNA, ANA and total IgG. The elevation of ILC3s and their correlations with autoantibodies were also observed in MRL/lpr mice. In the kidney, ILC3s were mainly localized within perivascular ectopic lymphoid structures, showing low expression of resident and proliferative markers. Interestingly, renal ILC3s shared high transcriptional similarity with gut-derived ILC3s, implying that the small intestine may be a potential source of renal ILC3s. After adoptive transfer of ILC3s into LN mice, both systemic autoimmune manifestations and renal damage were significantly exacerbated. Meanwhile, there were remarkable increases in the proportion of plasma cells and IgG B cells in the kidney after ILC3s transfer. Mechanistically, in vitro studies showed that ILC3s promoted the differentiation of B cells into plasma cells and antibody formation.

Conclusions: Our results showed that ILC3s were increased in LN, and accelerated the progression of LN by promoting B cell activation in the kidney.

Funding: Government Support - Non-U.S.
FR-PO687
Mechanistic Study of Cetastrol-Mediated Inhibition of Macrophage M1 Polarization in IgA Nephropathy via Downregulating ECM1
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Background: Macrophages play a vital part in amplifying the inflammatory cascade in IgA Nephropathy (IgAN), but the potential mechanism and targeted treatment strategies still need to be explored. The aim of this study is to investigate the therapeutic effect of cetastrol (CLT) on IgAN, as well as the mechanism of cetastrol-mediated inhibition of macrophage M1 polarization in IgAN nephropathy via down-regulating ECM1.

Methods: We established an IgAN mouse model treated with CLT and an M1 macrophage model induced by LPS in Raw 264.7 in vitro. The proteinuria, serum creatinine levels, renal lesions, and infiltration of M1 macrophages in mice were detected. The macrophage markers such as M1 (iNOS) and M2 (Arg-1) expression levels in vitro were checked, as well as expression situation of inflammatory factors such as IL-6 and TNF-α. The expression of ECM1 in renal biopsy of patients was observed and its clinical significance was analyzed. We detected the activation of the ECM1/STAT5 pathway in IgAN mice and M1 macrophage models. And we constructed stably transfected cells with ECM1 overexpression to detect the changes in macrophage M1 polarization after CLT treatment, as well as the expression of ECM1 and STAT5/p-STAT5.

Results: CLT effectively alleviated renal lesions and macrophage infiltration in IgAN mice, and improved renal function. In addition, after CLT intervention, the expression of iNOS, IL-6, TNF-α decreased and the expression of Arg-1 increased. ECM1 was obviously expressed in IgAN patient’s renal tissue and it was negatively correlated with eGFR, while positively correlated with 24-hour proteinuria. ECM1 was also highly expressed in IgAN mice and in M1 macrophage models. In the M1 macrophage model with overexpression of ECM1, CLT inhibits macrophage M1 polarization and the production of inflammatory factors by downregulating the ECM1/STAT5 pathway.

Conclusions: CLT can effectively alleviate IgAN renal inflammatory damage, inhibit macrophage M1 polarization, and reduce the production of inflammatory factors. ECM1 was obviously expressed in IgAN renal macrophages, and the increase in ECM1 expression was related to the severity of IgAN diseases. The therapeutic effect of CLT on IgAN may be related to its inhibition of macrophage ECM1/STAT5 pathway.

Funding: Other NIH Support - This work was supported by the National Natural Science Foundation of China (82070373) and (81770714), Government Support - Non-U.S.

FR-PO688
Spatial Profiling of Human Kidney Tissues Stratifies Disease Pathology
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Background: To make any scientific advancements, there should be an in-depth understanding of pathophysiology of tissue microenvironment. Newer multiplex imaging-based methods are providing important insights into cytoarchitecture of tissue. We recently developed a novel tissue imaging method, termed SeqStain, that allows rapid and easy immunofluorescence based multiplexed tissue imaging and analyses. Here, we utilize this approach to understand the complex assembly of cells and her interactions with each other in both healthy subjects and patients with various glomerular diseases.

Methods: We synthesized fluorescently-DNA-tagged antibodies for analyzing multiple kidney-specific antigens using cycles of staining and de-staining on a single tissue section. We probed different histological regions relevant to the kidney and used conventional immunofluorescence microscopy for imaging the tissues and HALO software for image analyses.

Results: We analyzed both paraffin-fixed and frozen tissue sections using off-the-shelf reagents and a confocal microscope. We were able to accurately image tens of antigens on single tissue specimens for healthy subjects, and from patients with lupus nephritis (LN) and diabetic nephropathy (DN). Analysis of various cellular biomarkers indicated enrichment of specific cellular clusters into distinct neighborhoods.

Conclusions: SeqStain proved to be a versatile, gentle, and easily adaptable method for multiplex imaging that can be highly effective in obtaining a spatial map of kidney. Generated spatial maps will provide important new insights about the disease pathobiology and improve future diagnostics and therapeutics for LN and DN.

FR-PO689
Lisinopril-Mediated ACE Inhibition Reduces Proteinuria and Sclerosis in the G1/G1 but not the G2/G2 APOL1 Mouse Model of FSGS
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Background: APOL1 gene variants G1 and G2 account for the 3 to 4-fold elevated risk of kidney disease in individuals of recent African ancestry. These variants confer protection against Trypanosoma infection, but individuals with two high-risk alleles are at high risk of developing GS and renal failure. Molecular mechanisms of disease remain controversial and targeted treatments for APOL1 kidney disease remain an unmet need.

Methods: Our lab has created APOL1 BAC transgenic mice that develop proteinuria and glomerulosclerosis upon injection of pcDNA3-free plasmid DNA encoding murine IFN-γ. After the expression of G1/G1 and G2/G2 mouse groups with IFNγ plasmid, mice were randomized on post-injection day 7 (after confirming proteinuria) to treatment with Lisinopril in the drinking water at 75 mg/L or to a no drug control group. Urinary albumin-to-creatinine ratio was measured biweekly. At time of sacrifice, kidney tissue was harvested, paraffin-embedded, and 4µm sections were stained with periodic acid-Schiff (PAS) stain. An FS100 score was computed from 30 glomeruli per mouse, each scored in a blind manner as normal or displaying segmental or global sclerosis.

Results: Treatment with the ACE inhibitor lisinopril reduced proteinuria by ~100- fold in APOL1 G1/G1 BAC-transgenic mice and greatly reduced severity of FSGS by histological criteria. In contrast, lisinopril treatment of G2/G2 mice produced improvement neither in proteinuria nor in the likelihood of developing severe FSGS in G2/G2 mice.

Conclusions: Lisinopril-mediated inhibition of ACE modified disease phenotype in the BAC-transgenic APOL1 G1/G1 mouse model of FS100, but not in the G2/G2 model. These findings add to our understanding of APOL1 disease mechanisms in mouse models of FS100 and may provide insight into APOL1-associated human kidney disease. Early genotyping should in future allow trials of inhibition of the renin-angiotensin-aldosterone system starting before clinical onset of glomerular disease in patients with high-risk APOL1 alleles.

Funding: Other U.S. Government Support, Private Foundation Support

FR-PO690
YBX1 Alleviated Kidney Injury as a “Reader” of m5C Methylation in Adriamycin-Induced FSGS Mice
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Background: Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome. Currently, effective treatments lack due to unclear understanding of its pathogenesis. Recently, Y-box binding protein 1 (YBX1) has been found as a 5 methylcytosine (m5C) ‘reader’ to stabilize mRNA and promote protein translation. However, the role of YBX1 in FSGS remains unknown.

Methods: FSGS mice were induced by adriamycin (ADR) in BALB/c mice. Adeno-associated virus 9 (AAV9) containing YBX1 was delivered to FSGS mice for overexpressing YBX1. Mice (n=24) were randomly divided into four groups: normal control (NC), ADR, ADR + AAV9-control, and ADR + AAV9-YBX1. Urine protein, serum protein, and serum creatinine were checked, as well as expression situation of inflammatory factors such as IL-6 and TNF-α. The expression of ECM1 and STAT5/p-STAT5 were analyzed by Western blotting and immunofluorescence (IF) staining. The co-localization of ECM1 and STAT5 was confirmed by confocal microscopy.

Results: YBX1 overexpression significantly reduced proteinuria in ADR + AAV9-YBX1 mice compared to ADR mice. Furthermore, renal injury was alleviated as the expression of ECM1 and STAT5 were decreased in ADR + AAV9-YBX1 mice. The levels of podocytic WT1, synaptopodin, and podocin as well as profibrotic proteins α-SMA, vimentin, and fibronectin (FN) were analyzed by Western blotting and immunofluorescence (IF) staining. The co-localization of ECM1 and STAT5 were confirmed by confocal microscopy.

Conclusions: YBX1 may play an important role in pathogenesis of FSGS by regulating synaptopodin mRNA and further alleviating glomerulosclerosis through serving as a m5C ‘reader’. YBX1 might be a novel therapeutic target for FSGS.

Funding: Government Support - Non-U.S.
FR-PO691

CD4+ T Cell Egress in Crescentic Glomerulonephritis Is Regulated by a Converse Expression of S1PR1 and CXCR6
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Background: Autoimmune diseases such as crescentic glomerulonephritis (cGN) are characterized by a dramatically increased migration of leukocytes to the inflamed tissue. Infiltration of CD4+ T cells play a key role in orchestrating the immune response during inflammation. However, little is known about the function and mechanisms of T cell exit out of the kidney. The aim of this study is to characterize the CD4+ T cell retention and emigration receptors and their implication on tissue injury, especially in the context of restitution vs chronication of tissue inflammation.

Methods: Lymph vessel staining of renal biopsy cores was performed by immunohistochemistry (IHC). For leukocyte trafficking analysis eGNI was induced in Kaede-mice, ubiquitously expressing the photoconvertible Kaede protein. Photoconversion of intrarenal leukocytes was performed by UV-A light (385 nm) exposure of the left kidney. Leukocytes from kidneys, blood and dLN were analyzed by scRNAseq, flow-cytometry and IHC. For analysis of the chemokine receptor CCR7 a CCR7 deficient mouse model was used, for analysis of CXCR6 a depleting antibody of its sole ligand CXCX6L1 was used. S1PR1 signaling was blocked using FTY720.

Results: In human biopsy cores an exit of CD4+ T cells but not CD68 macrophages via the lymphatics could be shown. Murine analysis of emigrated CD4+ T cells revealed a set of differentially expressed genes compared to resident CD4+ T cells, mainly a downregulation of the chemokine receptor CXCX6R and an upregulation of S1PR1. CCR7, although upregulated on CD4+ T cells showed to be dispensable for T cell egress. Depleting CXCR6 resulted in an increased migration of CD4+ T cells to dLN, while blocking S1PR1 signaling led to an increased retention of CD4+ T cells in the kidney and a marked increase in tissue damage.

Conclusions: CD4+ T cells egress via the lymphatics out of the inflamed kidney is tuned by the downregulation of CXCR6 and upregulation of S1PR1. Blocking T cells egress leads to an increase in tissue damage, thus proposing the importance of T cell egress to the dLN alters organ-specific immunity.

Funding: Government Support - Non-U.S.

FR-PO692

The Serine Protease HTRA1 Mouse Model: A Gateway to Identify the Cellular Origin of New Antigens
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Background: While initial membranous nephropathy (MN) autoantigens like PLATR were found to be transmembrane podocyte proteins, more recently identified antigens are secreted proteins or not clearly derived from podocytes. Whether immune complexes in these cases assemble in situ or are deposited after forming in the circulation remains unclear.

Methods: WT and HTRA1 KO mice were immunized with full-length human HTRA1. Immunofluorescence, confocal microscopy and RNAscope were used to identify the origin of autoantigens in HTRA1-associated MN.

Results: As shown in Figure 1, MN pathology with mouse HTRA1 mouse IgG immune complexes in a membranous loop pattern and more significant proteinuria was observed in WT, but not HTRA1 KO, mice that were previously immunized with recombinant human HTRA1, despite the presence of circulating anti-human HTRA1 in both animals. This finding suggested that mouse HTRA1 autoantibodies were formed against a shared epitope between human and mouse proteins, leading to in situ immune complex formation at the GBM. Furthermore, RNAscope (Figure 2) demonstrated podocytes to be the cellular source of HTRA1.

Conclusions: The presence of HTRA1-mIgG deposits in actively immunized WT but not KO mice, along with increased podocyte expression of HTRA1 by podocytes, argues against deposition of circulating immune complexes and instead argues for a podocyte origin of this secreted autoantigen and formation of in situ immune deposits. We will further confirm this hypothesis using a podocyte-specific HTRA1 KO.

FR-PO693

The Impact of Exposure to Air Pollution on the Progression of Primary Glomerular Disease
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Background: Exposure to air pollution is linked to chronic disease. Air pollution stimulates injury pathways that contribute to organ damage. However, there is limited information about its impact on the course of kidney disease or the molecular pathways involved.

Methods: Patients enrolled in the Nephrotic Syndrome Study Network (n=228) and Cure Glomerulonephropathy (n=697) studies with residential census tract data and ≥2 yr of follow-up were included. Three indices of air pollution exposure were assessed: (1) PM2.5, (2) Black carbon, and (3) Sulfates. The primary outcome was the hazard ratio for ≥40% decline in eGFR or end-stage kidney disease (eGFR<15 ml/min/1.73 m2, initiation of dialysis, or kidney transplantation). Air quality was categorized by census tract and assessed using modeled concentrations.

Results: PM2.5, black carbon, and sulfate exposure were comparable in the two cohorts but higher in Black participants (p<0.005). Baseline eGFR was lower and proteinuria higher in those with exposure above the median for all three pollutants. Among patients with disease duration ≥1 year, in an adjusted analysis, PM2.5, HR 1.23 [95% CI 1.05, 1.44], p=0.004, and black carbon, HR 1.42 [95% CI 1.18, 1.71], p<0.0002, were associated with increased likelihood of worsening kidney disease. Sulfate exposure was associated with increased urinary MCP-1 excretion (p=0.018) and increased serum TNF levels (p=0.003), while PM2.5 exposure was associated with increased serum IL-8 levels (p=0.025) (Figure 1).

Conclusions: In patients with primary glomerulopathies, exposure to air pollution is associated with an elevated risk for disease progression and increases in systemic biomarkers of inflammation.

Funding: NIDDK Support.
Determining Individual Glomerular Proteinuria and Periglomerular Infiltration in a Cleared Murine Kidney by 3D Fast-Marching Algorithm

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Background: Research in organs with a complex architecture like the kidney benefits from 3D image analysis. However, limited resolution and imperfections of real-world 3D image material often preclude algorithmic image analysis. We here present a methodical framework to overcome these obstacles.

Methods: We optimized our optical tissue clearing protocol to preserve fluorescence signals for light-sheet-fluorescence-microscopy and compensated attenuation effects using adjustable 3D correction fields. Next, we adapted the Fast-Marching algorithm (FMA) to conduct backtracking in 3D environments. Furthermore, we designed a local concentration measure termed Volumetric impact factor (VIF) to quantify extractable objects in 3D microenvironments.

Results: We applied this framework to cleared kidneys of mice with nephrotoxic nephritis, a model for human crescentic glomerulonephritis. Our framework generated a list of anatomical and functional parameters of each individual glomerulus of a murine kidney. Using FMA, we determined and visualized the individual proteinuria (Figure 1). Using VIF, we quantified the individual periglomerular dendritic cell infiltration in nephritic kidneys. By correlating these parameters, we disprove the intuitional assumption that the most infiltrated glomeruli are the most proteinuric. Instead, the glomerular density predicted proteinuria.

Conclusions: Our framework allows multiparameter image analysis and advanced 3D analysis of all nephrons of a murine kidney and facilitates understanding of renal immunopathology.

Funding: Government Support - Non-U.S.

Dense Deposit Disease: What Makes the Deposits Dense

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Background: C3 glomerulopathy (C3G) is a disease resulting from dysregulation of the alternative pathway (AP) of complement. C3G includes C3GN and DDD; both are characterized by bright glomerular C3 staining. However, on EM, DDD is characterized by dense osmiophilic mesangial and intramembranous deposits, while the deposits of C3GN are not dense.

Methods: We performed laser microdissection of glomeruli followed by mass spectrometry in 15 cases of DDD and 29 cases of C3GN to determine the proteomic profile and differences between C3GN and DDD.

Results: As expected, there was overlap in the proteomic profile of C3GN and DDD (figure 1). Both diseases showed high total spectral counts (TSC) of C3, CFHR5, CFHR1, CFHR2 and CFH. Although high TSC of terminal complement proteins (C5-C9) were present in C3GN and DDD, there was a 6-9-fold increase of C5-9 in DDD compared to C3GN. An unexpected finding was the 7-9-fold increase of apoliproteins (APO): APOE, APOA5, APOA2 and APOA4, in DDD compared to C3GN (figure 2). Controls cases showed no accumulation of APO. We also detected increased accumulation of HTRA1, C4b binding protein and SAP proteins in DDD. Immunohistochemistry is being performed to confirm and localize APO in the dense deposits of DDD and compare them with deposits in C3GN.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: There is a higher burden of terminal complement pathway proteins in DDD compared to C3GN. In addition, extensive deposition of APOE and APOA5 likely cause the deposits to appear dense in DDD.

Sample clustering

Overlap in the proteomic profile of C3GN and DDD.

FR-PO696
Gluromeral Spatial Transcriptomics and Integrated Gut Microbiome Analysis Reveals Pathogenetic Importance of Short-Chain Fatty Acid in IgA Nephropathy
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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, and the pathogenesis has been reported to be related to the gut microbiome. Additional studies focusing on the linkage between intra-glomerular transcriptomic alterations and associated microbial signals are warranted.

Methods: We performed glomerular spatial transcriptomic profiling of various glomerulopathies without a profound eGFR decrease and healthy controls using the GeoMx Digital Spatial Profiler. This included 8 IgAN, 10 donor kidney biopsy, 6 diabetic nephropathy, 7 focal segmental glomerulosclerosis, 13 minimal change disease, and 16 membranous nephropathy cases. The glomerular transcriptome was compared between the IgAN and each control group using the DESeq2 method, and gene ontology annotation analysis was used to predict metagenome functions, which were compared by ALDEx2 between the groups.

Results: We identified 1209 consistently highly expressed genes in the IgAN glomerulus, mainly annotated in major histocompatibility protein binding, immune cell adhesion, and extracellular matrix formation gene ontologies. On the other hand, 1050 genes were consistently lowly expressed in the IgAN glomerulus. Notably, the annotated gene ontologies included beta 1, 3 galactosyltransferase and short-chain fatty acid transporters or G protein-coupled receptor signaling pathways. Although there was an absence of a single taxa consistently showing a significant difference in the IgAN microbial community, the pathway analysis indicated that the methanogenesis from acetate pathway was significantly abundant in the IgAN gut microbiome.

Differences in protein expression in DDD compared to C3GN.

FR-PO697
Development and Application of Multiplexed Proteomics to Investigate Protein Complexes in Kidney Aging and Disease
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Background: Kidney aging is a complex process associated with a decline in renal function. This decline is due to several factors, including changes in cellular states driven by protein expression and their composition in complexes. Proteins rarely function alone, and their activity is often determined by their interactions with others. However, owing to the technical challenges, no attempt has been made to profile the global changes in protein complexes composition and abundance in the kidney as a function of age or disease.

Methods: Co-fractionation mass spectrometry (CF-MS) is an emerging unbiased method that identifies protein complexes in cell or tissue lysate. CF-MS first separates the proteins in a sample by chemical properties such as size and charge using native chromatography, and thereby proteins from the same complexes will co-elute into the same fractions. All the proteins in each fraction are then identified and quantified by MS and the complexes can be inferred using downstream bioinformatics analysis. In a classical CF-MS set-up, one fraction per sample is processed and analyzed by the MS at a time. As samples are fractionated into tens or hundreds of fractions, with each fraction requiring analysis, the large number of samples results in a highly time-consuming process both in sample preparation as well as data acquisition time. To address this bottleneck, we have explored using a multiplexed isobaric labeling strategy (Tandem Mass Tags, TMT) that can significantly reduce the acquisition time. We have applied this approach to analyze young and old human kidneys as well as kidneys from chronic kidney disease patients.

Results: We present the first comparison of profiling global changes in protein complexes in young vs old vs CKD human kidneys. We validate our novel TMT proteomics approach using known complexes before applying the technique to profile complexes in precious human kidneys. Our preliminary results suggest that the method is a promising high throughput tool for comprehensively studying protein complexes in kidney aging and disease.

Conclusions: Our approach of using CF-MS combined with TMT-MS offers a novel direction to explore changes in protein complexes with a great potential to identify new drug targets and therapies for kidney aging and diseases.

FR-PO869
Involvement of Kynurenine Metabolizing Enzymes and Its Metabolites in Antibody-Mediated Glomerulonephritis
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Background: Tryptophan (TRP) is eventually metabolized to NAD in kynurenine pathway (KP), and its metabolites (Figure) potentially exert many biological activities in immune system. The objective of the current study is to elucidate the role of TRP metabolism in the progression of glomerulonephritis.

Methods: We introduced antibody mediated glomerulonephritis by administration of rabbit anti-mouse nephrotoxic serum (NTS-GN) in mouse strains deficient in KP-related enzymes including indoleamine 2,3-dioxygenase 1, 2 (IDO1, IDO2-/-), and kynurenine 3-monooxygenase (KMO-/-) and performed functional and histological analyses in diseased kidneys. For the therapeutic intervention, we administrated kynurenic acid (KYN) into IDO1-/- with NTS-GN. In vitro, we analyzed morphology of bone marrow derived neutrophils on immune complexes (ICs).

Results: IDO1-/- demonstrated severe renal dysfunction and histological glomerular damage than WT, while those in IDO2-/- were comparable with WT. Conversely, crescent formation was significantly less in KMO-/- mice. Glomerular accumulation of neutrophils was significantly more in IDO1-/- mice, but less in KMO-/- mice. Neutrophils presenting "spread" morphology among attaching cells on ICs was significantly increased in IDO1-/-, whereas it was reduced in KMO-/- Administration of KYN into the diseased IDO1-/- significantly diminished glomerular crescent formation, which associated with the amelioration of renal dysfunction. Moreover, KYN treated IDO1-/- neutrophils demonstrated less percentage of "spread" cells on IC-coated dishes than non-treated cells.

Conclusions: IDO1/KMO-mediated alterations of TRP metabolism involve in the disease activity of NTS-GN. Of note, KYN negatively regulates to the disease pathogenesis by the alteration of IC-mediated neutrophil activity.
FR-PO700

Analysis of CD169 (Sialoadhesin)-Positive Activated Macrophages in Kidney Damage in Lupus Nephritis

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Background: CD169 (sialoadhesin; Sn+) activated macrophages (MQ) are associated with renal lesions in lupus nephritis (LN). However, the function of Sn+ MQ is unclear as Sn does not fit into the M1/M2 paradigm of MQ activation, and little is known of how steroid therapy affects Sn expression. This study examined the activation status of Sn+ MQ in biopsies of LN and cultured MQ.

Methods: Biopsies from 32 patients diagnosed as LN with ISN/RPS classification III or IV were examined for accumulation of Sn+ MQ by immunofluorescence staining, and correlated with clinico-pathological findings. For in vitro studies, normal human monocyte-derived MQs were incubated with IFNγ+LPS, with or without dexamethasone (DEX), and transcriptomic changes analysed by DNA microarray.

Results: In vitro, IFNγ+LPS induced an M1 pro-inflammatory MQ response with significant up-regulation of Sn mRNA levels. Dex suppressed the IFNγ+LPS induced M1-type response, but did not affect the increased Sn expression. In addition, Dex drove an M2-type response with up-regulation of the M2 marker CD163. Biopsies showed marked glomerular and interstitial infiltration of Sn+ MQ in all cases, which correlated with glomerular active lesions such as endocapillary proliferation and cellular or fibro-cellular crescents (p<0.0001) or interstitial fibrosis (p<0.05), respectively. Separating patients into those who did (n=15), or did not (n=17) have steroid therapy before biopsy; there was no difference in the number of glomerular or interstitial Sn+ MQ. However, the number of glomerular (but not interstitial) CD163+ M2-type activated MQ was significantly higher in steroid treated patients (p<0.0001). Furthermore, Sn+ MQ co-localized with T lymphocytes in glomerular, periglomerular and interstitial areas.

Conclusions: Sn may be a common activation marker for both M1 and M2 MQ in LN. Sn+ MQ infiltration correlates with disease activity and may play a role in regulating T lymphocytes in LN. The lack of impact of steroids on the Sn+ MQ subset indicates that alternative strategies are needed to target this mechanism of kidney injury.

FR-PO701

Cytokine Profiling in ANCA-Associated Vasculitides

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Background: ANCA-associated vasculitis (AAV) is a multisystem autoimmune disease that often affects the kidneys. It is unclear why some patients with AAV have kidney involvement while others do not. To investigate the mechanisms underlying these phenotypes, this study examined plasma and urine cytokine profiles in patients with active renal and non-renal AAV (AAGN and NR-AAV, respectively), and healthy controls (HC).

Methods: Levels of 200 cytokines were measured in the plasma and urine of 6 patients with active AAGN, 9 patients with NR-AAV, and 3 HC using a human cytokine array. Urine cytokine levels were corrected to urine creatinine and an analyte-to-creatinine ratio was utilized for analysis. Levels in the three groups were compared using ANOVA. Analyses with false discovery rate (FDR)-corrected p-values <0.05 were further compared using Tukey HSD post-hoc test.

Results: Patient Characteristics are depicted in Table 1. Most cytokines measured were similar between HC and NR-AAV patients. Compared to patients with NR-AAV, patients with AAGN had higher levels of plasma and urine cytokines that are involved in involved in Th17 signaling (IL-17A, IL-17F, IL-17R, IL-23, IL-6), Th1 response (IL-12, GM-CSF, IFNγ, TNFa), chemotaxis (especially for T-cells, monocytes, and dendritic cells - eotaxin-2, T-TAC, Lymphotactin, MCP-3, MIP-3a, CCL23), B and T-cell crosstalk (B7-1, CD40, CD40L), and angiogenesis (VEGFR1, FLT4, VEGF-C, VEGF-D, SDF1a) (Figure 1).

Conclusions: Compared to NR-AAV, AAGN is associated with an increase in plasma and urine levels of many pro-inflammatory cytokines. T-cell differentiation, signaling, and crosstalk seem to be the most prominent molecular processes that are active in patients with AAGN. These data suggest a prominent role of T-cells in AAGN which have the potential of being leveraged therapeutically.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
FR-PO702

Proteinuria Induces Tubular Cell Proliferation in Nephritic Syndrome Model Mice Without Causing Tubular Injury

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Background: Proteinuria exhibits a robust association with the progression of kidney diseases and causes pathological effects on tubular cells. Nevertheless, the precise molecular mechanisms underlying tubular injury induced by proteinuria remain largely unknown. To elucidate the transcriptome alterations in the kidney resulting from proteinuria, we conducted an RNA sequencing (RNA-seq) analysis on a mouse model of nephritic syndrome.

Methods: We used NEP25 mice, which express the human CD25 receptor on podocytes. Proteinuria was induced in these mice through the administration of an immunotoxin targeting the human CD25 receptor, LMB2 (0.625 ng/g body weight). After a period of seven days following LMB2 injection, the mice were euthanized, and RNA was extracted from the whole kidney. RNA-seq was performed using Illumina NovaSeq and differential expression genes (DEGs) were identified using the DESeq2 package in R. Subsequently, we conducted multiple immunostaining and in situ hybridization (ISH) of the DEGs to determine their cellular localization and specific cell types.

Results: Following the administration of LMB2, NEP25 mice exhibited significant proteinuria without exhibiting kidney dysfunction or histological damage. Through our kidney RNA-seq analysis of NEP25 mice, we identified 562 up-regulated and 430 down-regulated genes. Enrichment analysis revealed a notable up-regulation of genes associated with cell proliferation and differentiation. Notably, we observed a significant up-regulation of the transcription factor Foxm1, known to be involved in cell proliferation. Immunostaining and ISH confirmed the co-expression of Ki67 and Foxm1 in various tubular cells, including the proximal tubule, loop of Henle, distal tubule, and collecting duct.

Conclusions: The RNA-seq analysis of nephritic syndrome model mice revealed that tubular cell proliferation was triggered by extensive proteinuria without causing kidney dysfunction or histological damage. The up-regulated genes, including Foxm1, have been previously associated not only with cell proliferation but also with tissue fibrosis. Consequently, the modulation of these gene functions is possible to serve as novel targets for chronic kidney disease treatment.

FR-PO703

Gnaq Deficiency Enhances Il620b/Ifi116 and NF-kappaB Pathway in Kidney Endothelial Cell and Lupus Nephritis Pathology

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Background: Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE), the heterogeneity is still a great major challenge to study. Our previous study revealed a negative correlation between Gnaq (G protein subunit alpha q) and autoimmune diseases. As Gnaq was also relatively enriched in the kidney glomerular endothelium, in addition, Gnaq heterozygous knockout mice exhibited an aberrant glomerular endothelial phenotype. Hereon we found the role of GNAQ in LN remains unclear.

Methods: LN was induced by pristane in female appropriate age C57BL/6 Gnaq+/− and littermate Gnaq−/− mice. Renal disease was assessed by the quantification of proteinuria and histologic analyses. Transcriptomic analysis was conducted on leukocytes and glomeruli obtained from Gnaq−/− and Gnaq+/− mice for differentially expressed genes.

Results: Treatment with pristane induced diffuse proliferative LN characterized by kidney morphology and persistent albuminuria across the two centres. The mean age was 56 and there was a slight male predominance (Fig. 1). Nineteen new cases from centre one suggests a greater than four-fold increase in the incidence of AA V, as compared to data averages from the same centre for the previous decade (Fig. 2). 62.5% of patients had received a2 viral vector vaccines for COVID-19, whereas 83.3% of the centre two cohort received mRNA vaccines.

Conclusions: Our data shows a significant increase in AA V this year at one centre. More diagnoses were of the MPA phenotype, contradicting previous studies suggesting a higher prevalence of GPA in northern Europe. Possible explanations for the increase include autoimmune responses triggered by viral illnesses and COVID-19 vaccinations. Although not statistically significant, our data suggests a link between viral vector vaccines for COVID-19 and increased AA V incidence. Environmental factors such as air pollution have also been associated with higher autoimmune risk. The rising incidence suggests further research into the cause and raises questions about service provision, health promotion and management.

FR-PO704

The Correlation Between Urinary microRNA-5195 and Renal Parameters in Patients with IgA Nephropathy


Background: The microRNA-5195 (miR-5195) modulates cell proliferation by targeting the Cyclin L1 gene that regulates the cell cycle. In this study, we examined whether the urinary concentration of miR-5195 is related to clinicopathological parameters and short-term changes in renal function in patients with IgA nephropathy.

Methods: We extracted and quantified microRNAs in morning spot urine in 80 patients with IgA nephropathy at biopsy and four control subjects. Then we examined the relationship between clinical and histological parameters, one-year changes in eGFR, and urinary miR-5195. The concentrations of microRNAs and proteins were correlated to the concentration of urinary creatinine and were log-transformed for simple correlation analysis.

Results: The urinary excretion of miR-5195 was detected in all subjects, and the urinary concentration of miR-5195 in patients with IgA nephropathy was significantly lower than in controls. Among 80 patients with IgA nephropathy, urinary miR-5195 levels showed a significantly positive correlation with the urinary concentration of total microRNA (r=0.57), total protein (r=0.46), beta2-microglobulin (r=0.46), and N-acetyl-beta-D-glucosaminidase (NAG) (r=0.39), but not with baseline GFR, and urinary red blood cells. Concerning the histological parameters, the urinary miR-5195 levels showed a significant positive correlation with glomerular proliferation (r=0.24) but not with glomerular sclerosis and tubulointerstitial fibrosis. The one-year changes in eGFR after biopsy showed a significant inverse correlation with the urinary concentration of miR-5195 (r=-0.39) and total protein (r=0.37) but not total microRNA, beta2-microglobulin, and NAG. The correlation between urinary miR-5195 and one-year eGFR change was stronger in the subjects without steroid treatment (r=0.47) than those with steroid treatment (r=0.38).

Conclusions: In this study, the urinary excretion of miR-5195 was correlated with clinical and histological parameters and one-year changes in renal function in patients with IgA nephropathy, suggesting that urinary miR-5195 might be a useful biomarker of IgA nephropathy.

Funding: Government Support - Non-U.S.

FR-PO705

Unprecedented Rise in ANCA Vasculitis: Unveiling Patterns, Phenotypes, and Etiological Factors

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Background: There has been a perceived increase in the incidence of patients presenting with ANCA associated vasculitis (AAV). We aim to quantify the extent of this increase and identify trends and associations.

Methods: The incidence of newly diagnosed AAV was observed from two renal centres in the North West of England from 1st January to 30th April 2023. Retrospective data collection included demographics, serology, AAV phenotype and COVID-19 vaccination status. This data was compared to previous annual incidence rates of AAV diagnosis.

Results: A total of 25 new AAV patients were diagnosed across the two centres. The mean age was 56 and there was a slight male predominance (Fig. 1). Nineteen new cases from centre one suggests a greater than four-fold increase in the incidence of AAV, as compared to data averages from the same centre for the previous decade (Fig. 2). 62.5% of centre one patients had received a2 viral vector vaccines for COVID-19, whereas 83.3% of the centre two cohort received mRNA vaccines.

Conclusions: Our data shows a significant increase in AAV this year at one centre. More diagnoses were of the MPA phenotype, contradicting previous studies suggesting a higher prevalence of GPA in northern Europe. Possible explanations for the increase include autoimmune responses triggered by viral illnesses and COVID-19 vaccinations. Although not statistically significant, our data suggests a link between viral vector vaccines for COVID-19 and increased AAV incidence. Environmental factors such as air pollution have also been associated with higher autoimmune risk. The rising incidence suggests further research into the cause and raises questions about service provision, health promotion and management.
**FR-PO706**

Further Insights into Iptacopan Mode of Action in IgA Nephropathy Through Protein Profiling

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**Background:** IgA nephropathy (IgAN) can lead to progressive loss of kidney function, with ~30% of patients with proteinuria 1-2 g/day progressing to kidney failure within 10 years. Iptacopan is a proximal complement inhibitor that specifically binds factor B and inhibits the alternative complement pathway (AP). In a Phase 2 study (NCT03373461), iptacopan treatment led to a dose-dependent reduction in proteinuria and inhibition of the AP in patients with IgAN (1, 2).

**Methods:** SomaScan, a large proteomics platform, and statistical analysis were used to examine iptacopan’s impact on plasma proteins. Statistical threshold for biomarker definition was set to adjusted p-value < 0.05 and absolute log Fold Change > 0.1.

**Results:** Iptacopan resulted in a significant modulation of 81 distinct plasma proteins in IgAN patients after 90 days’ treatment, persisting at the 180-day timepoint. Except for four, proteins were downregulated. Approximately two-thirds of the proteins are likely originated from the kidney (Fig.1), amongst which 4 proteins were reported to have increased expression in kidney from IgAN patients (BCL2L1, HES1, LITB, C8). These proteins are thought to be released by cellular mechanisms like necrosis, apoptotic vesicles, proteolysis, and cell activation (Fig.1). From scientific literature, the findings are implicating changes in key biological pathways like inflammation, hypercellularity, fibrosis and atrophy. This underscores the potential of iptacopan to modulate protein expression across these pivotal biological processes in the context of IgAN patients.

**Conclusions:** This data suggests that iptacopan may contribute to reduction of renal inflammation, hypercellularity, fibrosis and atrophy in patients with IgAN. The relevance of these encouraging early findings will necessitate confirmation in a larger data set and at tissue level.

**Funding:** Commercial Support - Novartis Pharma AG

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**FR-PO707**

Anti-Glomerular Basement Membrane (GBM) Serum Effects on Kidney Function and Glomerulosclerosis in Mice

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**Background:** Antibody-induced glomerulonephritis (GN) is a condition characterized by causation by an inappropriate autoimmune response to renal antigens, such as the glomerular basement membrane (GBM), leading to progressive glomerulosclerosis and rapidly declining renal dysfunction for which there exist only few treatment options. Understanding the underlying mechanisms of GN is crucial for developing effective therapeutic strategies. In this study, we aimed to investigate the induction of antibody-induced GN by anti-GBM serum on kidney biomarkers, histology and transcriptome signatures.

**Methods:** Male C57BL/6J mice (n=15) were randomized into three groups (n=5 per group) and received either vehicle injection, 100, or 200 µl of anti-GBM serum. We measured urine albumin-to-creatinine ratio (ACR) as an indicator of renal function. Renal endpoints included urine albumin-to-creatinine ratio (ACR), AI-assisted glomerulosclerosis scoring, histomorphometric analysis of fibrosis (Col3a1), and RNA sequencing (RNA-seq) analysis.

**Results:** Compared to vehicle controls, both doses of anti-GBM serum significantly increased urine ACR, indicating renal dysfunction and glomerular injury. AI-assisted based histopathological scoring confirmed significant glomerulosclerosis in anti-GBM serum-treated groups. Additionally, IHC image analysis indicated renal fibrotic injury. Correspondingly, RNA-seq analysis revealed upregulated gene expression programs signifying renal extracellular matrix remodeling (e.g., Col1a1, Col3a1, Col4a1) inflammation (e.g., CD68, Ctcl, Il1b).

**Conclusions:** Anti-GBM serum induces fast onset of renal dysfunction, glomerulosclerosis, and fibrosis, in the mouse model of antibody-induced GN. The antibody-induced GN model in mice is highly applicable for probing test compounds with potential nephroprotective effects autoimmune GN.

**Funding:** Commercial Support - Gubra

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**FR-PO708**

Successful Use of Intravenous Immunoglobulin (IVIG) in Severe Life-Threatening Hypoalbuminemia in a Young African American (AA) Male with FSGS

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**Introduction:** Nephrotic syndrome (NS) relapses are common and are mostly managed by intensified doses of steroids with or without IV albumin infusion. In some instances, the relapses may be steroid resistant thereby warranting alternative immunosuppressive modalities. IVIG therapy has shown beneficial effects in patients with certain forms of glomerulonephritis but has been rarely used in steroid resistant NS patients. We hereby report an AA male adolescent with long standing FSGS who presented with NS relapses that are characterized by unusual severe life-threatening hypotensive crisis that was successfully treated with IVIG therapy.

**Case Description:** A 21-year-old AA male with known history of infrequent relapses of steroid resistant NS since the age of 3 yrs. At the age 18 years, he started having frequent relapses (9 events per year) and a repeat renal biopsy showed FSGS with 40% tubular atrophy and scarring. Relapses were characterized by precipitous events of heavy proteinuria (10-20 g/day), severe hypoalbuminemia (< 1 gm/dl), and a peripheral circulatory failure. The latter was complicated by cerebral hyperperfusion with a syncope and atrial fibrilation. He was not responsive to Mycophenolate Mofetil and Rituximab. There was an interval event of COVID-19 infection that warranted monoclonal antibody. Patient was reluctant to undergo a proposed medical and surgical nephrectomy. Given a concurrent severe hypoalbuminemia and hypogammaglobulinemia, an empirical treatment with a sequential IVIG was commenced. Consequently, frequency and severity of relapses had reduced for the past 10 months with no subsequent ICU admissons. His serum creatinine has always been normal (0.4-0.7 mg/dl). Genetic studies showed heterogeneous APOL1 haplotypes of G1 and G2 variants.

**Discussion:** We present a rare case of life-threatening episodes of severe NS relapses in a patient with FSGS and G1/G2 APOL1 gene mutation who had a superimposed COVID-19 infection that responded to serial doses of IVIG therapy. We believe the beneficial effect of IVIG might be related to an increase in intravascular oncotic pressure and immunologic effects. IVIG therapy may be considered in patients with steroid resistant NS that failed to respond to conventional immunosuppressive modalities.
We present a case of a patient who had all three diagnoses and treated with a Sodium-glucose cotransporter-2 inhibitor (SGLT2i).

Case Description: A 21 year old female presented with four month history of leg oedema, and subsequently confirmed nephrotic syndrome. She had recent diagnosis of hyphoproteinemia and coeliac disease prior to this presentation, and was established on glomerulonephritis with levothyroxine. At presentation, urine protein-to-creatinine ratio was 403.4mg/mmol with serum albumin of 2.9 g/dl. Complements C3 and C4 were normal, with no detected paraprotein and negative immunology (ANA, cryoglobulins, ANCA) and virology screen. Thyroglobulin and TSH receptor antibody levels were raised. Peripheral blood smear showed pernicious anaemia complex glomerulonephritis with MPGN pattern. She was commenced on maximally tolerated Angiotensin-converting enzyme inhibitor (ACEi) and SGLT2i. After 8 months, there was resolution of oedema, and marked improvement of proteinuria (123.5 mg/mmol) without need for immunosuppressive therapy.

Discussion: There have been five case reports of MPGN with nephrotic syndrome, associated with autoimmune thyroiditis. There have been biopsy studies showing thyroid antibody deposition in glomeruli, supporting this association. There have been four case reports of MPGN associated with coeliac disease. In these cases, a mix of pediatric and adult cases of hypocomplementemia was observed. In all the cases, gluten-free diet was sufficient to improve gastrointestinal symptoms, resolution of oedema and reduction in proteinuria. As we did in this case, we believe supportive therapy for MPGN associated with coeliac disease and/or autoimmune thyroiditis should include management of the associated conditions with gluten-free diet and maintaining euthyroid state. In addition, ACEi and SGLT2i have a role in managing MPGN, and may help avoid need for immunosuppression in such cases.

FR-PO710
Atypical Presentation of Atypical Anti-Glomerular Basement Membrane Disease
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Introduction: Anti-glomerular basement membrane (anti-GBM) disease is a rare aggressive autoimmune disease characterized by circulating anti-GBM Antibodies (Ab) leading to crescentic necrotizing glomerulonephritis with linear deposition of immunoglobulin G (IgG) along the GBM. As opposed to the classic anti-GBM disease, atypical anti-GBM glomerulonephritis is characterized by an indolent clinical course, undetectable circulating anti-GBM Ab, endocardial proliferation with only few crescents and limited IgG staining of the GBM. Herein, we present a case of atypical manifestation of atypical anti-GBM disease and emphasize the therapeutic dilemmas and challenges.

Case Description: 24-year-old male with a 3 weeks history of vomiting, was admitted to the hospital with severely impaired kidney function (creatinine 17 mg/dl), massive proteinuria without pulmonary involvement. Anti-nuclear, anti-neutrophil cytoplasmic, and anti-GBM Ab were negative (anti-GBM was examined by indirect immunofluorescence (IF) assay, and enzyme-linked immunosorbent assay (ELISA)). Kidney biopsy demonstrated 100% cellular crescents with linear polytypic IgG staining of the GBM and C3 on IF. Hemodialysis was started. The patient was treated with high-dose steroids, cyclophosphamide and plasma exchange, as for classic anti-GBM disease. As opposed to classic anti-GBM disease, duration of plasmaspheresis could not be dictated in the absence of detectable anti-GBM antibodies. The clinical course was ominous without improvement of his kidney function.

Discussion: The patient’s clinical course and pathological findings were consistent of classic anti-GBM disease. Therefore, the absence of circulating anti-GBM Ab was surprising and did not suit the aggressive course of his kidney disease and pathological findings. Several reports had been proposed to detect anti-GBM Ab including autoantibodies directed against GBM epitopes other than a3C1, quaternary epitopes of native a345NC1 hexamer or high avidity for anti-GBM Ab along the glomeruli leading to undetectable circulating ab. Modified assays to detect a wide range of antigens or epitopes, using more sensitive techniques like biosensors, can uncask circulating anti-GBM antibodies and help in making therapeutic decisions regarding duration of plasmaspheresis and immunosuppression therapy well as timing of kidney transplantation.

FR-PO711
Anti-Glomerular Basement Membrane Disease Overlap with Pauuci-Immune Glomerulonephritis: Temporal Concurrence at a Single Center
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Introduction: Anti-GBM and p-immune vasculitis are small vessel vasculitis and cause RPGN with diffuse alveolar hemorrhage (DAH). Overlap between these entities is rare. Up to 38% of the individuals with anti-GBM disease demonstrate double- positivity and approximately 38% of patients with ANCA vasculitis have positive titers of anti-GBM antibodies. We present two double-positive cases diagnosed within 6 weeks at our institution.

Case Description: Case 1: A 74-years-old white male with h.o SARS-COV19 two months previously presented with cough and metallic taste, BUN 60 with S/Cr 5.05 mg/dl, p-ANCA 1:640 and anti-GBM+. Kidney biopsy showing Diffuse crescentic GN with linear IgG staining of the GBM and C3 on IF. Hemodialysis was started. The patient was treated with hydralazine, drug-induced ANCA vasculitis is rarely reported. This case demonstrates a case of hydralazine-induced small vessel vasculitis. While immune-mediated complications have been frequently reported with the use of hydralazine, drug-induced ANCA vasculitis is rarely reported. This diagnosis should be considered in patients on hydralazine who develop pulmonary-renal syndrome. Diagnosis relies on serologic work-up and renal histopathology. Discontinuing hydralazine is the first step in treatment and this alone might be sufficient; however, more aggressive management including immunosuppression is frequently needed.

FR-PO712
Hydralazine-Induced ANCA Vasculitis Presenting with Pulmonary-Renal Syndrome
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Introduction: Hydralazine, an arterial vasodilator, is a frequently used medication for the management of hypertension and heart failure. It is generally well-tolerated and has a safe profile; however, hydralazine can induce immune-mediated complications. There are rare reports of hydralazine-induced ANCA associated vasculitis (AAV) with pulmonary manifestations, also known as hydralazine-induced pulmonary-renal syndrome (PRS). Here we report a case of hydralazine-induced alveolar hemorrhage and anti-neutrophil cytoplasmic antibodies (ANCA)-positive p- immune glomerulonephritis.

Case Description: A 75-year-old female with history of hypertension treated with hydralazine 75 mg TID for seven years, presented with five months of dyspnea on exertion, blood tinged sputum and unintentional weight loss. CT scan showed a cluster of pulmonary nodules with mediastinal lymphadenopathy. Transbronchial lung biopsy revealed alveolar hemorrhage. Serum creatinine was 2.8 mg/dl from baseline 1.0 mg/dl and urinalysis showed 2+ blood, 30-50 RBC/hpf and red blood cell casts. Urine protein to creatinine ratio was 0.7 gr/day. Given the complaint of hemoptysis, a vasculitis work-up was pursued. Work-up revealed p-ANCA > 1: 1280, elevated MPO antibodies, elevated PR-3 antibodies, and elevated inflammatory markers. Anti-histone antibodies were present. Additional immunologic and serologic work up was unremarkable. Renal biopsy was consistent with p- immune ANCA associated vasculitis with crescents. Hemoptysis for drug induced ANCA vasculitis was discontinued. She received 1 gm methylprednisolone for three days and received two doses of Rituximab followed by prednisone taper per the PEXIVAS trial. Hemoptysis resolved after treatment. She has remained off prednisone with stable renal function and minimal proteinuria.

Discussion: This case demonstrates a case of hydralazine-induced small vessel vasculitis. While immune-mediated complications have been frequently reported with the use of hydralazine, drug-induced ANCA vasculitis is rarely reported. This diagnosis should be considered in patients on hydralazine who develop pulmonary-renal syndrome. Diagnosis relies on serologic work-up and renal histopathology. Discontinuing hydralazine is the first step in treatment and this alone might be sufficient; however, more aggressive management including immunosuppression is frequently needed.

FR-PO713
Wrist Drop: An Unusual Initial Presentation of ANCA-Negative Pauuci-Immune Glomerulonephritis

Introduction: Pauuci-immune glomerulonephritis (PING) is often associated with the presence of antineutrophil cytoplasmic antibodies (ANCA). ANCA-negative PING is a rare variant, which primarily affects the kidneys, with fewer extrarenal manifestations as compared to ANCA-positive PING. Our case highlights the initial presentation of progressive neurological weakness in ANCA-negative PING.

Case Description: A 77-year-old male with medical history of hypertension and monoclonal gammopathy of undetermined significance (MGUS) presented with acute left wrist drop and progressive muscle weakness for six months. The weakness started in...
the lower extremities, and gradually involved the upper extremities. He denied numbness, tingling, rash, fever and gastrointestinal symptoms. Vital signs were stable. Neurological exam was positive for bilateral foot drop, left wrist drop, decreased sensation in all extremities, decreased deep tendon reflexes, and an unstable step gait. Laboratory tests showed elevated creatinine 1.82 mg/dL (baseline 0.7-0.9), low albumin 1.9 g/dL, and elevated CRP 7.5 mg/dL. Lumbar puncture and MRI spine was normal. Electronmicroscopy showed moderate acute-on-chronic symmetrical sensory motor polyneuropathy and left radial mononeuropathy. Subsequent nural nerve biopsy revealed marked axonal neuropathy. Patient’s kidney function continued to worsen with creatinine peaking at 2.1 g/dL. 24 hour urine collection revealed 2.5 g proteinuria, with an elevated urine albumin-creatinine ratio of 1300. Therefore, a renal biopsy was performed revealing pauci-immune proliferative and n ecrotizing glomerulonephritis with crescent formation, negative immunofluorescence with no amyloid and immune deposits. Treatment with intravenous steroids followed by rituximab was initiated, resulting in improved renal function with creatinine of 1.77 at discharge. He demonstrated further renal recovery on outpatient follow up with serum creatinine down to 1.32.

Discussion: ANCA-negative PING is a severe vasculitis with high morbidity and mortality. This is the first case to report severe neurological weakness as the initial presentation of ANCA-negative PING. It highlights the importance of considering PING in the differential diagnosis for patients presenting with neurological weakness and elevated creatinine, as prompt diagnosis and treatment can prevent adverse patient outcomes.

FR-PO714
A Case of Lupus-Like Nephritis in a Patient with a Negative Antinuclear Antibody (ANA)
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Introduction: Diagnosis of SLE cannot be made based only on kidney biopsy, however the histopathologic findings is one of the important cornerstone for the diagnosis of lupus nephritis.

Case Description: A 60-year-old male with PMH of HTN presented with worsening bilateral lower extremity edema with hematuria & heavy proteinuria for 4 months. Other symptoms significant of dyspepsia on exertion & a strong family history of kidney disease. Labs showed S. Cr 1.80 mg/dL (previous 0.86) & urine protein/creatinine >7.96 g/g. Workups including ANA, ANCAs, C3 (160), C4 (36), and ds-DNA (<1) were negative. Serum protein electrophoresis revealed two small oslgand bands with no monoclonal paraprotein. CXR, TTE & renal ultrasound were within normal limit. HBsAg, anti-HCV, RPR & HIV were also negative. A kidney biopsy revealed (50%) endocapillary proliferation, mesangial sclerosis, GBM thickening with two cellular crescents. Immunofluorescence (IF) studies showed full house positivity on immunoglobulins (IgA, IgG and IgM) & complement deposit. Electron microscopy (EM) showed subendothelial & mesangial electron dense depositions with no tubuloreticular inclusion identified. Patient was initially treated with IV methylprednisolone followed by prednisone with improvement in renal function. Patient was discharged on mycophenolate for outpatient follow up and monitoring.

Discussion: Here we presented a case of renal-limited, lupus-like nephritis in a patient with absent extrarenal manifestations & negative lupus serology. As per American Rheumatism Association (ARA) criteria, our patient did not fit into the diagnosis of SLE. However, the presence of immune-complex mediated glomerulonephritis and “full house” IF staining and EM showing subendothelial and mesangial electron dense deposits on kidney biopsy was highly suggestive of the lupus nephritis. There is a need for proper characterization of this disease pathogenesis, precise diagnostic criteria, standardization of treatment protocols & long term follow up studies to identify the true prognosis of this challenging clinical entity.

FR-PO715
Mixed Cryoglobulinemic Glomerulonephritis Triggered by Influenza Vaccination

Introduction: Mixed cryoglobulinemia is associated with viral infections such as hepatitis B or C virus, lymphoproliferative and autoimmune disorders. Influenza vaccine-induced cryoglobulinemia has been rarely reported. We present a rare case of cryoglobulinemic vasculitis following influenza vaccination with new onset renal involvement.

Case Description: A 68-year-old male with history of atrial fibrillation and chronic kidney disease presented in fall 2022 for a rash and edema of the lower extremities and thrombocytopenia after influenza vaccination. Prior, in both 2020 and 2021, he had similar presentation of rash and edema following annual influenza vaccine. His illness was self-limited, but evaluation had shown mixed cryoglobulins. A bone marrow biopsy was negative for intravascular and viral etiologies were negative. He was diagnosed with idiopathic mixed cryoglobulinemic vasculitis. For recent presentation, in addition to the edema and rash, he had thrombocytopenia and a positive rheumatoid factor (RF). Patient received intravenous immunoglobulin (IVIG) with improvement of rash and platelet count, but had thrombocytopenia; it was ruled out and was negative. He received IVIG and creatinine improved. A kidney biopsy showed endocapillary proliferative glomerulonephritis with organized deposits, consistent with mixed-type cryoglobulinemic glomerulonephritis treated with rituximab infusions, resulting in improvement in cryoglobulins and complement levels and renal function, with creatinine at 1.46 mg/dL in May 2023. Of note, plasmapheresis was only for rash from IVIG.

Discussion: Our patient had a favorable outcome after rituximab, IVIG, and plasmapheresis for diagnosis of mixed cryoglobulinemia triggered by the influenza vaccine, noting a reduction of cryoglobulins, improved renal function, and resolution of rash. Cryoglobulins can form as an immune response to infections though it is unclear why cryoglobulins are produced as a response to a vaccination. Understanding this novel association and interaction is important for prompt diagnosis and management.

FR-PO716
Poly cryoglobulinaemia and IgA Nephropathy: An Interesting Association

Introduction: IgA nephropathy (IgAN) is often associated with chronic kidney disease (CKD) which usually presents with anemia. We present a case IgAN-associated poly cryoglobulinaemia.

Case Description: A 46-year-old patient with known hypertension (HTN) was evaluated for progressive CKD. Serum creatinine (sCr) increased from 1.2 to 1.7 mg/dL over 5-6 years. Urinalysis showed microscopic hematuria and proteinuria of 1g/g of creatinine. A kidney biopsy showed IgAN with an Oxford classification score of M1H0S1T1-C0. He was treated with RAAS blockade and a 6 months course of steroid followed by dapagliflozin and currently with stable sCr and proteinuria of 0.13 g/g. In conjunction to IgAN, poly cryoglobulinaemia was noted for several years with Hematocrit (Ht) levels between 50-60%. The most recent Hemoglobin was 18.6 g/dL with normal platelets, white blood cell count and differential showing no evidence of sickled sized kidneys and no splenomegaly or hepatomegaly. Poly cryoglobulinaemia evaluation was unrevealing. The patient had no smoking history, and sleep study was negative. Genetic testing for Janus kinase 2 (JAK2) mutation as well as other poly cryoglobulinaemia-associated mutations was negative, excluding Polycythemia Vera. The final diagnosis from hematology was poly cryoglobulinaemia associated with IgAN with a recommendation for observation.

Discussion: The 4-hit hypothesis for IgAN pathogenesis involves galactose-deficient IgA1 targeting the hinge region, being recognized by IgG autoantibodies, leading to plasmacytoma in which no further cell maturation occurs. In vitro studies have shown that increased expression of Polymeric IgA (pIgA) and IgA1 complexes can stimulate red blood cell formation in some patients. In vitro study showed that the serum of patients with IgAN and unexplained poly cryoglobulinaemia increased the number of erythroid burst forming unit (BFU-E)-derived colonies from human progenitor CD34+ cells. Removal of IgA from IgAN-Poly cryoglobulinaemia patients normalized the number of colonies. These studies have shown that increased expression of Polymeric IgA (pIgA) was associated with increased hemoglobin levels without raising EPO levels likely by sensitizing cells to Epo through activating the transferrin receptor 1 (TIR1). We report an interesting association of IgAN and poly cryoglobulinaemia that is supported by in vitro findings of polygenic IgA1 stimulating RBC formation. Evaluation for other etiologies of poly cryoglobulinaemia needs to be done before considering the IgAN as the plausible etiology of poly cryoglobulinaemia.

FR-PO717
Outcomes from Acute Co-Infection of HIV and Hepatitis B Infection Nephritic Syndrome
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Introduction: We present a unique case of a previously untreated combined HIV and HBV co-infection presenting as HD requiring AKI with Nephritic syndrome and significant hyperparathyroidism.

Case Description: 40-year-old AA male with no past history who presented with anasarca, 3+ proteinuria and uremic symptoms of nausea/vomiting for 1-2 weeks. Labs significant for BUN/Cr 365.5:1, Alb =1.5, Urine Pro>500, Hgb 5.8, 56, CD4, 124, CD141, 141, and UPEP negative. Hep B and HIV viral quantitative PCR were 7.7million virions and 280,000. Negative for other serologies. Biopsy showed HIVAN with FSGS and mesangial lobular inclusion changes, MPGN, diffuse interstitial lymphocytosis syndrome (DILS) with dominant CDS cells along with lymphoplasmacytic infiltration. He needed emergent HD for AKIN Stage 4A. Serum urate and alkaline phosphatases were normal without renal response until he was started on a course of steroids, serendipitously for high intracranial pressures from Acute Toxoplasmosis on his second admission.

Histopathological images of a kidney biopsy
Discussion: DILS is a rare multisystemic syndrome characterized by CD8+ lymphocytes associated with a CD4+ T-cell infiltration of multiple organs, usually seen in uncontrolled or untreated viral infections but can also manifest itself independently of CD4+ T-cell counts. The rarity of DILS cases explains the lack of studies describing treatment options but the consensus is that the primary treatment line should be HAART. Specifically, for the renal condition, several case reports suggest the use of corticosteroid therapy. This is congruent with other studies showing initial response may be dramatic with corticosteroids adjunct to ART +/- AECI/ARB, even reversing dialysis dependence, but transient. Comorbid kidney disease in the setting of HIV/HBV is challenging to manage given that it is thought to be due active hepatitis C infection is appropriate antiviral agent in coinfection, tenofovir disoproxil fumarate (TDF), is potentially nephrotoxic. However, in immune-tolerant HBV, steroids could reactivate severe infection. In the current era of retroviral availability, it is extremely rare to see a case of classical HIVAN and DILS. Our case is unique as the patient had 2 viral infections and lymphocyte pattern of CD8 lineage that coincidently responded to high-dose steroids which were given for other reasons.

FR-PO718
Lactobacillus Endocarditis-Associated Crescentic Glomerulonephritis
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Introduction: Infection-related glomerulonephritis (IRGN) encompasses a wide range of clinical and pathologic manifestations. Up to 50% of patients can develop persistent kidney impairment and 1/3 can progress to kidney failure. (Medjeral-Thomas et al. Clin J Am Soc Nephrol. 2014.) Staphylococcus and Streptococcus are the most common pathogens isolated however IRGN in the setting of lactobacillus is considered rare.

Case Description: A 79-year-old male with history significant for heart failure with preserved ejection fraction, bioprosthetic AVR, and chronic kidney disease (CKD) IIIb had an episode of sepsis from a presumed urinary infection. He was noted. His course was complicated by acute on chronic kidney injury requiring dialysis. Workup included a 24-hour urine collection showing 2.4g of protein and 1.3g of albumin, normal serum free light chain ratio, normal serum protein electrophoresis, and normal C3 and C4 levels. Kidney biopsy performed revealed necrotizing and crescentic glomerulonephritis with immunofluorescence positive for IgG, IgM and C3; consistent with IRGN. Patient was started on ampicillin and a steroid course was proposed. However, the patient and his family declined given risk of exacerbation of infection and decision was made to pursue conservative management with antibiotics and dialysis which the patient is still on.

Discussion: The pathogenesis of IRGN involves glomerular immune complex deposition along with classical complement pathway activation. This is frequently associated with a reduction in serum C3 and normal C4 levels, but as illustrated in our case C3 levels can be normal. The mainstay of treatment is withdrawal of enticing agent (probiotics), treatment of the underlying infection and supportive care. The utilization of systemic steroids in these patients is highly controversial given no evidence of efficacy in IRGN patients at low risk for progression (Arivazhagan et al. Kidney Int Reports. 2022). This can be considered in specific cases, such as patients with diffuse crescentic and rapidly progressive GN.

FR-PO719
Hepatitis C Negative Type II Cryoglobulinemic Glomerulonephritis
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Introduction: Mixed cryoglobulinemia typically follows a chronic, smoldering course. Here we present a case of rapidly progressive mixed cryoglobulinemic glomerulonephritis (GN) in a hepatitis C negative patient.

Case Description: A 67-year-old female with a history of chronic kidney disease stage III and ophthalmologic Sjogren’s syndrome presented to the emergency department for labile blood pressures. Labs were notable for serum creatinine 1.49 mg/dL, positive anti SS-A, anti-B. C3 28 (low), C4 < 3, and negative hepatitis panel. Urine protein: 1+ IgG/IgA/IgM/C1q, 3+ C3, and 3+ kappa & lambda. Urinalysis revealed hematuria (30 RBC’s and RBC casts), proteinuria (300mg/dL), small leukocyte esterase, and leukocytosis (WBC 16.8k). Total protein and albumin were low. Urinary revealed hematuria (30 RBC’s and RBC casts), proteinuria (300mg/dL), small leukocyte esterase, 41 WBC’s and a urine protein to creatinine ratio of 4.4mg/g. Blood cultures were positive for MRSA, and TEE revealed TV endocarditis. Renal biopsy testing revealed a chronic, active hepatitis C infection and a cleared hepatitis B infection, HIV testing was negative. He underwent TV thrombectomy for vegetation removal and was initiated on antibiotics.

Discussion: The biopsy was consistent with a necrotizing, crescentic glomerulonephritis with mild interstitial fibrosis. The atypical P-ANCA was positive with a 1:40 titer, complements C3 and C4 were low. Renal biopsy was performed, and light microscopy revealed 61% crescents with focal segmental necrosis, and mesangial expansion. IF microscopy revealed mesangial staining of 1+ IgG/IgA/IgM/C1q, 3+ C3, and 3+ kappa & lambda.

FR-PO720
Infection-Related Rapidly Progressive Crescentic Glomerulonephritis
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Introduction: Rapidly progressive crescentic glomerulonephritis (RPGN) is characterized by progressive loss of renal function. Most cases are diagnosed with a renal biopsy. Here we examine a subtype of RPGN in the setting of IV drug abuse, hepatitis C, and tricuspid valve (TV) MRSA endocarditis.

Case Description: A 32-year-old male with a PMHx significant for IVDU presented with fever, chills, low extremity edema, and a dark discoloration to his urine. The patient had a new acute kidney injury (AKI) (Cr 1.66, BUN 35), anemia (Hgb 11.2), and leukocytosis (WBC 16.8k). Total protein and albumin were low. Urinalysis revealed hematuria (30 RBC’s and RBC casts), proteinuria (300mg/dL), small leukocyte esterase, 41 WBC’s and a urine protein to creatinine ratio of 4.4mg/g. Blood cultures were positive for MRSA, and TEE revealed TV endocarditis. Renal biopsy testing revealed a chronic, active hepatitis C infection and a cleared hepatitis B infection, HIV testing was negative. He underwent TV thrombectomy for vegetation removal and was initiated on antibiotics.

Discussion: The biopsy was consistent with a necrotizing, crescentic glomerulonephritis with mild interstitial fibrosis. The atypical P-ANCA was positive with a 1:40 titer, complements C3 and C4 were low. Renal biopsy was performed, and light microscopy revealed 61% crescents with focal segmental necrosis, and mesangial expansion. IF microscopy revealed mesangial staining of 1+ IgG/IgA/IgM/C1q, 3+ C3, and 3+ kappa & lambda.

Discussion: The biopsy was consistent with a necrotizing, crescentic glomerulonephritis with mild interstitial fibrosis. The atypical P-ANCA seropositivity was thought to be due active hepatitis C infection. In the context of MRSA bacteremia, active hepatitis C infection, and chronically inactive hepatitis B infection with rapid progression of renal injury, the patient was diagnosed with an infection related RPGN. Treatment was directed at the underlying cause of infection, however due to rapid progression of renal injury, and degree of proteinuria, he was started on a steroid taper. The patient will be treated for hepatitis C in the outpatient setting. In the context of an active infection and clinical evidence of RPGN, a renal biopsy should be performed for a definitive diagnosis. While treating the underlying infection is appropriate, immunosuppression should be considered in the right clinical context, in this case, rapidly progressive renal failure.
FR-PO721

Looks Can Be Deceiving: A Case of C3 Glomerulopathy


Introduction: Complement 3 glomerulopathy (C3G) is caused by an acquired or genetic dysregulation of the complement alternative pathway. It can be further classified into dense deposit disease (DDD) or C3 glomerulonephritis (C3GN). We present a case of a middle-aged male who presented with suspected infection-related glomerulonephritis (IRGN). However, his renal functions did not significantly improve with antibiotics. Renal biopsy was performed and he was diagnosed with C3GN.

Case Description: A 55-year-old male with past medical history of untreated hepatitis C and former intravenous drug use presented for evaluation of oliguric acute kidney injury, hematuria, and rash in the setting of MSSA empyema and chest wall osteomyelitis. He was septic and had acute renal failure requiring broad spectrum antibiotics and renal replacement therapy. Further GN work up was significant for proteinuria 11g/day, elevated Anti-DNASE, cryoglobulins 1.0%, undetectable C3, low C4 and M spike on SPEP. Patient was treated with prolonged course of antibiotics for presumed endocarditis. Differential included IRGN but due to multiple abnormal serological markers a renal biopsy was performed which revealed C3GN. He was started on steroid taper and mycophenolate mofetil with rapid improvement in edema and renal functions. Dialysis was discontinued and patient was discharged on immunosuppressive therapy.

Discussion: C3G is a difficult diagnosis and may often require immunosuppression (IS). Our patient above was requiring routine dialysis until the initiation of IS and was able to stop dialysis shortly after. Patients who are suspected to have IRGN that are not improving with antibiotics should have C3GN included in the differential. Biopsy is warranted in these patients and IS may help with improving outcomes.

FR-PO722

Mesangial Proliferative Glomerulonephritis and Neurocysticercosis: A Novel Association

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Introduction: The etiology of nephrotic syndrome is diverse, and parasitic infections typically do not cause this condition. Here, we present a case of nephrotic syndrome associated with parasitic infections.

Case Description: A 21-year-old man with a habit of eating raw fish presented with a 6-week history of bilateral limb edema, back pain and nausea. Nephrotic syndrome with acute kidney injury was diagnosed after finding a creatinine of 163 μmol/L, albumin of 19.7 g/L, and proteinuria (9.4 g/day). Peripheral blood eosinophilia was noted (5.78 x10³ cells/L). A renal biopsy revealed mesangial-proliferative glomerulonephritis and eosinophils within the renal interstitium. Serum was strongly positive for anti-Taenia solium antibodies (by enzyme linked immunosorbent assay). Cranial magnetic resonance imaging revealed a 9.8 x 12.8mm mass in the fourth ventricle. A specimen of cerebrospinal fluid was also weakly positive for anti-Taenia solium antibodies. On the basis of these findings, a diagnosis of neurocysticercosis was made. The patient did not consent to surgical exploration and removal of cyst in the fourth ventricle. Medical therapy was commenced with albendazole and glucocorticoids. Two months later, 24-hour urinary protein excretion had reduced to 0.8 g/day, and the blood eosinophil level was normal. At a follow-up visit 1 year later, the patient’s renal recovery was found to be complete. MRI of the brain revealed no change in the fourth ventricular cyst and he remained asymptomatic.

Discussion: This is the first reported case of mesangial-proliferative glomerulonephritis with eosinophilic infiltrate associated with cysticercosis. We hypothesize that this patient’s infection resulted from cross-contamination in the preparation of raw seafood.

Figure 1: Image a is from a renal biopsy, the arrow indicates eosinophils. Image b is from cranial MRI revealed a mass in the fourth ventricle.

FR-PO723

Anti-Tumor Necrosis Factor Antibody-Induced Lupus-Like Glomerulonephritis


Introduction: Anti-TNF agents can lead to expression of autoantibodies resulting in symptoms similar to systemic lupus erythematosus (SLE). This autoimmune expansion can be reversible with the discontinuation of the offending agent. We present a case of a 35-year-old female patient with drug-induced lupus nephritis caused by adalimumab.

Case Description: A 35-year-old female was evaluated for worsening renal function and microscopic hematuria. Her medical history was significant for RA on weekly adalimumab since 2011. Her serum creatinine increased from 0.8-1.7 mg/dL over a period of 2 years. Urine sediment demonstrated dysmorphic RBC’s. Urine protein to creatinine ratio (UPCR) was 3.7 g/g. Elevated protease 3 antibody, and anti-double stranded DNA antibody. She underwent a renal biopsy to determine the etiology of her worsening renal function. The biopsy revealed immune complex-mediated glomerulonephritis with a focal proliferative and membranoproliferative patterns of injury, as well as a background of 40-50% chronicity. Her findings were compatible with a lupus-like immune complex-mediated glomerulonephropathy, and were believed to be secondary to adalimumab. Adalimumab was discontinued and she was started on prednisone 1 mg/kg. Her most recent creatinine downtrended to 1.5 mg/dL, with UPCR 1.5 g/g.

Discussion: Anti-TNF drug induced lupus nephritis mechanism is unknown, is believed that this agents promotes anti-dsDNA antibody by inducing cellular apoptosis. Adalimumab has been associated with focal and diffuse membranoproliferative glomerulonephritis similar to our biopsy findings. In our case, the patient had significant renal function improvement after completing four weeks of prednisone therapy.
FR-PO724

Double Insult: Secondary IgA and Anticoagulant-Related Nephropathy
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Introduction: Acute kidney injury represents the most frequent nephrology consultation. In select cases, AKI is the result of series of cumulating insults overlapping previously undiagnosed conditions. These usually carry a significant negative impact towards renal recovery.

Case Description: This is the case of a 62-year-old male with a past medical history of peripheral arterial disease, s/p right below the knee amputation, severe ischemic cardiomyopathy s/p intra-cardiac device, atrial fibrillation on apixaban, diabetes mellitus and hypertension, who was admitted for cellulitis in the amputated stump. In addition to cellulitis, the patient reported a non-blanching petechial rash on the left arm which was present for several months. Hospitalization was complicated by AKI;and initial workup revealed a history of daily NSAID use and elevated vancomycin levels with granular casts noted on urine microscopy. An initial diagnosis on acute tubular necrosis due to intrinsic etiology was suspected. However, renal function continued to worsen, and given the patient’s rash, we suspected for acute interstitial nephritis or vasculitis. Skin biopsy revealed leukocytoclastic vasculitis that was negative for IgA deposition. Further immunologic workup was negative. No peripheral eosinophilia was observed, and blood cultures were positive for Staphylococcus Aureus. A renal biopsy was performed, which showed IgA-dominant immune complex deposition, likely secondary to infection, and numerous cortical and medullary RBC casts out of proportion to the degree of glomerular injury, concern for anticoagulant associated nephropathy. Moderate interstitial fibrosis and tubular atrophy with no crescents was described. Due to active infection, steroids were not recommended, and the patient’s anticoagulation was placed on hold. Unfortunately, due to significant renal injury the patient was initiated on hemodialysis and subsequently, did not show signs of renal recovery.

Discussion: Our patient has dialysis-dependent AKI complicated by secondary IgA nephropathy associated with infection along with anticoagulant-associated nephropathy, related to eliquis. Comorbidities such as diabetes, hypertension, and advanced age can negatively impact the response to therapy. In our case, the patient was also diagnosed with anticoagulant-associated nephropathy which further decreased his chances of recovery.

FR-PO726

Molecular Similarity Between Chronic Active Antibody-Mediated Rejection (CA-ABMR) and Acute T Cell-Mediated Rejection (TCMR) of Human Kidney Allografts
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Background: CA-ABMR, even without concomitant histological TCMR, is characterized by an increased abundance of NK Cells and T cells. We RNA-sequenced kidney allograft biopsies to test the hypothesis that CA-ABMR, but not active-ABMR, is exemplified by the overexpression of key gene sets that are similar to TCMR.

Methods: We did RNA-seq of 57 biopsies from 57 kidney transplant recipients; 39orchestraplas (15 CA-ABMR, 17 TCMR, & 7 active-ABMR), and 18 surveillance biopsies (no rejection [NR]). All biopsies were evaluated independently by two transplant pathologists. We isolated total RNA from stored biopsy samples, prepared cDNA libraries, and sequenced pooled libraries on an Illumina sequencer. After appropriate quality checks, we used standard bioinformatic tools for data analysis.

Results: There were 1425 genes increased and 29 reduced between CA-ABMR and NR biopsies (FC>2 & P-FDR<0.05); 1829 were increased and 164 were reduced between TCMR and NR biopsies. T and NK cells were the top cell types and pathways of CA-ABMR and TCMR biopsies yielded only one gene, MARCHF4, that was significantly different. Cellular deconvolution revealed a similar proportion of immune cells in the three rejection categories; principal component analysis of deconvoluted immune cell transcriptionomes separated CA-ABMR and TCMR from active-ABMR and NR biopsies (Fig.2).

Conclusions: CA-ABMR exhibits an immune transcriptome profile that resembles TCMR biopsies. Our findings, besides advancing our knowledge of the pathogenesis of CA-ABMR, provide a compelling argument for the pharmacological targeting of T cells and NK cells in CA-ABMR.

Funding: Other NIH Support - NIAID
proteins upregulated in ABMR (Figure 1). pathDIP analysis showed that upregulated proteins mapped significantly to pathways involving the immune system (glomeruli, q=7.6e-8; tubulointerstitium, q=3.8e-11), antigen processing (glomeruli, q=5.6e-11) and integrin activity (tubulointerstitium, q=1.0e-8), while downregulated proteins mapped to tight junction regulation (glomeruli, q=1.9e-5) and cellular metabolism (tubulointerstitium, q=1.8e-9).

Conclusions: Our preliminary results suggest that ABMR in DSA+ patients is strongly linked to dysregulated immune and cellular responses in multiple kidney tissues. These findings will ultimately help us identify novel targets for the development of therapeutics for kidney transplant recipients.

Funding: Government Support - Non-U.S.

FR-PO728
Role of Urine Exosomal Proteome for Identifying Potential Biomarkers to Predict Renal Allograft Survival
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Background: Urine contains proteins bound to extracellular vesicles (exosomes) which are secreted by the cells into the urine as a result of renal insult. We propose to identify exosomal protein markers in urine to predict allograft survival. Molecule-bearing urinary exosome is altered in various kidney diseases. Exosomal molecules such as Aquaporins (AQPs) can be used as potential biomarkers.

Methods: Post renal transplant patient urine samples at 6th/7th day were collected using standard protocol. Urine samples were collected at 3, 6, 12 months post transplant and at the time of graft dysfunction. Further, characterization of exosomal proteins was done through Flow cytometry, Western blotting and NTA (Nano-particle tracking analysis). Exosomal proteome was analysed through LC-MS.

Results: Samples were collected from 13 renal allograft patients and 14 healthy controls. There was decreased abundance of urinary exosomal aquaporin-1 observed in allograft transplant recipients in the immediate post transplant and in those with allograft dysfunction. Molecule-bearing urinary exosome was altered in various kidney diseases. Exosomal molecules such as Aquaporins (AQPs) can be used as potential biomarkers.

Conclusions: Our preliminary results suggest that ABMR in DSA+ patients is strongly linked to dysregulated immune and cellular responses in multiple kidney tissues. These findings will ultimately help us identify novel targets for the development of therapeutics for kidney transplant recipients.

Funding: Government Support - Non-U.S.

FR-PO729
GADD45A and GADD45B as Novel Biomarkers Associated with Chromatin Regulators in Renal Ischemia-Reperfusion Injury and Their Correlation with Immune Cells
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Background: The role of chromatin regulators (CRs) in the pathogenesis of renal ischemia-reperfusion injury (IRI) remains unclear.

Methods: We performed a bioinformatic analysis on the differentially expressed genes of CRs in renal IRI patients using machine learning models. The hub CRs identified were used to develop a risk prediction model for renal IRI, and their expressions were validated using a murine renal IRI model. We also examined the relationships between hub CRs and infiltrating immune cells in renal IRI.

Results: GADD45A and GADD45B were upregulated in renal IRI. GADD45A and GADD45B were chosen to develop a renal IRI risk prediction model and showed good performance. GADD45A and GADD45B showed correlations with plasmacytoid dendritic cells (pDCs) in infiltrating immune cells analysis.

Conclusions: Dysregulation of GADD45A and GADD45B is related to renal IRI and the infiltration of pDCs.

Funding: Government Support - Non-U.S.
FR-PO730

Renal Denervation Is Protective Against the Development of CKD in a Rat Model of Tacrolimus Nephrotoxicity


Background: Tacrolimus is the most widely used immune suppressant medication after solid-organ transplant, however it is associated with significant morbidity due to nephrotoxicity and the development of chronic kidney disease. It has recently been appreciated that recipients of transplanted kidneys, which lack intact renal nerves, have a lower incidence of tacrolimus-induced nephrotoxicity. Here we present data demonstrating that denervated kidneys are protected from the development of tacrolimus nephrotoxicity in rats.

Methods: Male and female Sprague-Dawley rats (n=6) underwent either total renal denervation (TRDN) or sham denervation and were subsequently treated with either 2 mg/kg tacrolimus for 14 days or the equivalent dose of vehicle. At the end of treatment BUN was assessed as a marker of renal function. Histology was performed to assess renal fibrosis and glomerulosclerosis. RNA was extracted from the cortex and medulla, and then transcriptome was assessed.

Results: BUN was significantly lower in TRDN animals compared to sham (26 vs 38 mg/dl, p < 0.01). Additionally, medullary fibrosis was decreased in denervated rats. RNA-sequencing studies to further investigate the mechanism behind this protection are ongoing.

Conclusions: These findings present an exciting new avenue for the use of renal denervation – if confirmed these would provide the foundation for prophylactic renal denervation in non-renal transplant patients requiring tacrolimus.

Funding: Other NIH Support - R01 HL 116476, T32 HL 144472
FR-PO732
Cellular Responses to BK Polymavirus Infection in Transplanted Kidneys
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Background: BK virus (BKV) infection remains problematic following kidney transplantation. Despite delineation of tubular responses in cell culture, the effect of an immune system on the cell-specific response in vivo to BKV is less well-understood.

Methods: Single-cell RNA sequencing of kidney biopsies (12 surveillance, 5 peak viremia, and 9 resolving viremia) from the Michigan Human Kidney Transplant Transscriptomic Atlas study were analyzed for cell type-specific transcriptomic responses to viremia and viral nephropathy and compared with healthy surveillance biopsies and BKV-infected cells in culture.

Results: BKV transcripts were found in tubular cells and immune cells, confirmed in lymphoid clusters by VPI immunohistochemistry. Cytokine signaling, cell-cycle regulation, translation, and wound healing were activated in BKV-infected tubular cells but not in tubules of viremic patients without nephropathy where stress-signaling and immune response predominated. During peak viremia there was an expansion of adaptive but not innate immune response. BKV-infected tubules showed increased cytokine, interferon γ, and tumor necrosis factor (TNF) signaling in humans. In contrast, TNF signaling was reduced in cell cultures.

Conclusions: Differential transcriptional responses to BKV infection in vivo and in vitro highlight the complex cellular and immune crosstalk not captured in 2D models. These findings also point towards exploration of anti-TNF therapies for BKV.

Funding: NIDDK Support

FR-PO733
Cyclosporine Distinctly Damages Proximal Tubules, Tacrolimus the Filtration Barrier in Calcineurin Inhibitor Nephrotoxicity

Background: Calcineurin inhibitors (CNI) are the backbone for immunosuppression after solid organ transplantation. Although successful in preventing kidney transplant rejection, their nephrotoxic side affects notably contribute to allograft injury despite attempts to optimize their application, often with additional medications. Complex renal parenchymal damage occurs for cyclosporine A (CsA) as well as for the currently favoured tacrolimus (Tac). We asked whether CsA and Tac exert distinct damage patterns during onset stages CNI nephropathy. We combined multiomics analysis with histopathology from rat kidney exposed to continuous CNI delivery.

Methods: Single-cell RNA sequencing of kidney biopsies (12 surveillance, 5 peak viremia, and 9 resolving viremia) from the Michigan Human Kidney Transplant Transscriptomic Atlas study were analyzed for cell type-specific transcriptomic responses to viremia and viral nephropathy and compared with healthy surveillance biopsies and BKV-infected cells in culture.

Results: BKV transcripts were found in tubular cells and immune cells, confirmed in lymphoid clusters by VPI immunohistochemistry. Cytokine signaling, cell-cycle regulation, translation, and wound healing were activated in BKV-infected tubular cells but not in tubules of viremic patients without nephropathy where stress-signaling and immune response predominated. During peak viremia there was an expansion of adaptive but not innate immune response. BKV-infected tubules showed increased cytokine, interferon γ, and tumor necrosis factor (TNF) signaling in humans. In contrast, TNF signaling was reduced in cell cultures.

Conclusions: Differential transcriptional responses to BKV infection in vivo and in vitro highlight the complex cellular and immune crosstalk not captured in 2D models. These findings also point towards exploration of anti-TNF therapies for BKV.

Funding: NIDDK Support

FR-PO734
Human Kidneys House Tissue-Resident B Cells with a Distinct Anatomical Location and Phenotype that Changes with Age
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Background: B cells play a central role in humoral immunity but have also antibody-independent functions, important for generating local immune responses and tolerance. Kidneys are the most commonly transplanted solid organ worldwide but whether they harbor B cells in homeostasis and how they change with donor age has received little attention.

Methods: We examined the number, phenotype and clonality of B cells in human kidneys that were perfused to remove circulating cells, and in matched splenic tissue obtained from the same transplant donor (N=19, median age 56 years: range: 18–80). Suspensions from homogenized organs were analyzed using a 35-marker mass cytometry panel and single-cell RNA sequencing (Figure A). B cells were also sorted for bulk BCR-sequencing.

Results: The frequency of B cells within kidney CD45+ cells was lower than in spleen (8.8% vs. 26%, P<0.005). The renal cortex harbored ten times more B cells per gram of tissue than medulla. In contrast to spleen, B cell count and B:T cell ratio in renal cortex significantly increased with age (Figure B). Kidney B cells were enriched for non-naïve (CD27+ IgD and double-negative) subsets with innate-like characteristics when compared to spleen or younger donors. BCR analysis showed CD3R3 repertoire differences between kidney and spleen, suggesting a specific antigenic exposure, but also clonotypes sharing between matched organs and across donors.

Conclusions: Our study shows that under homeostatic conditions, human kidneys harbor both antigen-experienced and innate-like B cells, mirroring studies of murine tissue-resident T cells. These cells expanded with age and showed a specific anatomical location to the outer part of the kidney, an area specialized for filtration of blood. These kidney B cells may play a role in local immune defense or contribute to immunopathology (autoimmunity, organ rejection), and further studies on diseased tissues and murine models are underway.

Funding: NIDDK Support

FR-PO735
Cell-Specific Expression of Class II HLA Genes in Rejecting Kidney Transplant Biopsies by Single-Cell RNAseq
Andrew F. Malone, Aidan Leckie-Harre, Venkatrao Nunna, Benjamin D. Humphreys, Chang Liu, Washington University in St Louis School of Medicine, St Louis, MO.

Background: Antibody-mediated rejection (AMR) remains one of the major causes of allograft failure. Anti-HLA antibody binding to endothelial cells is thought to be a central event driving AMR. Expression of both alpha and beta chains encoded by class II HLA genes is required for complete HLA class II protein expression on the cell surface.

Methods: We determined the expression of HLA-DR and HLA-DQ genes from single cells from two datasets of human kidney transplant biopsies. The proportion of cells expressing both alpha and beta chains for HLA-DR (DRa/DRb1, or DRab hereafter) and for HLA-DQ (DQA1/DQB1 or DQab hereafter) was determined across all rejection phenotypes. The gene expression pattern in endothelial cells with DRab or DQab was compared to that of endothelial cells not expressing DRab or DQab.

Results: We analyzed two datasets for this study: A) 81139 cells from 5 biopsies (AMR or no-rejection) published previously, and B) new data of 31,203 cells from 11 biopsies (no-rejection, AMR, TCMR or mixed). In dataset A, DQab expression was restricted to endothelial cells (EC) and immune cells with little expression in other cells of the kidney. DRab was widely expressed in all cell types. Similar profiles were found in dataset B (fig1a+b). In EC, PLAI, a molecular marker for AMR, showed a significantly increased expression in EC positive for DQab or DRab when compared to EC negative for DQab or DRab (fig1c+d).

Conclusions: Cell specific class II HLA gene expression can be determined from single-cell RNAseq data. Expression of DQab/DRab in ECs is associated with molecular markers for AMR, which may provide diagnostic and mechanistic insight for AMR.

Funding: NIDDK Support
Sirolimus Toxicity Manifested with Fanconi Syndrome in a Kidney Transplant Patient
Christopher F. Middleton, Megha R. Joshi, Walter Reed National Military Medical Center, Bethesda, MD.

Introduction: Sirolimus, a mechanistic target of rapamycin (mTOR) inhibitor, decreases antigen and cytokine stimulated T-lymphocyte activation and proliferation, and inhibits antibody production. It has been shown to prolong kidney allograft survival, and reverse acute rejection. In transplant patients with recurrent basal and squamous cell carcinomas, sirolimus is frequently used to prevent or reduce recurrence of these malignancies. This case highlights a rare but important risk of the drug and how it can be managed.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
therapy. Within the following two weeks, the patient's urine output and Cr recovered to baseline status and she was continued on anticoagulation thereafter.

Discussion: RVT in new transplants has a high risk of poor outcomes. Events usually occur within the first two weeks and can present with worsening renal function, oliguria, hematuria, and/or abdominal pain. Early detection with Doppler ultrasound is key to evaluating for potential RVT and initiating further diagnostic actions or interventions to prevent complications. Interventions may include direct surgical thrombectomy, endovascular thrombectomy or thrombolytic therapy, although studies are lacking in identifying an optimal first-line intervention. Having a high suspicion for RVT and acting quickly is vital in avoiding critical complications in new allografts.

FR-PO740
Transplant Renal Vein Thrombosis
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Introduction: Transplant renal vein thrombosis (TRVT) is a dire complication of kidney transplantation and can lead to graft failure. This case highlights the importance of awareness of this infrequent complication and the importance of reviewing donor anatomy to assist in timely diagnosis.

Case Description: A 40-year-old male with ESKD due to IgAN diagnosed at 17 was on peritoneal dialysis since age 36 and underwent a deceased donor kidney transplant (KT). The KDPI was 12%, calculated PRA were 0%, and EPTS was 13%. The donor renal artery was anastomosed to the recipient’s external iliac artery. As the right renal vein (RV) is shorter an IVC extension graft is utilized for anastomosis. Despite the atypical incision on the donor IVC, the surgeon achieved a good extension for anastomosis to the recipient’s external iliac vein. The kidney perfused well with immediate graft function. Immunosuppression induction was with anti-thymocyte globulin and steroids and maintenance with MMF and tacrolimus. Creatinine improved to 1.8 mg/dl by POD4 (9.4 mg/dl preoperatively). He was re-admitted on POD 8 with hematuria, abdominal pain & reduced urine output. Creatinine was 2.4 mg/dl. CT scan showed a hypoattenuating KT. Ultrasound (fig A) showed diastolic reversal of arterial flow and absence of RV doppler signal. Venography showed thrombosis of the transplant RV up to the anastomosis. Rheolytic thrombectomy of the transplanted RV, balloon angioplasty (Fig B), and stent placement of the juxta-anastomotic stenosis was done with fast outflow (Fig C) seen from the allograft. The allograft was salvaged & urine output is > 1L/day, but he is dialysis dependent. The venous stent thrombosed 2 months post-transplant requiring thrombectomy and balloon angioplasty. Currently, the allograft outcome remains guarded.

Discussion: AKI in transplant patients has a broad differential, and there should be a high suspicion index for TRVT. Knowing donor anatomy and the operative course aids in rapid diagnosis. Despite prompt therapy, TRVT causes profound ischemic damage leading to allograft loss and nephrectomy.

FR-PO741
Renal Allograft Lymphangiectasia After Kidney Transplantation
Fun Jeong Ko, Byung Ha Chung, Chul Woo Yang. The Catholic University of Korea, Seoul, Republic of Korea.

Introduction: Renal lymphangiectasia is a rare condition setting of transplant kidney. We report a case of renal lymphangiectasia after kidney transplantation

Case Description: A 43-year-old man received living donor kidney transplantation due to IgA nephropathy. 14 years after transplantation, he presented with abdominal distension, and dyspnea. Serum creatinine level was elevated to 1.6mg/dl. Computed tomography (CT) showed multi-septated cystic lesions around the graft kidney with a large amount of ascites. Ascites profile showed transudative, non-chylous, suggesting lymphatic fluid. There was no evidence for infectious or malignant disease. At first, tacrolimus was switched to sirolimus for anti-lymphangiogenic effect, consequently the amount of ascites was significantly reduced. However, 3 weeks after, large amount of ascites were recurred. Surgical approach with explore laparotomy, argon coagulation and helixor injection through Hemo-vac drain were performed. Also, lymphatics embolization was performed using lipiodol. Nevertheless, massive ascites recurred just after 1 week from procedures, therefore, allograft nephrectomy was inevitable.

Discussion: Post-transplant renal lymphangiectasia is a rare but critical complication of allografts, still poorly understood. However, once it happens, active treatment is required.

FR-PO742
Unrecognized Ureteral Injury After Attempted Hysterectomy in Transplant Patients
Amber Anwar, Saed Shawar, Kareem Eid. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Although frequently overlooked, ureteral injuries are well-documented complications following gynecologic surgeries, potentially causing acute kidney injury and failure. To mitigate these undesirable outcomes, involvement of a multidisciplinary team, including transplant surgeons, is highly recommended in complex patients. We present a unique case of a simultaneous pancreas-kidney transplant patient with an unrecognized ureteral injury during an attempted hysterectomy.

Case Description: A 42-year-old woman with End-Stage Renal Disease due to Type 1 Diabetes Mellitus and status post simultaneous kidney and pancreas transplant in 05/2021. Induced with Atelemazumab and Solnemodur and maintained on Tacrolimus, Mycophenolate Moftel, and Prednisone, with creatinine range 0.8-1mg/dl, alongside normal amylase and lipase levels. In 07/2022, the patient attempted a laparoscopic hysterectomy at a local hospital for unresolved menorrhagia. However, the surgery was abandoned due to extensive intraabdominal adhesions, with partial adhesiolysis performed before closure. Following discharge on the same day, she presented with acute abdominal pain, anuria and rise in creatinine 11mg/dl from 0.93mg/dl. CT scan revealed an edematous transplant kidney with hydrourerteronephrosis and intra-abdominal and pelvic ascites. The Transferred to Vanderbilt University Medical Center, where ultrasound confirmed hydrourerteronephrosis and a discontinuity of the ureter with the bladder. In addition, CT cystogram showed lack of opacification of the reimпланanted uter, concerning for ureteral injury. An urgent laparotomy was performed by a multidisciplinary team of urologists and renal transplant surgeons, resulting in drainage of three liters of urine from the abdominal cavity and the identification of a transected ureter above the urinary bladder. Assisted cystourethroscopy was utilized to repair and reimplant the ureter to the urinary bladder, resulting in the resumption of urine output and a rapid decrease in creatinine levels to baseline.

Discussion: For complex intra-abdominal or pelvic surgeries, involvement of transplant surgeons is paramount. Negligence can lead to significant postoperative complications, such as acute kidney injury, increasing morbidity and mortality. Prompt interventions, like ureteral repair and reimplantation conducted in this case, can lead to a remarkable recovery from severe complications.
Infection: A Potential Trigger of Recurrent C3 Glomerulonephritis in a Kidney Transplant Recipient
Amber Anwar, Sarah Abu Kar, Laura Binari, Yihan Wang, Saed Shawar.
Vanderbilt University Medical Center, Nashville, TN.

Introduction: C3 Glomerulonephritis (C3GN) is a rare kidney disease caused by dysregulation of the alternative complement pathway through genetic or acquired alteration in regulatory protein. 67-84% of kidney transplant recipients have recurrence within median time of 14-28 months and graft loss at 18 months after diagnosis. Therapy for recurrent C3GN can include immunosuppression, plasmapheresis, and complement targeting agents like Eculizumab. We present a case of recurrent C3GN in a kidney transplant recipient.

Case Description: A 57-year-old male with end-stage kidney disease secondary to C3GN on monthly Eculizumab underwent a living unrelated kidney transplant with Alemtuzumab and Solunmedrol for induction. He had immediate graft function with nadir creatinine (Cr) of 1.05 mg/dl, and urine protein of 0.1 g/g, and maintenance immunosuppression was Tacrolimus, Mycophenolate Mofetil (MMF) and Prednisone. Two months post-transplant, he was admitted with periodontitis treated with Augmentin. Also he had neutropenia which improved with doses of fligrastim and transient discontinuation of MMF, Bactrim and Valcyle. He was maintained on Tacrolimus and Predniason 10mg. At 1 week follow up, Cr was 1.9 mg/dl attributed to CNI toxicity and Tacrolimus dose was adjusted. However, he soon after developed hypertension, hematuria, and proteinuria (0.75g/g), thrombocytopenia and AKI with Cr 2.7 mg/dl. An allograft biopsy was performed, showed C3GN recurrence with mesangial proliferative GN with C3-deposit and monocytoid IgG dominant deposits. Functional complement panel showed high C3 nephritic factor (34/ml/ml). He was treated with 7 plasmapheresis sessions and induction with Eculizumab 900mg IV weekly for 4 weeks and then 1200mg every 2 weeks. A repeat C3 nephritic factor level was undetectable. At 3 months, the Cr stabilized at 2.0mg/dl and proteinuria resolved.

Discussion: We speculate that C3GN recurrence was triggered by infection and reduction in immunosuppression. Prompt control of disease activity can be achieved with removal of offending proteins via plasmapheresis and stabilization of complement activity with Eculizumab. Close surveillance is deemed necessary for control of disease progression.

LDL/HDL ratio is associated with MACE and all-cause mortality by multivariate analysis.

Hemophagocytic Lymphohistiocytosis in Adult Renal Transplant Patients: A Case Series of Three Patients

Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disease that presents with non-specific symptoms, leading to a delay in diagnosis and early initiation of treatment. We present 3 cases of HLH in renal transplant patients at our institution.

Case Description: 1) 40-year-old female with end stage renal disease (ESRD) on hemodialysis (HD), diabetes mellitus (DM), and hypertension (HTN) who underwent simultaneous kidney-pancreas transplant (SPK) with Thymoglobulin induction on 9/2021, admitted with neutropenia 2 months later. She developed fever, mental status changes, and cholestatic jaundice. CT abdomen showed mild hepatosplenomegaly. Labs showed WBC 0, plt 32, Hgb 6.6, ferritin 11k, CMV 1852, EBV 346, elevated soluble interleukin-2 (sIL-2). Bone marrow biopsy (BMB) revealed hemophagocytic cells. The probability of HLH was 54%-70% based on H score. She was treated with dexamethasone and Etoposide without response. She expired 2 months post presentation. 2) 34-year-old male with chronic kidney disease stage 5, DM, HTN who underwent SPK with thymo induction on 1/2022 admitted with fever and fatigue one month post transplant. Labs showed WBC 0, plt 27, hgb 6.4, ferritin 68k, CMV 1741, EBV 28600, transaminists, and elevated sIL-2. The probability of HLH was 54-70% based on H score. BMB showed hypocellular marrow (5-10%) with many histiocytes and markedly decreased trilineage hematopoiesis. He received dexamethasone, eltrombopag and cyclosporine without response and expired 6 weeks post presentation. 3) 62-year-old male with DM, HTN, ESRD on HD, who underwent deceased donor kidney transplant with thymo induction on 9/2021, admitted with fever, malaise, and vomiting 4 months post transplant. Labs showed hgb 6.7, ferritin >100k, elevated triglyceride and sIL-2. CT scan revealed splenomegaly, and BMB showed HLH secondary to histoplasmosis. He received Amphotericin with good response and was discharged after 5 months of prophylaxis.

Discussion: Idiopathic HLH carries a poor prognosis with high mortality, but HLH secondary to infection has better prognosis if the infection is treated successfully. Early identification and treatment are crucial to optimize outcomes.
FR-PO747
Progressive Multifocal Leuкоencephalopathy (PML): A Dreaded Complication of Immunosuppression
Nora H. Hernandez GarciaLoz, Sarthak Virmani, William S. Asch. Yale School of Medicine, New Haven, CT.

Introduction: JC virus (JCV) can cause progressive multifocal leukoencephalopathy (PML), a demyelinating disorder, in immunosuppressed patients. This infection may present with a variety of neurologic symptoms, ranging in severity and duration, usually identified by the area of white matter lesion. We share a case of a patient who presented with neurologic weakness & was found to have PML in the cerebellar region yet no signs of cerebellar dysfunction.

Case Description: A 77-year-old lady, PMH of ESKD due to RPGN received a live donor KT in 2021, on MMF, prednisone & belatacept, presented with lower extremity motor weakness for 2 months without sensory deficits. No cause was identified on clinical exam & lab work. Allograft function was intact. A brain MRI showed a left cerebellar peduncle lesion and surrounding enhancement which did not explain her weakness. This prompted a biopsy that showed features of PML. CSF later resulted positive for JCV by PCR. To reduce her immunosuppression(IS) and belatacept effect, a plasmapheresis session was performed followed by administration of one dose of IVIG 25g. Unfortunately, the next day she had worsening headaches prompting a CT which revealed a large bleed in posterior fossa originating from the biopsy site. Given poor neurological prognosis, decision was made to transition to hospice care, and she died shortly after.

Discussion: PML is catastrophic in patients on chronic IS. It’s insidious presentation makes it challenging for an accurate & timely diagnosis. While the site of white matter involvement is associated with signs & symptoms, one must be mindful that lack of classical findings should not rule out a diagnosis of PML. Lack of targeted treatment for JCV infection leaves (IS) withdrawal as the only option which becomes challenging in patients on novel agents with more prolonged half-lives.

FR-PO748
The Importance of Enzyme Replacement Therapy After Kidney Transplantation in Fabry Disease
Manal Alotaibi, Mohamed G. Atta, Daniel C. Brennan, Sam Kant. Johns Hopkins University, Baltimore, MD.

Introduction: Fabry disease (FD) is an X-linked disease caused by an enzyme alpha-galactosidase defect due to GLA gene mutations. It can lead to multi-organ involvement including kidneys, heart and nervous system. We present a case of Fabry disease in a patient who received a kidney transplant was initially unable to afford and continue enzyme replacement therapy (ERT) and developed extra-renal complications of FD.

Case Description: A 51-year-old woman with a history of Fabry disease was referred to us with progressive kidney disease. The patient was diagnosed with Fabry disease at the age of 32 and subsequently received ERT. However, her therapy ceased due to medical insurance issues. She had progressive kidney disease and development of dilated cardiomyopathy. Genetic testing revealed a novel heterozygous mutation variant c.820G>C (p.Gly274Arg) in the GLA gene that was deemed of unknown significance. A native kidney biopsy revealed glomerular inclusions with diffuse renal parenchymal scarring, Figure 1. The patient was eventually prescribed agalsidase beta due to non-amenability to chaperone therapy with migalastat. However, she progressed to ESRD and subsequently received a kidney transplant with excellent function. She was prescribed agalsidase maintenance therapy. She was admitted 3 months posttransplant with chest pain and found to have increased septal hypertrophy and progression of aortic stenosis. The patient reported that she had been off agalsidase for over 9 months due to a recurrence of medical insurance issues.

Discussion: ERT and migalastat are currently the only approved specific therapies for Fabry disease in pediatric patients with ESRD due to Fabry nephropathy, kidney transplantation is recommended. ERT is safe after kidney transplantation and recommended to be continued posttransplant for extrarenal manifestations, with observational studies demonstrating a slower increase in left ventricular mass index in transplanted patients who continued ERT.

FR-PO749
Combined Liver and Kidney Transplantation from Living Donors in a Young Patient with Primary Hyperoxaluria Type 1: A Case Report
Mohamed M. Ahmed, Magdy ElSharkawy, Hala Talkihan, Ahmed Emara. Ain Shams University Faculty of Medicine, Cairo, Egypt.

Introduction: Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inherited disease, caused by mutations in AGXT gene. Combined liver kidney transplant (CLKT) is the preferred transplant option for most patients with PH1 since orthotopic liver transplantation replaces the deficient enzyme, thus restoring normal metabolic oxalate production.

Case Description: We present a case of a 27-year-old male with end-stage kidney disease (ESKD). The patient had a right nephrectomy due to recurrent renal stones and chronic pyelonephritis. Histological analysis of the right kidney revealed calcium oxalate deposition within tubules, and genetic testing confirmed the diagnosis of PH1 with a mutation in the AGXT gene. He was maintained on hemodialysis since 2020. Preoperatively, he patient received daily high flux hemodiafiltration (HDF) sessions for ten days. The CLKT was performed using living donors, with his mother donating a kidney and an unrelated person as a liver donor. Perioperative period was uneventful, with both grafts functioning well. His serum creatinine level returned to normal after three days, and his plasma oxalate level decreased from 65 to 22 µmol/L (normal ≤ 30 µmol/L) after 20 days postoperatively. The patient was maintained on immunosuppressive therapy consisting of prednisolone, mycophenolate mofetil, and tacrolimus after the surgery.

Discussion: This case report highlights the successful role of CLKT from living donors in a patient with PH1 with good outcome. Also, preoperative HDF dialysis intensification reduced the oxalate burden, and may reduce incidence of oxalate deposition postoperatively. Crystallization inhibitors may be used postoperatively for a long time to prevent urinary oxalate deposition.
Primary Hyperoxaluria Type 3 Diagnosed After Kidney Transplant
Kirsten Martin, Marwa Abdalla, Chnanig Nilubol. MedStar Georgetown University Hospital, Washington, DC.

Introduction: Primary hyperoxaluria (PH) is a group of genetic disorders that lead to increased hepatic production of oxalate. PH type 3 (PH3), the most recently identified subtype results from mutations in the mitochondrial 4-hydroxy-2-oxoglutarate aldolase gene (AGT). To date, there have been 3 cases of kidney failure reported in PH3 patients. Here we report a case of a man with recurrent kidney stones in his childhood who was diagnosed with PH3 late in life after receiving a kidney transplant.

Case Description: A 74-year-old Norwegian man with a history of recurrent kidney stones since infancy leading to left nephrectomy at the age of 12 presented with proteinuric chronic kidney disease (CKD). His eGFR based on serum Cr of 2.6 mg/ dl was 23 ml/min/1.73m². His urine protein-creatinine ratio was around 2 gm/gm. An ultrasound showed a 13.8 cm right kidney with 2 non-obstructing stones. His CKD was presumably due to secondary focal segmental glomerulosclerosis from adaptive hyperfiltration. Fifteen months later, he received a pre-emptive deceased donor kidney transplant out-of-state with an excellent allograft function. Due to the unclear diagnosis of his kidney disease, he completed a genetic testing panel which was positive for homozygous AGT1 mutation. His 24-hr urine collection showed a mildly elevated oxalate level at 40 mg/day. This may have reflected his habitual dietary oxalate restriction since childhood. The differential diagnosis may have included oxalate nephropathy in his native kidney.

Discussion: Our case signifies the necessity of metabolic workup and genetic testing in patients with kidney stones, particularly in recurrent cases. PH3 was described as a less severe form of PH. Our case is unique in that despite his severe disease early in life, he did not progress into end-stage renal disease until 5 decades after his nephrectomy. Not until the recently approved Ocalair (tiranoxan), an RNA interference agent, as a medical therapy for PH type 1, the only curative treatment for PH had been a liver transplant or a combined liver/kidney transplant. While our patient may have missed the opportunity to receive a combined liver/kidney transplant, the impact of PH on his metabolis profile is mild and medically manageable. The RNA interference agents for PH type 2 and type 3 are being developed, but are not yet FDA-approved. Our patient may be a candidate for such therapy in the future.

Megalocytic Interstitial Nephritis in a Renal Transplant Patient
Shihpa Sannapaneni, Elissa Foster, Akinwande A. Akinfolarin, Kim Rice. Baylor Scott & White Health, Dallas, TX.

Introduction: Megalocytic interstitial nephritis is a rare form of interstitial nephritis first described by Zollinger in 1945. The exact mechanism of the pathology is unknown but is presumed to be secondary to impairment of bacterial clearance by neutrophils and macrophages, especially in immune-deficient patients. It is clinically identical to the ineffective inflammatory process called malakoplakia. Here we present a unique case of megalocytic interstitial nephritis in a renal transplant patient.

Case Description: A 68-year-old male with medical history of end stage renal disease who underwent a transplant allograft biopsy, 15 months prior, presented with volume overload and acute kidney injury. He was diagnosed with cirrhosis after his transplant and clinical course was complicated by recurrent ascites requiring paracentesis, upper gastrointestinal bleeding requiring variceal banding. His exam was significant for bilateral leg swelling, tense abdomen. Labs on presentation were significant for creatinine of 4.26 mg/dl which was up from his baseline of 1 mg/dl. He underwent paracentesis on admission and the peritoneal fluid analysis was consistent with spontaneous bacterial peritonitis. He was started on antibiotics. His kidney function did not improve and biopsy was performed which showed megalocytic infiltration. He remained dialysis dependent despite antibiotics.

Discussion: Our patient developed megalocytic interstitial nephritis in the setting of spontaneous bacterial peritonitis, likely as a consequence of seeding to the graft, in the setting of his kidney transplant immunosuppression. It is a rare disorder and can only be diagnosed by histological examination. A high index of suspicion is required in immunosuppressed patients with slow renal recovery in setting of infection. Treatment of this disease includes antibiotics to control the infection and high dose steroids.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author. 611
FR-PO755

A Case of Self-Limited Thrombotic Microangiopathy (TMA) After an ABO Incompatible (ABOi) Kidney Transplant (KT)


Introduction: TMA is a potentially fatal complication that occurs after solid organ transplant. Post transplant TMA development most commonly triggered with antibody mediated rejection (AMR) and calcineurin inhibitors (CNI).

Case Description: A 44 year old male with CKD secondary to congenital anomalies of kidney and urinary tract who underwent a preemptive living donor ABOi KT (blood type A to O). Anti-A titers prior to transplant were 1:4, and had no donor specific antibodies. Was started on mycophenolate prior to transplant, did not need any further desensitization therapies. Intraop course was unremarkable with immediate graft function. Induction regimen included thymoglobulin 6 mg/kg, received rituximab and was started on tacrolimus on POD 1. He had worsening anemia and thrombocytopenia on POD 2 with high LDH level and low haptoglobin concerning for TMA. He underwent one session of plasmapheresis on POD 4. His kidney function continued to improve since transplant. Hemolysis improved on POD 5, so further pheresis sessions were held. An allograft biopsy on POD 7 showed acute endothelial injury, diffusely enlarged endothelial cell with mitotic figures and entrapped RBC fragments but no fibrin thrombi. There was no concern for AMR with absence of glomerulitis and peritubular capillaritis. C4d was positive as excepted in ABOi KT.

Discussion: TMA is encountered twice as much in ABOi KT compared to other KT. The rapid clinical improvement with minimal therapy and while remaining on tacrolimus, and the absence of pathological evidence makes AMR and CNI use as less likely triggers of TMA. Evidence of early onset TMA, with injury isolated to endothelial cell, likely from an immune mediated injury triggered by isohemaglutinins against endothelial cells bearing blood group A antigens. The self-limited nature of this insult is possibly similar to the accommodation phenomena which is seen in ABOi KT.

FR-PO754

A Unique Case of Prolonged Bile Cast Nephropathy (BCN) Status After Orthoptic Liver Transplant

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Introduction: BCN or Cholemic Nephropathy refers to AKI in the setting of Decompensated liver injury with elevated bilirubin levels. Even though it was first described in 1899 by Quicke while studying cadaveric kidneys, it is still not well investigated, contributing to its limited appearance in current medical literature. It is a multidimensional entity resulting in tubular and interstitial inflammation, tubular obstruction, direct bile salt-induced tubular toxicity, and altered renal hemodynamics.

Case Description: Our patient is a 56-year-old female with history of ESLD due to EtOH s/p Orthoptic liver transplant 3 years ago and ESRD due to ESLD s/p DDKT 1.5years ago. Post transplant course significant for biopsy proven TCMR with suspicion for AMR, treated with IV steroids, PLEX x4 rounds and IVIG. She was also started on mycophenolate mofetil and prednisone, did not need any further desensitization therapies. Intraop course was unremarkable with immediate graft function. Induction regimen included thymoglobulin 6 mg/kg, received rituximab and was started on tacrolimus on POD 1. He had worsening anemia and thrombocytopenia on POD 2 with high LDH level and low haptoglobin concerning for TMA. He underwent one session of plasmapheresis on POD 4. His kidney function continued to improve since transplant. Hemolysis improved on POD 5, so further pheresis sessions were held. An allograft biopsy on POD 7 showed acute endothelial injury, diffusely enlarged endothelial cell with mitotic figures and entrapped RBC fragments but no fibrin thrombi. There was no concern for AMR with absence of glomerulitis and peritubular capillaritis. C4d was positive as excepted in ABOi KT.

Discussion: TMA is encountered twice as much in ABOi KT compared to other KT. The rapid clinical improvement with minimal therapy and while remaining on tacrolimus, and the absence of pathological evidence makes AMR and CNI use as less likely triggers of TMA. Evidence of early onset TMA, with injury isolated to endothelial cell, likely from an immune mediated injury triggered by isohemaglutinins against endothelial cells bearing blood group A antigens. The self-limited nature of this insult is possibly similar to the accommodation phenomena which is seen in ABOi KT.

FR-PO756

Non-ADAMTS13-Mediated Hemolytic Uremic Syndrome (HUS) in a Kidney Transplant Recipient due to SARS-CoV-2 Infection and Its Response to PLEX: A Case Report

David A. Mornand, Surakshya Regmi, Lakshmi Ganesan, Rafael Villicana, Aamir Raza, Sami M. Akram. Loma Linda University Medical Center, Loma Linda, CA

Introduction: During the COVID-19 pandemic many new complications in kidney transplant recipients have arisen. One such entity is Hemolytic Uremic Syndrome characterized by Thrombotic Microangiopathy. Here, we report a rare case of non-ADAMTS-13 and non-complement mediated TMA in a kidney transplant recipient with mild COVID-19 disease.

Case Description: 27 y/o F with a history of GN-mediated ESRD, status post DDKTx in April 2016, thymo induction, on tacrolimus, mycophenolate mofetil and prednisone, presented with a two-day history of fevers and diffuse myalgias. Lab work-up positive for COVID19 and AKI with Cr 4.6 mg/dL and oliguria (baseline Cr 0.8 mg/dL). On day 3, platelets decreased to 68K cells/mm³. Peripheral smear performed showing many schistocytes with low haptoglobin and elevated LDH. C3 and C4 were normal. Alternate
complement pathway function (Mayo laboratory) was normal. Negative for Shiga toxin in stool and the ADAMTS13 activity 73%. Von Willebrand Factor distribution normal. PLEX initiated with high dose steroids with resolution of schistocyte index and AKI.

Discussion: HUS after COVID19 has been reported. The virus can cause HUS directly or indirectly by reducing ADAMTS13. The distribution of vWF multimers can be altered by the virus. A case of Dengue virus causing non-ADAMTS13 HUS has been reported before. Another mechanism of HUS/TMA is dysfunction of alternative complement pathway (inherited or acquired). Also, complement inhibitors such as Eculizumab may not be helpful. Empiric therapy with PLEX was helpful as illustrated by schistocyte response. To the best of our knowledge this is the first case report showing a schistocyte response with two sessions of PLEX in a SARS-CoV-2 mediated HUS.

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FR-PO758

Post-Transplant Thrombotic Microangiopathy After Kidney Transplant

Amer A. Belal, Andrew Slater, William L. Clapp, Hisham Ibrahim, Alfonso Santos, Rohan V. Mehta. University of Florida College of Medicine, Gainesville, FL.

Introduction: Thrombotic microangiopathy (TMA) can present with hemolytic anemia, thrombocytopenia, and organ damage. Risks associated with post-transplant TMA include immunosuppressive drugs, viral infections, antibody-mediated rejection, and ischemia-reperfusion injury. We report a case of tacrolimus (TAC) induced TMA early after a kidney transplant (KT).

Case Description: A 73-year-old white woman with ESRD due to acute kidney injury (AKI) from high output ostomy, ulcerative colitis, proctocolectomy and ileostomy, and hepatitis C was admitted for a deceased donor KT. Induction immunosuppression was with Basiliximab and maintenance was with Prednisone, Cellcept, and TAC, initiated within 24 hours post-KT. On postoperative day (POD) 4, hemoglobin (Hb) and platelets (PLT) dropped to 8.2 g/dL and 37,000/\(\mu\)L respectively. Haptoglobin was <30 mg/dL, lactate dehydrogenase was 1640 IUL, and peripheral smear revealed schistocytes. Hematology was consulted for concern for TAC-induced TMA. ADAMTS13 activity was 72%, and the Coombs test was negative. She developed AKI requiring hemodialysis (HD) on POD 5. Allograft biopsy revealed severe TMA with coagulative necrosis (Figure 1). TAC was held, and Belatacept was initiated on POD 6. Hematology started Eculizumab on POD 7. PLT improved to 145,000/\(\mu\)L and the patient was discharged on dialysis on POD 12. Genetic susceptibility testing for atypical hemolytic uremic syndrome (aHUS) came back negative. She achieved renal recovery with the last HD on POD 31 and maintained a baseline creatinine of 2.2. Eculizumab was discontinued on POD 48 after 4 doses.

Discussion: Drug-induced TMA (DITMA) due to TAC can present early after KT. DITMA could be idiiosyncratic or dose-related. Timely diagnosis and discontinuation of the offending agent are key to management. Eculizumab can be used as rescue therapy in severe cases.

Figure 1 Arterial fibrin thrombi and cortical necrosis (PAS, 200x)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO759

Ocular Toxoplasmosis After Kidney Transplant
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University of Florida College of Medicine, Gainesville, FL.

Introduction: Toxoplasmosis (TOXO) is a zoonotic infection where the parasite persists dormant within tissue cysts and can result in a life-threatening infection in immunocompromised patients. Acute retinal necrosis (ARN) is a vision-threatening necrotizing retinitis with the most common cause being due to the herpes virus family. We describe a case of ocular TOXO after a kidney transplant (KT).

Case Description: A 58-year-old woman with a history of ESRD due to diabetes and hypertension received a deceased donor KT and was directed to the ER by ophthalmology for severe vision loss (counting finger vision) 2 months post-transplant (PT). At transplant, both recipient and donor were positive for Toxoplasma, CMV, and EBV IgG antibodies and induction was with alemtuzumab followed by triple tacrolimus-mycophenolate-mofetil-prednisone regimen. Her PT course was complicated by slow graft function, persistent hyperkalemia and neutropenia necessitating switching of TMP/SMZ to pentamidine and BK viremia requiring immunosuppression reduction at the 1st and 2nd month PT, respectively. Based on a funduscopic exam, the ophthalmologist diagnosed her with ARN (Figure 1). She was empirically started on intravitreal ganciclovir and IV acyclovir, which was changed to Valtrex. Subsequently, her aqueous sample, which was negative for CMV, VVZ, and HSV, tested positive for TOXO PCR. She was started on induction dose Bactrim DS PO BID for 6 weeks followed by lifelong Bactrim prophylaxis. Her steroids were increased to reduce ocular inflammation and tissue damage. On follow-up, her ocular pain improved but significant vision impairment in the left eye (20/200) remains.

Discussion: A high index of suspicion for toxoplasma disease should be maintained when prophylaxis without coverage for toxoplasma is used in kidney transplants where donor and/or recipient has positive toxoplasma serology.

FR-PO760

Post-Transplant Thrombotic Microangiopathy: A Miraculous Outcome with Eculizumab and Belatacept
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Introduction: Post-transplant TMA is a rare but devastating complication, often resulting in graft loss. Calcineurin-inhibitors, antibody-mediated rejection and complement pathway mutations are commonly implicated but the diagnosis is often challenging. We present a case of TMA highlighting these diagnostic challenges.

Case Description: A 57-year-old woman with ESKD from reflux nephropathy underwent her 3rd deceased donor kidney transplant (prior grafts failed from chronic AMR, cPRA 100%, KDPI 1%, ratio for induction and tacrolimus/MMF/pred maintenance), complicated by delayed graft function. On post-op day 6, she developed microangiopathic hemolytic anemia, thrombocytopenia, and a kidney biopsy with focal TMA, 10% cortical necrosis, and negative C4d. HLA testing revealed persistent preformed low-level B and new Bw4 DSAs (MFI 3537). Plasmapheresis x 5, IVIG and rituximab were employed for complement-related TMA, experience with belatacept is limited. The treatment of calcineurin-inhibitor induced TMA is withdrawal of the offending agent but there may be refractory cases like ours. A regimen of belatacept and the mTOR inhibitor, sirolimus, resulted in rapid improvement in graft function in our patient. While AMR was probably contributing to the TMA, treatment with lowering of DSA levels did not immediately improve graft function. Testing for complement pathway mutation is not readily available and has a long turnaround time. But this should not deter physicians from sending this as it is a valuable guide for continued use of eculizumab.

FR-PO761

Successful Kidney Transplant in a Patient with Overlap C3 Glomerulonephritis and Thrombotic Microangiopathy Treated with Ravulizumab
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Introduction: Overlap of C3 glomerulopathy (C3G) and thrombotic microangiopathy (TMA) has recently been acknowledged as one of the possible manifestations of a dysregulation of the alternative complement pathway. C3G of genetic cause has high risk of recurrence after kidney transplant (KT). Data of KT in patients with overlap C3G and TMA is scarce.

Case Description: A 30-y/o woman with kidney failure secondary to overlap C3G/TMA received a deceased-donor KT 6 years ago with primary graft failure secondary to early recurrence of C3G and TMA. Genetic study showed two pathogenic variants in complement-factor H. Post-KT PRA was 100%. While on dialysis she received immunoglobulin for desensitization. She then received a second deceased-donor KT. Flow cytometry (FC) crossmatch (XM) was negative. Ravulizumab, thymoglobulin and steroids were used for induction and five sessions of plasma exchange were performed (one pre-KT). She developed DGF requiring dialysis for 3-4 weeks after KT. Graft biopsy one-week post-KT revealed signs of ATN without signs of TMA or antibody-mediated rejection (Fig. 1), with negative C4d. DSA anti-HLA antibodies class I and II were positive and FC XM was positive (T and B). She was discharged on dialysis with tacrolimus, mycophenolate and prednisone. Four weeks after KT creatinine dropped to 2.9 mg/dL, leading to interruption of dialysis. Since then, allograft function has improved to creatinine of 1 mg/dL at month 3 post-KT.

Discussion: Overlap C3G and TMA is an infrequent condition with a high risk of recurrence. While C3G component secondary to a genetic cause has no treatment available, TMA can be successfully treated with complement inhibitors. This case shows a successful KT in a patient with overlap of C3G and TMA secondary to genetic cause and could therefore serve as guidance to the management of KT in these patients.

FR-PO762

A Case of Collapsing Focal Segmental Glomerulosclerosis (cFSGS) After Kidney Transplant (KT): Association with SARS-CoV-2 Infection
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Introduction: cFSGS is manifested by high grade proteinuria and rapid decline in kidney function leading to end stage kidney disease (ESKD). Viral infections including HIV, cytomegalovirus, BK and SARS-CoV-2 can trigger FSGS in KT. High-risk APOL1 genotype in donors is linked with higher risk of cFSGS and poor allograft outcomes.

Case Description: This is the case of a 70-year-old white man with history of renal cell carcinoma requiring unilateral nephrectomy and eventually ESKD. He received a successful deceased donor KT. After 1.5 years from KT, he developed nephrotic syndrome (creatinine (Cr) 2.2 from 1.1, proteinuria 18-21 g/24h). He had mild COVID infection 2 months prior. On biopsy, glomeruli showed podocyte hyperplasia and hypertrophy consistent with cFSGS. He had diffuse glomerulitis and peritubular capillaritis (ptc)

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
suspicious of antibody mediated rejection. C4d ptc stain was negative with no evidence of donor specific antibodies. In addition to proteinuria management with RASS blockade, SGLT2i and spironolactone, he completed 13 sessions of plasmapheresis, 2g/kg of IVIG and 2 doses of rituximab. Follow-up biopsy (5 months later) showed progressive glomerular injury (cg2), but improvement of cFSGS. Follow-up Cr is 1.5 and proteinuria is 5 g/g. The donor reported race is white, and APOL1 genotype was negative for high-risk allele.

**Discussion:** This is a case of COVID-related de novo cFSGS after KT in APOL1-negative donor and recipient. It is unique as cFSGS manifested 2 months after COVID resolution. Though, case series have shown a link of APOL1 high-risk genotype with COVID-19-related cFSGS, cFSGS in KT recipient from APOL1-negative donors has been reported. It is important to rule out a concomitant or recent history of rejection or viral infection in KT recipients with cFSGS. Aggressive treatment is warranted to salvage the kidney allograft.

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**FR-PO764**

### An Unusual Cause of Reversible Nephrotic Syndrome in a Kidney Transplant Recipient

**Wang, Zhengyuan**

**Poster/Friday**

**Introduction:** A 73-year-old female with diabetic nephropathy underwent deceased donor kidney transplantation using Thymoglobulin induction and tacrolimus/ mycophenolate mofetil maintenance along with infection prophylaxis using valgancyclovir and trimethoprim-sulfamethoxazole. There was prompt allograft function with a nadir serum creatinine of 1.3 mg/dL. Serum creatinine started increasing 4 months post-transplant and patient developed significant edema along with worsening hypertension. Further evaluation revealed new nephrotic range proteinuria, hypoalbuminemia, no DSA, along with negative infectious and monoclonal gammapathy work up. Kidney allograft biopsy showed no rejection, negative immunofluorescence, with segmental foot process effacement without transplant glomerulopathy or immune deposits on electron microscopy. Repeat allograft biopsy 2 weeks later showed similar findings. Allograft Doppler ultrasound revealed increased peak systolic velocity of 240 cm/sec in the renal artery which increased to 289 cm/sec on repeat Doppler study 2 weeks later. Based on the Doppler finding, persistent allograft dysfunction and hypertension, patient underwent CO2 angiogram that revealed severe stenosis of the transplant renal artery near the anomostomes with external iliac artery. Stenosis was successfully treated with balloon angioplasty. Within next several weeks, there was improvement in serum creatinine to 1.29 mg/dL and proteinuria to 0.5 g/dL.

**Discussion:** Nephrotic range proteinuria is an uncommon presentation of renal artery stenosis (RAS) that has previously been reported in native kidneys. Our case shows that similar presentation can occur in allograft kidneys. Transplant RAS should be considered as a potential cause for nephrotic syndrome in KTRs.
ANCA-Associated Vasculitis Recurrence After Kidney Transplantation

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Introduction: ANCA-associated vasculitis (AAV) is a well-recognized cause of End Stage Kidney Disease (ESKD). It is a necrotizing vasculitis that affects small vessels without immune complex deposition. About 20-25% of patients will progress to ESKD in a few years after diagnosis. AAV may recur in about 5-10% of cases after kidney transplantation despite standard immunosuppression. Here we present a case of AAV recurrence in a kidney transplant recipient.

Case Description: A 49-year-old white female with a past medical history of HTN and ESKD secondary to p-ANCA positive, pauci-immune glomerulonephritis received DDKT 3 years ago with post-transplant course complicated by cryptococcus meningitis and mycobacterium avium infection. She was maintained on cyclosporine and prednisone. Her creatinine rose from baseline of 0.9 to 2.3 along with new onset of microscopic hematuria and proteinuria and UPCR of 2.6 g/g. Her p-ANCA titer is 1:640. Cyclosporine levels ranged from 100-144 ng/ml. Kidney biopsy showed focal crescentic and necrotizing glomerulonephritis, borderline acute TCMR, and diffuse acute tubular injury. Of 22 glomeruli, 3 glomeruli contain cellular, 3 glomeruli contain fibrocellular, 2 glomeruli contain fibrous crescents and 2 glomeruli with cellular crescents also have fibrinoid necrosis. A focal segmental granular mesangial and loop staining is seen with IGG (trace), IGM (1+), C3 (1+), C1q (1+), kappa (trace), and lambda (trace). There is 1+ arteriolar and 2+ focal segmental tubular basement membrane staining with C3. Tubular casts are equally positive with IGA, kappa, and lambda. Electron microscopy with no deposits in any locations. The patient received a 3-days of pulse methylprednisolone, one dose of rituximab and is scheduled to receive a second dose of rituximab in two weeks. The patient was discharged on prednisone with plans for gradual taper over 4-6 months.

Discussion: The diagnosis of AAV flare post transplantation is difficult as relapses may mimic infections and other complications of immunosuppression. Disease recurrence of AAV should be considered in the differential diagnosis of sudden worsening of kidney function and must be confirmed by biopsy. Rituximab is the therapy of choice both in ESKD and kidney transplant patients. It is recommended to maintain continuous vigilance in all AAV transplant recipients for early detection of relapses.

Outcome of Renal Allograft with Preexisting Lupus Nephritis

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Introduction: Preexisting glomerulonephritis(GN) was not a contraindication for kidney donation. The outcome of renal allograft with pre-existing GN was not clearly demonstrated. Here, we presented a case of renal allograft with pre-existing proliferative lupus nephritis(LN).

Case Description: A 31-year-old female with diffuse sclerotic GN accepted deceased donor kidney transplantation(KT) at 2020. The 32-year-old female donor died of frontal lobe ependymoblastoma, with a medical history of systemic lupus erythematosus. At the time of death, the donor had proteinuria(urine ALB: 3.72g/L), increased serum creatinine(Scr)(180 umol/L), positive ANA(18.4U/ml) and dsDNA(~300.00IU/ml). Pre-implantation histological examination of the kidneys showed “full-house” deposition in immunofluorescent(IF), diffuse mesangial and endothelial proliferation with immune complex(IC)deposition under light microscope(LM), suggestive of RPS I/IV/V(Remuzzi scoring=1. After KT, the recipient’s Scr decreased while nephrotic range urine protein was notified. At 10th day post-KT, her Scr dropped to 100 umol/L and remained stable afterward, while her urine ALB was 4.34g/L and descended slowly. 3 months later, she undertook allograft renal biopsy with persistent proteinuria(urine ALB:111.5mg/L). The IC deposition persisted in glomerular base membrane with decreased intensity in IF, resembling membranous nephropathy(MN) in LM and electronic microscope. No hypercellularity or rejection was identified. Her urine protein turned negative 4 months after KT. Only slight transient ANA elevation was noted within the first 2 weeks (15:22 U/L), while dsDNA remained negative all throughout.

Discussion: Glomerular IC deposition is common in donor kidney biopsies, which would eventually “wash-out” over time. In our case, the allograft still presented with proteinuria and MN-like change 3 months after KT, indicating that IC clearance was slower than disappearance of hypercellularity. Hence allograft with pre-existing GN should undergo careful surveillance before radical clearance of IC to avoid possible complication caused by GN.
Curious Case of De Novo Lupus Nephritis in Geriatric Patient After Kidney Transplant
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Introduction: Glomerular nephritis after transplant can develop De novo or as a recurrence of primary GN. Glomerulonephritis (GN) after a kidney transplant significantly contributes to long-term graft loss. We present a rare de novo lupus nephritis (Membranous GN) case after a kidney transplant.

Case Description: A 73-year-old African American Male with a history of ESRD, presumed secondary to chronic allograft nephropathy diagnosed on kidney biopsy. He was restarted on hemodialysis and subsequently underwent a second DDKTs, Donor 38 AAF, KPD 61%, CPA 98%, CMV -/+, EBV +/-, Cold time 13 hours, induction therapy with Anti Thymoglobulin, bortezomib and Solumedrol and maintenance with Tacrolimus, Mycophenolate Mofetil, and prednisone. The post-transplant course was complicated by delayed Graft Function (DFG), 2nd-degree AV block type 1 Weneckebaek, and paroxysmal atrial fibrillation. He has maintained the patient on dialysis for DGF. Laboratory studies revealed hemoglobin of 9.5 g/dL, platelets 200 x100 /uL, Leukopenia of 3.200, Creatinine 8 mg/dL, Urine with <500 protein, and 24 protein excretion in 4 grams. Urine Microscopy was bland. Work up for proteinuria; HIV, Hepatitis B, and C are negative, Low C3, and normal C4, Normal PT/INR and APTT. A kidney biopsy was done in the second week of the transplant and showed Membranous GN, focal glomerulonephritis, and extraglomerular immune complex deposit, EXT2 positive favoring a post-infectious process. In this case, we present an unusual presentation of the renoprotective effect of combined natulimun modifier and immunosuppressive therapy. Antitumoral activities of monoclonal antibodies fix complement to produce IgG4 and collectively release inflammatory cytokines. Fibroblasts replace the inflammatory milieu with stromal tissue. IgG4 antibodies play an unknown role. Renal involvement can be intrinsic or secondary to extraocular fibrosis. Intrinsic disease typically manifests as TIN. Laboratory findings of TIN include pyuria, variable proteinuria, hypercocomplementemia and elevated IgG4 subclass. Histologic evaluation demonstrates IgG4+ plasma cell infiltrate, storiform fibrosis, and obliterator phlebitis. Progression to renal failure is uncommon and kidney transplant occurs rarely. Treatment of IgG4-RD includes glucocorticoids and rituximab. We present a case of recurrent IgG4-RD TIN in a kidney transplant.

Case Description: A 53-year-old Latino male with history of Class IV Lupus nephritis (LN) 27 years post living related kidney transplantation, maintained on azathioprine and prednisone with good medical adherence presented for a follow-up. He was noted to have a rise in creatinine of 1.51mg/dL (baseline of 1.1-1.3mg/dL) and a urine protein creatinine ratio of 500mg/g. Work-up was significant for suppressed complements, an elevated Anti-Ds DNA (160U/mL), with positive Anti-cardiolipin, Anti-smooth muscle, and Anti-SS-A/SS-B antibodies. A kidney biopsy showed Focal segmental glomerulosclerosis (FSGS), with endocapillary hypercellularity, hyaline deposits, and sclerosis. The patient was initiated on tacrolimus and mycophenolate (MMF). Two years post-transplant creatinine increased from 1.0 to 1.5. Allograft biopsy showed IgG4+ plasma cells consistent with TIN from recurrence of IgG4-RD. He started on prednisone and rituximab with improvement of his creatinine to 1.2. Steroids were tapered over months. Creatinine remained stable. Ten months post-transplant, the patient received a repeat allograft kidney biopsy, which showed no evidence of recurrence of IgG4-RD. He required no further doses of rituximab and remains on prednisone, tacrolimus, and MMF. 11 years after transplantation his creatinine remains 1.1.

Discussion: IgG4-RD is characterized by autoimmune dysregulation of IgG4+-plasma cells impacting many organs in an inflammatory to fibrotic process. T cells stimulate B cells to produce IgG4 and collectively release inflammatory cytokines. Fibroblasts replace the inflammatory milieu with stromal tissue. IgG4 antibodies play an unknown role. Renal involvement can be intrinsic or secondary to extraocular fibrosis. Intrinsic disease typically manifests as TIN. Laboratory findings of TIN include pyuria, variable proteinuria, hypercocomplementemia and elevated IgG4 subclass. Histologic evaluation demonstrates IgG4+ plasma cell infiltrate, storiform fibrosis, and obliterator phlebitis. Progression to renal failure is uncommon and kidney transplant occurs rarely. Treatment of IgG4-RD includes glucocorticoids and rituximab. We present a case of recurrent IgG4-RD TIN in a kidney transplant.

Case Description: A 38-year-old male with ESRD secondary to Alport Syndrome had two kidney transplants, the most recent being a deceased-donor kidney transplant in 2/2022. He was induced with alemtuzumab and maintained on tacrolimus, mycophenolate mofetil, and prednisone. His post-transplant course was complicated by antibody-mediated and cellular rejection in 12/2022, which were treated with PLEX, IVIG, rituximab, and thymoglobulin. His condition was stable until 3/2023 when he started having left-sided facial pain and congestion. A sinus CT scan showed mild mucosal thickening of the left maxillary sinus ethmoidal cells. Levofloxacin was given for presumed bacterial sinusitis and a same day ENT appointment was scheduled, but he was lost to follow-up. Three weeks later, he presented with aggraivated facial pain and left-sided numbness, with no other neurological or pulmonary symptoms. A follow-up sinus CT scan suggested progressive chronic sinusitis without aggressive features. However, given the concern for fungal infection, ENT was consulted and did a nasal endoscopy which revealed black necrotic inferior and middle left turbinates, suggesting invasive fungal sinusitis. The patient underwent surgical debridement and pathological examination confirmed invasive mucormycosis. Amphotericin therapy was initiated. A chest CT revealed a mass-like consolidation in the right middle lobe indicative of fungal pulmonary involvement. Following weekly debridements and amphotericin therapy, the patient improved and transitioned to isavuconazole therapy, further alleviating his symptoms. This is the first reported case without concurrent rejection and the first case demonstrating successful treatment of recurrent IgG4-RD post-transplant. Our case suggests effective use of rituximab, glucocorticoids, and MMF for recurrent IgG4-RD TIN in a post-transplant patient.

Symptomatic Cytomegalovirus (CMV) Infection and Antibody-Mediated Rejection (ABMR) of Kidney Allograft
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Introduction: CMV infection is a common complication after transplantation, occurring in up to 50% of kidney transplant recipients. The main risk factor for CMV viremia varies depending on the immunological milieu. In patients on high-dose immunosuppression, direct virus-induced cytoytic effect on host cells in various systems, such as pulmonary, liver, and kidney, can occur. Moreover, in patients with chronic allograft nephropathy, CMV viremia is serological mismatch between the donor and the recipient. Infection can lead to direct virus-induced cytoytic effect on host cells in various systems, such as pneumonia, liver, and kidney.
gastrointestinal disease, hepatitis, and even invasion of the transplanted organ. However, mechanisms of allograft injury are not limited to direct viral cytotoxicity only, as CMV infection has been shown to promote immune-mediated transplant rejection. We present a patient with symptomatic CMV infection leading to antibody-mediated allograft rejection requiring dialysis, with complete renal recovery after antiviral treatment.

Case Description: A 59-year-old male CMV D+/R- kidney transplant recipient presented seven months after transplantation with fever, chills, fatigue and acute kidney injury. Within four days, creatinine worsened to 4.6 from a baseline of 1.3. He was found to have CMV viremia with a peak of 8350 copies/mL and was started on intravenous ganciclovir. He had previously been on valganciclovir as prophylaxis. Kidney allograft biopsy demonstrated features of antibody mediated rejection, albeit with anti-HLA antibodies only against third party antigens. Despite intravenous methylprednisolone and five sessions of plasmapheresis, renal function continued to deteriorate to a creatinine of 11.3, along with signs of azotemia and volume overload prompting initiation of dialysis two weeks after the initial presentation. The patient continued to receive intravenous ganciclovir throughout hospitalization and CMV viral load decreased to 104 copies/mL by the time of dialysis initiation. After 1 week of dialysis, kidney recovery ensued and CMV viral load was undetectable. Repeat allograft biopsy three weeks after initiation of dialysis and natural treatment showed signs of resolving ABRM. Patient has been off dialysis and showed complete recovery of function, with creatinine levels back at baseline two months after initial presentation.

Discussion: The immune nature of antibody-mediated allograft rejection may mislead clinicians into overlooking viral infections as a potential underlying etiology. This case highlights the importance of identifying CMV viremia as a trigger of ABRM in kidney transplant recipients, as adequate treatment can lead to complete allograft recovery.

FR-PO777
Donor-Derived Disseminated Bartonella Infection After Renal Transplant
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Introduction: Bacillary angiomatosis is a manifestation of the rare infection caused by Bartonella quintana, with disseminated or chronic relapsing infection occurring most often in the immunocompromised. This organism is usually transmitted between hosts via the human body louse. Donor related infection is rare and screening is not routine. Those infected commonly complain of fever, headache, joint pain or weakness. Diagnosis is challenging as typical serologic testing may be negative in the immunocompromised.

Case Description: A 59-year-old male with CKD secondary to biopsy proven lupus nephritis underwent a deceased donor renal transplant. He received induction immunosuppression with Basiliximab and continued on standard immunosuppression, achieving good graft function, with creatinine 1800mg/dl. The patient did not encounter clinical rejection. His background medical history was significant for amyloidosis, with disease quiescence confirmed on bone marrow aspirate and trephine biopsy pre-transplant. He had travelled extensively, had secure housing and owned a dog and chickens with no other animal exposures. Over the next several months, the patient presented with recurrent episodes of profound fatigue, weakness, headaches and occasional fever with a septic appearance on clinical examination and associated leukocytosis. Broad microbiological work-up was negative. This included serology for Bartonella species. Six months after his original presentation, the patient described small cherry red lesions on his thigh, arm and buccal mucosa. Bacillary angiomatosis was suspected. Warfarin and clopidogrel, were negative. Bartonella quintana was confirmed on PCR. Serology later returned a positive result. He was treated for disseminated infection with doxycycline 100mg BID. Rifampicin was not used due to interaction with immunosuppressants. Subsequent testing of donor serum confirmed the presence of Bartonella quintana antibodies. On follow-up, the patient demonstrated improvement with resolving symptoms and lesions.

Discussion: This case highlights the challenges inherent in atypical donor derived infections. Patient serology was uninformative, being initially negative after several months of symptoms and became positive much later. Given the prolonged period of infection and the inherent difficulties in diagnosis, reviewing risk factors for infection in the donor may have been useful.

FR-PO775
Concern for Donor-Derived Candidiasis Causing a Mycotic Aneurysm in the Transplanted Renal Artery
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Introduction: Donor-derived infections can be associated with dire consequences in transplant recipients. Although extremely rare, fungal infections in renal allografts can result in renal arteritis, urinoma, graft site abscess, and surgical site infection. We present a clinical case of a mycotic aneurysm secondary to Candida krusei infection in a kidney transplant recipient.

Case Description: A 75 year old male with end stage kidney disease secondary to presumed diabetic nephropathy underwent a deceased donor kidney transplantation. At the time of transplantation, a 59 year old donor was noted to have untreated candida species isolated from both urine and sputum. His post-operative course was complicated by delayed graft function and post-operative myopathy. On POD 11 he was found unresponsive and pulseless in his hospital bed. Chest compressions were emergently initiated with return of spontaneous circulation. Labs were notable for new lactic acidosis, acute anemia, and hyperkalemia. CT scans of his abdomen and pelvis were obtained and notable for a large pelvic hematoma with active extravasation. He underwent emergent re-exploration of his kidney transplant and was found to have a 23 cm hematoma, and a necrotic posterior wall of his main renal artery with concern for a ruptured mycotic aneurysm (Figure 1).

Discussion: Allograft artery mycotic aneurysm is an extremely rare and life-threatening complication that can develop following kidney transplantation. A high index of suspicion is needed to make the correct diagnosis of Candida associated mycotic aneurysms due to its insidious presentation.

FR-PO776
A Rare Cause of Early Graft Failure: Mycotic Aneurysm
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Introduction: Pseudomycosis of the kidney artery is a rare complication, seen in <1% of transplant recipients, generally secondary to infectious causes and at the anastomotic site(1). Kidney allograft artery thrombosis is also a rare complication similarly seen in <1% of transplant recipients. Mycotic pseudomycosis can present variably from being asymptomatic to fever, abdominal pain, pulsatile expanse mass, and hemorrhagic shock from rupture (2, 3). We present a case of acute allograft dysfunction in a kidney transplant patient caused by mycotic pseudo-aneurysm of the transplanted renal artery (TRA) complicated by thrombosis leading to allograft nephrectomy.

Case Description: A 40-year-old male with a history of ESKD status post deceased donor kidney transplant presented for allograft biopsy for AKI and worsening proteinuria (2.27 g/g from 0.67 g/g). Pre-Biopsy kidney ultrasound showed a new pseudoaneurysm of TRA. He underwent urgent surgical exploration and a cadaveric iliac bypass to the renal artery was done. Subsequently, to reduce the chances of pseudoaneurysm rupture given its friability, interventional radiology was consulted for a covered stent in the aneurysm. Pre-procedure angiogram showed thrombosed transplanted renal artery graft, occlusion of the right external iliac and bypass, and transplanted nephrectomy was performed. The infected pseudoaneurysm led to disruption of flow to the TRA leading to thrombosis Surgical pathology of the allograft kidney showed organizing thrombi in the main renal artery and segmental branch, acute tubular damage. Clinically the patient remained afebrile, infectious disease workup including blood and urine cultures were negative. Culture of the thrombosed pseudomycosis grew Staphylococcus hominis which was treated with IV antibiotics. 

Discussion: Renal artery thrombosis and renal artery pseudocyst are themselves rare complications seen in kidney transplant recipients, here we highlight a rare case of pseudomycosis contributing to thrombosis, which may further demonstrate urgency in the treatment of pseudomycosis.
elevated C-reactive protein. Although CT chest with contrast showed a small amount of pericardial effusion, he was carefully monitored without further workup. A week ago, he gradually felt weak and developed a fever. On the presentation day, he was unable to move and call an ambulance. On arrival, he was confused and hypotensive. A physical exam showed elevated jugular venous distension with a muffled heart sound. Transesophageal ultrasound demonstrated pericardial effusion with the diastolic collapse of the right ventricle. Pericardiotension was performed, draining 200 mL of purulent fluid. He was diagnosed with bacterial pericarditis and started on meropenem and ticlopiplan. The culture returned positive for C. f. Then antibiotics were switched to ampicillin according to the susceptibility report. He was discharged on 31 hospital-day to home for rehabilitation.

Discussion: Based on the clinical presentation and orbit MRI results that showed marked perineural enhancement of the optic nerve (a surrogate of meningeval inflammation) and the temporal association with her diagnosis of cryptococcal meningitis, it was deemed to be the most likely etiology of her vision loss. This is an unusual and rare presentation of cryptococcal meningitis but has been described in the literature. With her long-term use of CNIs, tacrolimus induced optic neuropathy was considered. This rare side effect, however, usually affects both optic nerves and orbital MRI reveal optic disc or nerve inflammation in the form of contrast enhancement. The common clinical practice is to switch tacrolimus to another immunosuppressive agent but as her clinical presentation was not consistent with this and her immunosuppression regimen was not altered.

FR-PO779

Neuro-Ophthalmic Manifestation of Cryptococcus Meningitis in a Kidney Transplant Patient

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Introduction: Cryptococcus is the third most common cause of invasive fungal infection in solid organ transplant recipients- cryptococcal meningitis is the main clinical presentation. Vision loss in cryptococcal meningitis can be due to papilledema or optic nerve sheath infiltration. The common clinical practice is to expedite treatment delays and disease progression. With no standardized treatment guidelines for TS, patients can undergo several ineffective treatment trials. The presentations varied from bacteremia, menigitis to splenic abscesses. Interestingly, none of the five cases reported any history of exposure to cattle or sheep or raw meat intake. Nevertheless, this case reminds us of the need for guidance regarding raw meat consumption in patients who take immunosuppressive medications.

FR-PO780

A Case of Hemorrhagic Cystitis Leading to Disseminated Disease from Adenovirus in a Renal Transplant Patient


Introduction: Adenovirus can cause many infections in immunocompromised hosts including nephritis and hemorrhagic cystitis. It commonly occurs in immunocompromised patients from reactivation of latent infection or primary infection. It is especially concerning in patients with renal transplants. The diagnosis requires the use of multiple diagnostic specimens to detect viral shedding. Diagnosis is also made in the context of clinical manifestations, as in our patient who developed adenovirus infection with hemorrhagic cystitis.

Case Description: This is a 63-year-old woman with a history of ESRD secondary to hypertensive nephrosclerosis status-post DDRT on 9/13/2016. Her post-transplant course was uneventful and she was discharged with a creatinine of 0.7 mg/dL. She presented to the hospital six years post-transplant with dysuria, urinary urgency, urinary frequency and lower abdominal pain with urination. Her creatinine at this time was 0.6 mg/dL. Her urinalysis showed 37 white blood cells and > 182 red blood cells. She was started on Zosyn for possible pyelonephritis. Her urine culture had no growth and was discharged on levofloxacin. She was readmitted about one week later with recurrence of urinary symptoms and hematuria. Her urinalysis showed > 182 red blood cells and her creatinine was 1.6 mg/dL. A CT urogram was done and was unremarkable. Due to her AKI, a renal biopsy was performed which was unable to be analyzed due to an inefficient tissue sample. She was found to be positive for adenovirus PCR DNA and was started on cidofovir and probenicid. Her creatinine normalized to her baseline. She continued on her immunosuppression regimen of Myfortic, Envarsus and prednisone. She completed treatment for her adenovirus infection after two months with resolution of her symptoms and notable clearance of adenovirus DNA in the serum.

Discussion: Most adenovirus infections are self-limited and treatment is usually supportive. However, adenovirus can be fatal in immunocompromised hosts with high mortality and morbidity. Disseminated adenovirus disease may be preceded by a period of asymptomatic viremia. Thus, the diagnosis can be missed leading to poor outcomes. The early identification of the disease by monitoring viremia has been shown to be beneficial, as we see for CMV infections in immunocompromised patients.
KS involving the renal allograft

Involvement of the renal allograft by KS is extremely rare. Here, we present two cases of post-transplant lymphoproliferative disease (PTLD) and Kaposi sarcoma (KS).

Case Description: 54-year-old female underwent kidney transplant from HCV positive deceased donor. Immunosuppression (IS) included Thymoglobulin followed by tacrolimus and mycophenolate (MMF). She was successfully treated for donor-derived HCV infection with Sofosbuvir/Velpatasvir. Baseline serum creatinine was 1.4 mg/dl. She developed CMV Viremia that responded well to reduced IS and valganciclovir. However, creatinine increased to 2.3 mg/dl, and transplant biopsy was done to rule out rejection. It showed foci of vascular proliferation, prominent mitoses, atypical cells with enlarged nuclei (Fig 1) and positive Immunostain for HHV8 (Fig 2) indicating KS. Her MMF was switched to Everolimus. She had no cutaneous lesions on exam and has been referred to Oncology.

Discussion: Increasing proportion of PHS high risk organ recipients are at risk for HHV8 infection and KS. To our knowledge only 8 cases of KS involving renal allograft have been described, with only 2 derived from HCV positive donors. With limited pre transplant testing of donors for HHV8 infection, close monitoring of recipients with PHS high risk organs for KS is suggested.

FR-PO783

“Goose Bumps” Trichodysplasia spinulosa Viremia in a Patient with Kidney Allograft


Introduction: Trichodysplasia Spinulosa (TSPyV) is a DNA virus in the polyomaviridae family first identified 1995 and genotyped 2010. This virus is ubiquitous in immune competent humans and immunosuppressed patients rarely have clinical manifestations of viremia.

Case Description: 35-year-old man with h/o ESKD due to an unknown etiology s/p (DDKT) in June of 2021, HTN, Crohn’s, asthma, and anaphylaxis to peanuts was seen in transplant clinic for maintenance of immune suppression on tacrolimus (Tac), mycophenolate (MMF), and prednisone. The patient developed a rash involving his gluteus, face, nose, and extremities 7 months post-transplant. (See image) He described it as “bumps with feathers growing out of them.” A shave biopsy revealed hyperkeratotic and parakeratotic debris in the hair shaft consistent with TSPyV. Treatment advised was a reduced Tac goal and reduced MMF dose as well as initiation of topical cidofovir. The patient went on a 6-month trekking trip where lesions worsened and was not available for follow up. At this time, he self-discontinued prednisone due to GI upset and stopped cidofovir after 1-2 weeks of use due to skin breakdown. He was switched from MMF to everolimus, but he stopped this due to cystic acne which he attributed to everolimus. After 13 months of adjustments the patient showed improvement of skin lesions and continues Tac with goal of (4-5) and MMF 500mg BID off prednisone Cidofovir and everolimus.

Discussion: TSPyV viremia may have significant dermatologic manifestations and the renal allograft threatening implications in the management which typically includes topical antivirals, clinical monitoring, and reduction of immune suppression with lower Tac goals in the 4-5 range. It is important for clinicians to counsel patients on the importance of medication adherence and follow up regarding complications of immune suppression.*Viremia not confirmed. Diagnosis made by clinical presentation and histopathological appearance.

FR-PO782

Kaposi Sarcoma Involving the Renal Allograft: Report of Two Cases

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Introduction: The use of immunosuppressive agents for prevention of allograft rejection increases the risk of malignancy. The magnitude of the higher risk is dependent on cancer types, with the greatest risk in viral-related and immune driven cancers such as post-transplant lymphoproliferative disease (PTLD) and Kaposi sarcoma (KS). Involvement of the renal allograft by KS is extremely rare. Here, we present two cases of KS involving the renal allograft.

Case Description: Case 1: Sudanese gentleman who was diagnosed to have ESRD. He had live unrelated kidney transplant in June 2014. His course was unremarkable till 7/2015 when he presented with acute graft dysfunction and MRI abdomen revealed: bulky transplanted kidney with multiple livers, splenic and vertebral lesions. Anti-human herpes virus 8 (HHV-8) antibody was positive and transplanted kidney and liver biopsies revealed KS. Immunosuppression was reduced and patient experienced improving general condition later. Case 2: 46 years old Mozambican gentleman, known case of ESRD. Underwent living unrelated renal transplant then 10 months after transplant, patient was admitted with rising serum creatinine and pancytopenia. Transplanted kidney biopsy revealed: extensive infiltration by Kaposi sarcoma with negative C4d and SV-40. HHV8 was positive in the nuclei of most of the tumor cells. Then patient decided to return back to his home country.

Discussion: Kaposi sarcoma (KS) was first reported in 1872 by Moritz Kaposi, a Hungarian physician. Several reports have documented an endemic form of KS mostly encountered in Africa. Indeed, the incidence of KS is now known to reflect differences in the prevalence of Kaposi Sarcoma Virus (KSHV). This virus is also known as Human Herpes Virus 8 (HHV8). Patient 1 was from Sudan which generally not considered a Sub-Saharan country but it nevertheless has high incidence of KS. Patient 2 was from Mozambique, a country in Sub-Saharan known to have high incidence of KS. Involvement of the renal allograft by KS however is extremely rare with only eight cases reported in the literature. The patient’s age ranged from 28 to 71 year and in all cases, KS was diagnosed within 12 months after transplantation. Reduction of immunosuppression resulted in regression of the tumor in most cases. In conclusion we present 2 cases of KS in the renal allograft which brings the number of cases to 10.
FR-PO784

Donor-Derived West Nile Virus Infection After Renal Transplant Treated with Plasmapheresis

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Introduction: West Nile Virus is a single-stranded RNA Flavivirus usually transmitted through mosquito bites. The clinical presentation usually varies from asymptomatic, mild gastrointestinal symptoms and fever to <1% developing Neuroinvasive disease. The literature showed that organ derived WNV infection is associated with 70% of neurological sequelae and 30% of severe morbidity and mortality. The onset of symptomatic WNV infection post-organ transplant is usually around 13 days however the range varies from 5-37 days.

Case Description: A 50 Y/O male who presented for a Deceased Donor kidney transplant. His previous history included ESRD on Peritoneal dialysis, Focal segmental Glomerulosclerosis, and Hypertension. He denies any sick contacts and recent travel. His review of systems and physical examination were normal. He developed fever, altered sensorium and seizures almost 16 days post-transplant. On neurological examination, he was found to be minimally responsive. Initial work including CSF fluid analysis and a CT scan of the Brain was inconclusive. His MRI showed linear symmetric restricted diffusion in both cerebellar hemispheres and his post-transplant CT scan showed a colonic mass. The patient was given two sessions of plasmapheresis based on the pertinent MRI findings and suspicion of paraneoplastic syndrome. His lab reported later showed positive paraneoplastic panel. The primary team sent the WNV panel to the Department of Hematology and it came back positive for WNV IgM. His serum and urine PCR also came back positive for WNV antigen. Plasmapheresis was stopped and IVIG was started based on some previous case reports. Additional two sessions of plasmapheresis were given post-IVIG, and his blood and urine turned negative for WNV IgM after 14 days of treatment. Repeated MRI also showed stable restriction diffusion defects.

Discussion: The treatment for WNV is usually supportive, reduction of immunosuppressants and IVIG. Some case reports show additional benefits of plasmapheresis especially in neuroinvasive disease. So far only IVIG has been used and showed benefits in West Nile Virus Infection after solid organ transplant. This was the first-time plasmapheresis was done and showed a significant response. WNV screening should be considered a routine workup for potential organ donors living in endemic areas.

FR-PO785

Concurrent Epstein-Barr Virus (EBV) Viremia, Non-Tuberculosis (TB) Mycobacterial Infection, and Acute T Cell-Mediated Rejection (TCMR) in Kidney Transplant (KT) Recipient

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Introduction: Managing concurrent rejection and infection after KT is a therapeutic challenge. M. genavense is rare, difficult-to-identify mycobacterial infection. We present a case of simultaneous EBV viremia, disseminated M. genavense infection, TCMR.

Case Description: A 54yo man with ESKD due to HTN underwent deceased donor KT with thymoglobulin induction followed by tacrolimus dosed for goal trough 10-12 and mycophenolate mofetil (MMF) 1g BID. EBV IgG detectable in donor but not recipient. Initial post-KT course was uncomplicated (nadir Cr 1.19) until developing EBV viremia (1,992 cop/ml) and night sweats 6 months post-KT. MMF was stopped. PET-CT revealed 1.8cm FDG-avid posterior mediastinal node, diffuse increased marrow activity, and mild splenomegaly (1,992 cop/ml) and night sweats 6 months post-KT. MMF was stopped. PET-CT revealed 1.8cm FDG-avid posterior mediastinal node, diffuse increased marrow activity, and mild splenomegaly (1,992 cop/ml) and night sweats 6 months post-KT. MMF was stopped. PET-CT revealed 1.8cm FDG-avid posterior mediastinal node, diffuse increased marrow activity, and mild splenomegaly (1,992 cop/ml) and night sweats 6 months post-KT. MMF was stopped. PET-CT revealed 1.8cm FDG-avid posterior mediastinal node, diffuse increased marrow activity, and mild splenomegaly. His lab reported later showed elevated C-reactive protein, creatinine (2.5 mg/dL). Abdominal computed tomography confirmed pneumonia, pneumoperitoneum, gastric wall thickening. Tacrolimus and mycophenolic acid were discontinued, and steroid therapy was continued. Meropenem was initiated. An endoscopy performed within 12 hours of symptom onset revealed multiple areas of diffuse gastric necrosis and purulent material. Lincosidol was added to the treatment regimen, and a nasojejunal tube was placed for total enteral nutrition. Pseudomonas aeruginosa putida and Candida alabarata were isolated from the gastric tissue. He was discharged on day 27 with a baseline creatinine level of 0.9 mg/dL, and on cyclosporine and prednisone.

Discussion: This is a rare case of a 36-year-old man with a history of type 2 diabetes, systemic arterial hypertension, chronic kidney disease, who underwent a living-related kidney transplant in 2022, with a PRA-SA of 0/0%. He received induction with basiliximab and methylprednisolone, and maintenance immunosuppression with tacrolimus, mycophenolic acid, and prednisone. With baseline creatinine of 1.0 mg/dL.

FR-PO786

Phlegmonous Gastritis After Renal Transplantation First Case Reported in the Literature

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Introduction: Phlegmonous gastritis (PG) is a rare condition. Approximately one case per year has been reported in the literature, with a total of around 500 reported cases. We present the first case of phlegmonous gastritis following kidney transplantation, to the best of our knowledge based on the literature available.

Case Description: This is about a 36-year-old man with a history of type 2 diabetes, systemic arterial hypertension, chronic kidney disease, who underwent a living-related kidney transplant in 2022, with a PRA-SA of 0/0%. He received induction with basiliximab and methylprednisolone, and maintenance immunosuppression with tacrolimus, mycophenolic acid, and prednisone. With baseline creatinine of 1.0 mg/dL.

Two months after the transplant, he developed fever, oral ulceration. He was hospitalized, and a fever of 40 °C was documented, mild epigastric tenderness was noted on abdominal examination. Laboratory tests revealed leukocytosis, elevated C-reactive protein, creatinine (2.5 mg/dL). Abdominal computed tomography confirmed pneumonia, pneumoperitoneum, gastric wall thickening. Tacrolimus and mycophenolic acid were discontinued, and steroid therapy was continued. Meropenem was initiated. An endoscopy performed within 12 hours of symptom onset revealed multiple areas of diffuse gastric necrosis and purulent material. Lincosidol was added to the treatment regimen, and a nasojejunal tube was placed for total enteral nutrition. Pseudomonas aeruginosa putida and Candida alabarata were isolated from the gastric tissue. He was discharged on day 27 with a baseline creatinine level of 0.9 mg/dL, and on cyclosporine and prednisone.
FR-PO787
Progressive Dysphagia in Kidney Transplant Recipient: An Unusual Cause
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Introduction: Upper gastrointestinal (GI) symptoms such as dysphagia and odynophagia in immunocompromised hosts are generally caused by viral or fungal infections. We present a kidney transplant recipient who developed progressive dysphagia and odynophagia caused by mycobacterium, and should be considered as a potential etiology of dysphagia in a transplant recipient. 

Case Description: A 49-year-old male (CMV IgG-, EBV IgG+) received kidney transplantation from deceased donor, zero HLA mismatches, non-sensitized, started with fever and oral ulcers three days prior admission to the hospital. The patient’s immunosuppression was tacrolimus and mycophenolate. He had been on treatment with Valganciclovir for 20 days due to asymptomatic cytomegaly with positive antigenemia. The patient was hospitalized and started on empirical IV Ganciclovir due to possible cytomegalovirus (CMV) disease. Despite the treatment, he maintained fever episodes and experienced worsening of oral ulcers, and onset of odynophagia, with the presence of esophageal ulcers in the upper digestive endoscopy. Biopsy of esophageal ulcers was performed with the presence of gram-positive colonies and Actinomyces spp. The patient was treated with IV ceftriaxone, and then oral amoxicillin for 4 months with clinical improvement.

Discussion: The case reported above is a rare presentation of Actinomycosis, a disease with low prevalence and difficult diagnosis. The occurrence of oral and esophageal ulcers is uncommon with few cases reported. Main clinical forms comprise cervicofacial features with the occurrence of chronic cutaneous nodules and emergence of gastrointestinal tumors, usually in the ileocecal region, presenting with abdominal pain, weight-loss and weakness. In this case, the diagnosis was challenging due to a large number of possible infections such as herpes simplex, CMV, oral moniliasis, among others, especially in the first 6 months after kidney transplant.

FR-PO788
Eosinophilic Gastroenteritis due to Belatacept: Novel Side Effect of a Novel Agent
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Introduction: Belatacept is a novel fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), selectively inhibits T-cell activation through costimulation blockade. Eosinophilic Gastrointestinal Disease (EGID) is a rare disorder characterized by focal or diffuse eosinophilic infiltration of the bowel wall with various gastrointestinal manifestations.

Case Description: Our Patient was a 24-year-old Caucasian Male with ESRD s/p LRKT 10 years ago. The patient was induced with Simulect(Basiliximab), thereafter he was started on immunosuppresion regimen with Belatacept 750mg intravenous injection, Cellcept 750mg twice daily and tapering doses of Prednisone and has had a smooth post transplant course. About two years after the transplant, he started complaining of epigastric pain, worsen on ‘bending forward’. Laboratory data revealed peripheral eosinophilia 9% and iron deficiency anaemia. Endoscopy revealed mucosal edema with extensive ulcerations and nodularity of esophagus, duodenum, and terminal ileum. Histopathology revealed extensive ulcerations of esophagus, duodenum, and terminal ileum with diffuse eosinophilic infiltration. Belatacept was stopped resulting in complete resolution of clinical symptoms, peripheral eosinophilia, Anaemia and also complete resolution of the esophageal and duodenal ulcerations with resolution of eosinophilic infiltration.

Discussion: Drug induced EGIDs are very rare and there are only few case reports of drug induced EGIDs. Diagnosis is usually lead by high index of suspicion paired with exclusion of other causes of peripheral eosinophilia. Final diagnosis is made with biopsy proven eosinophilic infiltration of bowel wall. T-cell co-stimulation through CD28 and B7-2 plays an important role in allergic responses and administration of a CTLA-4 immunoglobulin blocks this interaction. Thus, we may surmise that costimulation blockade with Belatacept could trigger allergic conditions such as EGIDs.

FR-PO789
An Uncommon Presentation of Esophageal Actinomycosis in a Patient with Recent Kidney Transplant
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Introduction: Actinomycosis is a rare granulomatous disease, caused by a gram positive anaerobic bacterium, which inhabits the gastrointestinal tract and oral cavity in a commensal manner, but can cause an infectious process by invading injured tissue. Actinomyces israelii is the main human pathogen. The most common site of involvement is cervicofacial region with formation of abscesses and granulomas, followed by abdominal and thoracic involvement.

Case Description: A 33-years-old male, three months after kidney transplant from deceased donor, zero HLA mismatches, non-sensitized, started with fever and oral ulcers three days prior admission to the hospital. The patient’s immunsuppression was tacrolimus and mycophenolate. He had been on treatment with Valganciclovir for 20 days due to asymptomatic cytomegaly with positive antigenemia. The patient was hospitalized and started on empirical IV Ganciclovir due to possible cytomegalovirus (CMV) disease. Despite the treatment, he maintained fever episodes and experienced worsening of oral ulcers, and onset of odynophagia, with the presence of esophageal ulcers in the upper digestive endoscopy. Biopsy of esophageal ulcers was performed with the presence of gram-positive colonies and Actinomyces spp. The patient was treated with IV ceftriaxone, and then oral amoxicillin for 4 months with clinical improvement.

Discussion: The case reported above is a rare presentation of Actinomycosis, a disease with low prevalence and difficult diagnosis. The occurrence of oral and esophageal ulcers is uncommon with few cases reported. Main clinical forms comprise cervicofacial features with the occurrence of chronic cutaneous nodules and emergence of gastrointestinal tumors, usually in the ileocecal region, presenting with abdominal pain, weight-loss and weakness. In this case, the diagnosis was challenging due to a large number of possible infections such as herpes simplex, CMV, oral moniliasis, among others, especially in the first 6 months after kidney transplant.
**FR-PO791**

**Health Equity Gaps in Access to Kidney Transplant**

Chiao Wen Lan,1 Deidra C. Crews,2 Sumit Mohan,3 Sherri Morgan-Johnson,4 Melissa Murphy,4 Health Services Advisory Group Inc, Phoenix, AZ; Columbia University, New York, NY; Johns Hopkins Medicine, Baltimore, MD; Centers for Medicare and Medicaid Services (CMS), Baltimore, MD.

**Background:** Research has documented cascading barriers to care, while accessing kidney transplant across neighborhood characteristics have not been fully examined.

**Methods:** ESRD Quality Reporting System (EQRS) data between 1/1/2015-5/20/2023 were analyzed. Access to transplants is examined, including calculating time on dialysis to listing and time on list before transplanted. Data were linked to the Area Deprivation Index (ADI), a neighborhood-level metric that combined 17 specific indicators (e.g., poverty, housing).

**Results:** 9.5% of patients added to the waitlist were from the most disadvantaged neighborhoods, while 14.6% of ESRD patients residing there. Among patients who received transplants, waitlist time was consistently longer for Black patients compared to White patients (p<0.001), and the difference has narrowed over the years, yet the gap remains. Neighborhood characteristics are associated with health disparities, where patients from more disadvantaged neighborhoods waited longer on the list before getting transplanted than those from the least disadvantaged areas (15.3 vs. 13.4 months, p<0.0001). Racial disparities exist across neighborhood socioeconomic level. White ESRD patients in the most disadvantaged neighborhoods were added to the waitlist faster than Black patients in the least disadvantaged neighborhoods (38.6 vs. 43.2 months, p<0.01). The time on the list before transplantation among White patients in the most disadvantaged neighborhood was shorter than Black patients in the least disadvantaged neighborhoods (14.9 vs. 16.1 months, p<0.0001).

**Conclusions:** The results show significant disparities in access to care among ESRD patients in disadvantaged neighborhoods and that Black patients have reduced access to the transplant waitlist regardless of neighborhood characteristics. Researchers emphasize the need for policies and strategies that overcome structural racism barriers in access to transplants.

**Funding:** Other U.S. Government Support

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**FR-PO792**

**Outcome of Organ Procurement and Transplantation Network (OPTN) Policy Allowing for Waiting Time Modification for Candidates Affected by Race-Inclusive eGFR Calculations: Early Impact from a Single Center**

Debra Wekesa, Scott G. Westphal, Clifford D. Miles. University of Nebraska Medical Center, Omaha, NE.

**Background:** Black patients have a high burden of kidney disease yet experience lower rates of waitlisting and kidney transplantation. There is a myriad of reasons for these disparities, including the historic race modifier used for GFR estimation, which ascribes a higher GFR at a given serum creatinine level in black individuals. Since eGFR ≥ 20 ml/min is required for waiting time accrual, the eGFR race modifier could delay listing for some black patients. In January 2023, the OPTN implemented a policy whereby registered black transplant candidates could receive waiting time adjustment if a prior race-inclusive eGFR calculation yielded values such that “non-African American” eGFR was ≥ 20 ml/min, but the “African American modified” eGFR was ≥20 ml/min.

**Methods:** Upon enactment of this policy, our transplant program identified potential candidates, and through internal EMR review, communication with patients, their nephrologists, and PCPs, eligible candidates were identified for waiting time modification. Here, we report the impact of this policy change at a single center one month after submission for waiting time modification for eligible candidates.

**Results:** 37 adult patients on our waitlist had self-identified as Black or African American. In 19 (51.4%) patients, historic race-inclusive GFR estimates were found that allowed for waiting time modification. In these patients, a mean 753 ± 788 and median 407 (327, 901) additional days of waiting time was added. The maximum time added for a single patient was 3,323 days (9.1 years). 4 of the 19 (21%) candidates received a deceased donor kidney transplant within 1 month of waiting time modification.

**Conclusions:** At a single center, >50% of patients were eligible for waiting time addition, with an average of ~2 years of waiting time added per eligible candidate. Importantly, this modification yielded near immediate impact, with ~20% of patients receiving a transplant within the first month of the modification. While the number of black patients on our waiting list is small relative to many centers, this early assessment of the policy impact demonstrates the potential of its intended effects. Centers with large numbers of black patients will require a coordinated effort to ensure timely identification and implementation of appropriate waiting time addition.

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**FR-PO793**

**Bridging the Literacy Gap in Living Kidney Donation Information by ChatGPT**

Oscar A. García Valencia,1 Jasmina Cracić,1 Caroline Jadlowiec,2 Shennen Mao,3 Michael A. Mao,4 Napat Leepaphorn,3 Pooja Budhiraja,2 Charat Thonggrayoon,1 Wisit Cheungpasitporn,3 Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN; Mayo Clinic Arizona, Scottsdale, AZ; Mayo Clinic in Florida, Jacksonville, FL.

**Background:** Improving diversity and equity in living kidney donation requires ensuring that information on the topic is accessible to people with different levels of literacy. The average American adult reads at an eighth-grade level, highlighting the need to modify complex medical information for easier comprehension. ChatGPT, an AI language model, has the potential to modify medical information to improve readability. This study aimed to assess the effectiveness of ChatGPT in modifying living kidney donation information to an eighth-grade reading level.

**Methods:** We collected 27 questions and their answers from a widely accessible FAQs website (Donate Life America) related to living kidney donation. ChatGPT (03/23 Version) modified the text of the answers to make them easier to comprehend for those who read at or below an eighth-grade level. Original and modified information were assessed for readability using the well-validated Flesch-Kincaid formula. The grade level of each answer was compared before and after modification, and a paired t-test was used to evaluate the significance of any reduction in grade level.

**Results:** The average grade level of the original answers was 9.6±1.9, while the average grade level of the modified answers was 7.7±1.8, indicating a significant reduction in grade level (p=0.001). ChatGPT was able to modify the information to an eighth-grade reading level or below in 16 out of 27 cases (59%). The grade level of the modified answers ranged from 3.4 to 11.3.

**Conclusions:** Our study demonstrates that ChatGPT can be a useful tool in improving the grade level readability of information on living kidney donation for individuals with lower literacy levels. Although ChatGPT was not able to modify all the information to below an eighth-grade reading level, it significantly reduced the grade level readability of the modified information compared to the original information. This suggests that ChatGPT may potentially play a role in promoting diversity and equity in living kidney donation by making information more accessible to a wider range of individuals. Our study also shows that ChatGPT significantly reduces the grade level readability of modified versions, there is still room for improvement.

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

Underline represents presenting author.
FR-PO794
Strategies to Increase Deceased Organ Donation: A Single-Center Experience from an Inner-City Hospital in the Bronx
Oscar Y. Pena,1 Shiny Teja Kolli,2 Vishal Reddy Bejuguam,2 Roxanne Todor,1 Anjali Acharya,
1New York City Health and Hospitals Jacobi, Bronx, NY; 2NYC Health and Hospitals North Central Bronx, New York, NY.

Background: Kidney transplantation is the treatment of choice for end-stage kidney disease as it improves the quality of life and reduces the mortality risk. However, the average wait time ranges from 4 months to > 6 years, with 1 out of 20 (5%) patients dying each year while waiting. According to a 2022 report by the New York Organ Donor Network, the Bronx has the lowest organ donation rate at 11.3% vs. 18.1% in New York City. The Bronx had the highest number of people on the waiting list, with 1,500 people. Several factors, including SDOH contribute to the Bronx’s low organ donation rate. Centers for Medicare & Medicaid Services (CMS) introduced the End Stage Renal Disease Treatment Choices Learning Collaborative (ETCLC) in August 2021 with the goal to accomplish one of the goals of the Advancing American Kidney Health by increasing kidney transplants.

Methods: From June 2020 to March 2022. We excluded patients under 18 years old and those who died upon arrival. Electronic medical records were reviewed, and statistical analysis was performed using StataBE17.

Results: There were a total of 375 patient deaths. Of these, 212 were male (56.53%), and 163 were female (43.47%). The mean age was 68.9 years. Thirty-three patients (8.8%) were diagnosed with brain death. Of these, 14 patients (42%) became organ donors. Acute kidney injury (AKI) was present in 42% of patients with brain death. The breakdown of AKI severity was as follows: KDIGO I: 28% KDIGO II: 50% KDIGO III: 22%. Timely referral to the OPO was made in 65% of the cases. Nephrology was contacted for 12% of these patients and all 12% required kidney replacement therapy

Conclusions: Identifying the missed opportunities for deceased organ donations is the first step in improving the process. We have implemented processes such as ongoing education of the stake holders and we are committed to working with our partners at the New York Organ Donor Network to ensure that every eligible patient has the opportunity to receive a life-saving organ transplant.

June 2021 - March 2022 Observations (%)

<table>
<thead>
<tr>
<th>Decedent Patients</th>
<th>375 Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male 212 (56.53%) Female 163 (43.47%)</td>
</tr>
<tr>
<td>Brain death (BD)</td>
<td>33 (8.8%) of 375</td>
</tr>
<tr>
<td>Harvest Organ</td>
<td>375 (100%)</td>
</tr>
<tr>
<td>AkI in BD</td>
<td>19 (57%)</td>
</tr>
<tr>
<td>KDIGO I</td>
<td>12 (41%)</td>
</tr>
<tr>
<td>KDIGO II</td>
<td>7 (21%)</td>
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<tr>
<td>KDIGO III</td>
<td>4 (13%)</td>
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<tr>
<td>KPT in BD</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Kidney transplant</td>
<td>3 (9%)</td>
</tr>
</tbody>
</table>

Brain death (BD), Kidney replacement therapy (KRT), Acute Kidney Injury (AKI)

FR-PO795
Perceived Barriers to Transplantation in the Hispanic Community
Arturo Lope. University of Kansas Medical Center Department of Internal Medicine, Kansas City, KS.

Background: Hispanics have a higher prevalence of kidney disease but a lower rate of kidney transplantation (KT). Multiple barriers have been proposed, but patient reported barriers have not been assessed. We interviewed Hispanic patients with kidney failure to assess first-hand reports of patient perceived barriers to KT.

Methods: We interviewed patients from dialysis units and clinics between June and October 2022. The inclusion criteria were age 18-65, eGFR of ≤ 20 ml/min, and Spanish as the primary language. Interviews were conducted in Spanish, audio recorded, and transcribed to English, and uploaded to a qualitative data analysis software DEDoose. The interviews were then analyzed and coded into a priori twenty-three communication-based categories created by a communications framework.

Results: Most patients felt willing and able to undergo KT. Patients lacked knowledge about the KT process and could not make a well-informed decision. Living donation (LD) was discussed with very few; in general, patients lacked knowledge about LD. Some viewed LD as a significant health risk to the donor. Misconceptions were evident, with a few patients reporting discussions on emigration to their native countries increasing their chances of KT. Lack of insurance or cost of KT were common concerns. Patients reported infrequent counseling, with most interactions with individuals other than a nephrologist. Often, the initial communication regarding KT occurred in the emergency room or when initiating dialysis. Use of translators and Spanish-speaking providers was common. Discussions were limited when a Spanish interpreter was absent. Occasionally, the translation was inadequate or difficult to understand.

Conclusions: Multiple patient perceived barriers to KT were noted during our interviews. These included acess to nephrologists, barriers in communication despite language barriers, and infrequent counseling. Additional resources and efforts are needed to improve KT rates in the Hispanic population.

FR-PO796
Promoting Transplant Equity: Characterizing Deceased Organ Donation by Noncitizens in the United States
Katherine M. Rizzolo,1,2 Jesse D. Schold,3 Lilia Cervantes,3 Boston Medical Center, Boston, MA; 1University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: There are no citizenship restrictions to receiving or donating a kidney transplant per the United Network for Organ Sharing and the Organ Procurement Transplantation Network. However, the major barrier to transplant for most undocumented immigrants is insurance barriers as undocumented immigrants are barred from receiving federal insurance. Non-citizens are aware of the double standard allowing them to donate organs despite the restrictions to receiving them. Restricting access to organ transplant pool while being able to contribute to it is inequitable. However, the degree of contribution to the organ pool by non-citizens has not been recently assessed. The aim of this study is to illustrate the degree to which non-citizens contribute to the organ pool in the US between 2015 and 2020.

Methods: We utilized UNOS data examining deceased organ donors in the US between 2015 and 2020. To summarize recipient and donor characteristics, median and interquartile range (IQR) were used for continuous variables and counts and percents were used for categorical variables. Characteristics were stratified by reported citizenship status. To test for differences across groups, ANOVA (for normally distributed) or Kruskal-Wallis (non-normally distributed) tests were used for continuous variables after testing for normality via the Shapiro-Wilk test and Chi-square tests were used for categorical variables.

Results: Non-US Citizen/US Residents (NCR) accounted for 2.8% and Non-US Citizens/Non-US Residents (NCNR) accounted for 0.4% of the donor population. The majority of US citizens, non-citizen residents were more likely to be older, male, O blood type and have diabetes. Regarding citizenship status of donors and recipients, 91% of NCR and 90% of NCNR organs (n=5581) were received by US citizens. 5.8% of organs (n=9172) donated by US citizens were received by NCR or NCNR recipients.

Conclusions: There are no citizenship restrictions on organ donation from deceased individuals, however, restrictions on federal insurance is a barrier to transplant for non-citizens. We illustrate that non-citizens donate healthy, viable organs to the US organ pool, the majority of which are received by US citizens. Any system that uses these gifts from individuals who would themselves not be considered eligible for an organ transplant is unjust.

Funding: NIDDK Support, Commercial Support - Davita

FR-PO797
Renal Transplant Outcomes Among Pediatric Non-English Language Preference Patients
Yaritz M. Asadillo, Ponmali Le, Sonia Solomon. Westchester Medical Center, Valhalla, NY.

Background: Non-English language preference (NELP) is associated with disparities in health care access and quality and worse clinical outcomes in children. To our knowledge, no studies characterize the role of NELP in the renal transplant process. The primary aim of this study is to compare pediatric renal transplant outcomes among NELP and English Language Preference (ELP) populations.

Methods: This retrospective single-center study included pediatric patients between the ages of 0 to 21 who received renal transplants between January 2014 and September 2014. The determination of NELP was made based on interpreter use, language spoken at home, or explicit documentation of NELP in the electronic medical record. Proportions were compared using Mann-Whitney, Chi-squared tests, and unpaired t-test. Two-tailed p values of <0.05 were considered significant.

Conclusions: Of 45 renal transplant recipients were included. 26% (12) of these patients were identified as NELP. The average age at transplant for NELP patients was 12.3 (± 5.3) and ELP was 10.7 (± 5.4). Those identified as NELP were significantly less likely to have a

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Transplantation, Waitlist Status, and County Indices of Economic Health in West Virginia

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Background: Kidney transplantation is the optimal treatment for patients with end stage kidney disease. Many patients are never waitlisted for transplant. West Virginia (WV) has a high poverty rate (PR) (17.1 vs 12.8% for the US) with 33 of its 55 counties recognized as economically distressed or thereby at risk. We searched for a potential association between transplant waitlisting and the receipt of a transplant with indices of economic health.

Methods: Data on initiation of kidney replacement therapy with dialysis or transplant, waitlist for transplant and death between 1965 and 2020 for WV patients were collected from USRDS. Data on county PR and economic distress including composite index (CI) for national economic status were collected from the Appalachian Regional Commission.

Results: Of the 23,055 WV patients identified in USRDS data, 2,999 (13%) were transplanted compared to 514,050 (15.3%) for the rest of the US (p < 0.001). Patients who never received a kidney transplant were from counties with higher PRs (18%) compared to transplanted patients (17.5%); p < 0.001. Overall, waitlisted patients (2,375) came from counties with lower PRs than those who were never waitlisted (17.6 vs 18%); p < 0.001. Waitlisted patients were less likely to be from distressed or at-risk counties (32 vs 34.3%; p < 0.05) or counties with lower CI (141.9 vs 145.2; p < 0.001) than patients who were never waitlisted. Among those who were never transplanted, waitlisted patients (792) came from counties with lower PRs (17.1 vs 18%; p < 0.001), less distressed or economically at-risk counties (28.9 vs 34.5%; p < 0.003) and counties with a lower CI (139 vs 145.5; p < 0.001) than those who were never waitlisted (20,479). In multivariable logistic regression, county PR remained an independent predictor of lower odds of being transplanted (OR 0.91; 95% CI: 0.85-0.97; p < 0.005) or waitlisted (OR 0.9, 95% CI: 0.84-0.96; p < 0.001) per 5% increase in poverty rate after adjusting for age, sex, BMI, tobacco use, functional status, comorbid medical conditions and drug dependence.

Conclusions: Waitlisted patients and transplant recipients from WV were more likely to hail from counties with lower PRs and those in better economic health.

FR-PO799

Assessment of Disparities in Access to Valganciclovir Cytoimmunovirus Prophylaxis in High-Risk African American Kidney Transplant Patients

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1Medical University of South Carolina College of Medicine, Charleston, SC; 2Medical University of South Carolina Department of Surgery, Charleston, SC; 3Jordan University of Science and Technology, Irbid, Jordan.

Background: While access and outcomes disparities in African American (AA) kidney transplant recipients are well-known, there are limited studies assessing medication access disparities in transplant medicine. Cytomegalovirus (CMV) is a common viral infection that can cause serious complications in transplant recipients, with potential excess burden in AA communities. The high out-of-pocket costs associated with valganciclovir prophylactic therapy likely affect its use, so research is needed to fully understand differences in access to antiviral CMV prophylaxis and its impacts on CMV infection in AA transplant recipients.

Methods: This was a single-center, retrospective longitudinal cohort study in high-risk (CMV serostatus D+/R-) adult kidney recipients transplanted between 6/1/2010 and 5/31/2020, representing a 10-year cohort. Data was collected through electronic and manual medical record abstraction. Standard univariate comparative statistics were utilized in conjunction with binary logistic regression for multivariable modeling.

Results: 418 kidney transplant recipients were included, of which 179 (42.8%) were AA and 239 were non-AA. Baseline demographics were significantly different in mean age in years (46.5 ± 12.9 AA vs. 50.9 ± 13.9 non-AA; p < 0.001) and private and Medicaid insurance status (p < 0.001). AA experienced higher rates of death-censored graft loss (10.6% AA vs. 5.0% non-AA; p < 0.031). There was no difference in CMV infection rate, opportunistic infection rate, or death between AA and non-AA patients. AA patients were 42% less likely to receive valganciclovir prophylaxis in covering out-of-pocket costs (assistance programs and/or fundraising/savings) use compared to non-AA patients (OR 0.58, 95% CI [0.379-0.892], p < 0.013). In a multivariable model including age, Medicaid status, and donor mortality variables, the impact of AA race on use of these assistance programs was no longer statistically significant (OR 0.70, 95% CI [0.448-1.094], p = 0.118).

Conclusions: In univariate analyses AAs were significantly less likely to utilize assistance programs or fundraising/savings to access valganciclovir, which was somewhat explained by age, insurance status, and donor type. Despite this, CMV infection rates did not differ significantly between the AA and non-AA cohorts.

FR-PO800

Structural Racism and Access to Kidney Transplantation: Examining Residential and Transplant Center Segregation

Yiting Li1, Gaythri Menon,1 Byoungjun Kim,1 Evelien Quint,2 Maya N. Clark-Cutaia,1 Wenbo Wu,1 Sarah Szanton,3 Deidra C. Crews,2 Tanjala S. Purnell,1 Dorry L. Segesv,3 Mara McAdams-DeMarco.1 New York University Grossman School of Medicine, New York, NY; 2Johns Hopkins University, Baltimore, MD; 3The Johns Hopkins University School of Medicine, Baltimore, MD; 4Universitair Medisch Centrum Groningen Centrum voor Congenitale Hartafwijkingen, Groningen, Netherlands.

Background: Disparities in kidney transplantation (KT) access exist for systematically disadvantaged communities. Racial/ethnic segregation, a marker of structural racism, in a candidate’s residential neighborhood and their transplant center’s neighborhood may drive KT disparities.

Methods: We identified 158,506 Black and White KT candidates (age≥18) first listed between 1995-2021 using SRTR. Segregation scores were calculated based on Thiel’s H method. These scores were subsequently categorized into tertiles. We used proportional hazards models, adjusting for individual- and neighborhood-level factors, to quantify the likelihood of deceased donor KT (DDKT) and live-donor KT (LDKT). We also assessed the differential impact of segregation on KT access for Black candidates, using an interaction term of segregation tertiles and candidate race.

Results: Black candidates were more likely to reside in high-segregation neighborhoods (70.1% vs. 39.9%; P < 0.001) and be listed at transplant centers located in these neighborhoods (63.9% vs. 38.2%; P < 0.001). Candidates living in a high-segregation neighborhood were less likely to receive LDKT but not DDKT; furthermore, residence in a high-segregated neighborhood was associated with lower access to LDKT for Black candidates (HR 0.88, 95%CI 0.82-0.95) but not White candidates (P = 0.017). Candidates listed in centers in a high-segregation neighborhood had lower access to DDKT, independent of race. However, LDKT access was lower for Black candidates listed at centers in a high-segregation neighborhood (aHR=0.90, 95%CI: 0.84-0.97; Pinteraction = 0.042).

Conclusions: Access to LDKT was significantly lower for Black candidates who resided in or were listed in centers in segregated neighborhoods, and access to DDKT was lower for all candidates whose centers were in high-segregation neighborhoods. Targeted efforts should address the impacts of racial/ethnic segregation on equitable access to KT.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging, National Institute of Allergy and Infectious Diseases
Impact of Race on Estimated Post-Transplant Survival Score in Patients with ADPKD

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University of Chicago Division of the Biological Sciences, Chicago, IL.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) affects individuals of every race equally. Access to kidney transplant (Tx) and post-Tx outcomes may vary by race. Estimated Post Transplant Survival (EPTS) scores are used to allocate high-longevity kidneys to patients who are expected to receive the most years of graft function. We examined EPTS scores in ADPKD by race, and compared these results to Tx recipients with other kidney diseases.

**Methods:** ADPKD and non-ADPKD patients aged ≥30 years who received Tx 1/2000-3/2021 were selected from OPTN/UNOS data when ethnicity was unambiguously identified as White, African American, Hispanic, or Asian with available EPTS scores. Using the current EPTS table, EPTS percentages were categorized as ≤20%, >20-80%, and >80%. The four components of EPTS (age, diabetes, prior Tx, and years of dialysis) were analyzed by race for both groups.

**Results:** Overall, ADPKD patients were more likely (43.5%) to have EPTS ≤20% compared to other kidney disorders (26.1%). Although African American, Hispanic, and Asian ADPKD patients were more likely to have EPTS ≤20% than other kidney disorders, differences in EPTS ≤20% were greater across race in ADPKD individuals than those with other kidney disorders. In ADPKD patients, White patients had significantly lower duration of dialysis and EPTS was predominantly determined by dialysis duration. In non-ADPKD patients, diabetes and prior transplantation were more often determinants.

**Conclusions:** Overall, transplanted ADPKD patients had significantly lower EPTS scores than other transplant recipients. However, increased dialysis time among non-white ADPKD patients leads to less favorable EPTS scores reducing allocation of best-quality kidneys to minority patients with ADPKD.

![Expected post transplant survival scores, by diagnosis and race.](image)

FR-PO801

The Association of Altered Sense of Smell with Nutritional Status in Patients with Advanced CKD

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**Background:** Anorexia is common in patients with advanced CKD and could lead to protein energy wasting (PEW). Altered sense of smell, a reflection of olfactory dysfunction, is a potential mechanism that exacerbates the impact of anorexia on PEW. In this study, we examined the extent of altered sense of smell and its association with PEW in patients with moderate to advanced CKD.

**Methods:** We studied 139 participants (34 healthy subjects, 50 patients with stage 3-4 CKD, 55 patients on maintenance hemodialysis (MHD)) using the odor identification test (Sniffin' Sticks odor screening test containing 12 different smells). Odor identification test were scored as correct or incorrect, and a total odor score was calculated for each participant. Malnutrition Inflammation Score was used to assess PEW.

**Results:** CKD patients had elevated levels of C-reactive protein and reduced eGFR and serum albumin concentrations compared to controls (Table1). There was a gradual decrease in the total odor score between groups, controls with highest and MHD patients with lowest scores. A similar gradual worsening was observed in MHD scores with MHD patients displaying worst nutritional score (p < 0.001) (Figure 1), more mismatch, dialysis years, diabetes, immunosuppression, CMV, cold ischemia, center distance, PRA, private insurance, donor KDP, delayed graft function, and living/pre-emptive Tx were included with W as the reference.

**Results:** Among 32,611 ADPKD recipients, W, AA, H, and A were 76.4, 10.7, 9.8, and 3.1% respectively (Table 1). Compared to W, all others had more dialysis years and more mismatch, but less private insurance and fewer living and preemptive Tx. There was more delayed graft function, despite more lymphocyte depleting induction and corticosteroids.

**Conclusions:** Tx recipient survival did not differ between W and AA ADPKD patients, but was superior in H and A patients. Decreased allograft survival in African American ADPKD patients persisted after adjustment, suggesting that additional biological or social/economic factors remain to be identified.

![Patient Characteristics by Race](image)

Patient and Allograft Survival

FR-PO803

Impact of Race on Kidney Transplant Outcomes in Patients with ADPKD

Rita L. McGill, Sambhavi Krishnamoorthy, Niveditha Girimaji Sathischandra, Arlene B. Chapman.
University of Chicago Division of the Biological Sciences, Chicago, IL.

**Background:** Autosomal dominant polycystic kidney disease (ADPKD) is equally present in all ethnicities. Disparities in access to transplant (Tx) exist for African American (AA) and Hispanic (H) ADPKD patients. We examined outcomes among ADPKD patients who received kidney Tx, by self-reported race.

**Methods:** OPTN/UNOS files were used to identify ADPKD patients aged ≥30 receiving Tx 2000-2021, and ethnicity was White (W), AA, H, or Asian (A). A Cox model provided hazard ratios for death and a subdistribution hazards model for graft failure accounted for death as a competing outcome. Adjustments for age, gender, BMI, HLA/DR mismatch, dialysis years, diabetes, immunosuppression, CMV, cold ischemia, center distance, PRA, private insurance, donor KDP, delayed graft function, and living/pre-emptive Tx were included with W as the reference.

**Results:** Among 32,611 ADPKD recipients, W, AA, H, and A were 76.4, 10.7, 9.8, and 3.1% respectively (Table 1). Compared to W, all others had more dialysis years and more mismatch, but less private insurance and fewer living and preemptive Tx. There was more delayed graft function, despite more lymphocyte depleting induction and corticosteroids.

**Conclusions:** Tx recipient survival did not differ between W and AA ADPKD patients, but was superior in H and A patients. Decreased allograft survival in African American ADPKD patients persisted after adjustment, suggesting that additional biological or social/economic factors remain to be identified.

| Patient and Allograft Survival | FR-PO803 | The Association of Altered Sense of Smell with Nutritional Status in Patients with Advanced CKD | Raqihe Gulsaib Dilaver,1 Zeynep Bağ,2 Andrew Guide,3 Robert Greevy,3 Talat Alp Ikizler.1 1Vanderbilt University Division of Nephrology and Hypertension, Nashville, TN; 2Ankara Egitim Ve Arastirma Hastanesi, Ankara, Turkey; 3Vanderbilt University Medical Center Department of Biostatistics, Nashville, TN. | Background: Anorexia is common in patients with advanced CKD and could lead to protein energy wasting (PEW). Altered sense of smell, a reflection of olfactory dysfunction, is a potential mechanism that exacerbates the impact of anorexia on PEW. In this study, we examined the extent of altered sense of smell and its association with PEW in patients with moderate to advanced CKD. | Methods: We studied 139 participants (34 healthy subjects, 50 patients with stage 3-4 CKD, 55 patients on maintenance hemodialysis (MHD)) using the odor identification test (Sniffin’ Sticks odor screening test containing 12 different smells). Odor identification test were scored as correct or incorrect, and a total odor score was calculated for each participant. Malnutrition Inflammation Score was used to assess PEW. Results: CKD patients had elevated levels of C-reactive protein and reduced eGFR and serum albumin concentrations compared to controls (Table1). There was a gradual decrease in the total odor score between groups, controls with highest and MHD patients with lowest scores. A similar gradual worsening was observed in MHD scores with MHD patients displaying worst nutritional score (p < 0.001) (Figure 1), more prominently observed in the CKD and MHD groups. Conclusions: This cross-sectional study suggests that olfactory dysfunction, as assessed by an odor identification test, is altered in patients with advanced CKD, most notably in ones on MHD. In CKD patients, the severity of the loss of sense of smell is directly associated with worse protein-energy wasting. Further studies are needed to examine the casual relationship between odor sensation and development of PEW in patients with CKD. |
FR-PO804
Effect of Kidney Transplant (KT) on the Sense of Taste and Its Association with Nutritional Status in Patients with ESRD Who Receive Kidney Transplantation

Background: Taste alteration of bitter, sour, sweet, salty and umami test are common, and to prevent or improve malnutrition. There is not information regarding the change of taste perception after renal transplantation, and the association of taste change with nutritional status.

Methods: Prospective cohort in receptors of 1st transplant (Jan-Oct 2022). Subjects with dental prostheses, oral alterations, and active infection were excluded. The sample was 47 patients, and only 21 have completed the evaluation after the transplant. Subjective global assessment, pica questionnaire, current medications, and taste perception test. Anthropometric measurements were taken.

Results: Forty seven patients were included, 38.8 years old (mean); 70% were male, 51% had unknown cause of ESRD, 51% had hemodialysis, 43% peritoneal dialysis and 6% early trasplant.

Conclusions: There is a beneficial effect of kidney transplantation on the sense of taste and nutritional status. Patients with indicators of adipsy have an alteration of taste before the KT. The umami taste significantly increases the perception of intensity, and the sour taste presents a not significant trend, this after renal transplantation, despite that almost all taste intensities increases. Patients who present BMI 25-30 kg/m2 before the transplant decrease significantly after the transplant and muscle mass indicators (AMA) present a trend.

Funding: Government Support - Non-U.S.

Comparison of nutritional status according to taste alteration

<table>
<thead>
<tr>
<th>Variable</th>
<th>No taste alteration N=38</th>
<th>Taste alteration N=38</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry weight (kg)</td>
<td>58.1 (54.6-62.3)</td>
<td>68.0 (57.1-80.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>21.4 (19.2-24.0)</td>
<td>26.1 (23.5-30.9)</td>
<td>0.004</td>
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<td>Subscapular skinfold (cm)</td>
<td>12.0 (10.0-14.7)</td>
<td>16.5 (11.7-9.2)</td>
<td>0.04</td>
</tr>
<tr>
<td>Triceps skinfold (cm)</td>
<td>10.5 (6.5-7.0)</td>
<td>13.5 (10.4-19.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Mean ankle circumference (cm)</td>
<td>25.8 (21.8-26.7)</td>
<td>27.1 (24.8-31.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anterior iliac crease</td>
<td>27.9 (20.2-36.2)</td>
<td>33.3 (26.2-43.4)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

Figure 1

FR-PO805
Association Between Physical Activity and Cardiovascular Events, Tumors, and All-Cause Mortality in Patients with Maintenance Hemodialysis with Different Nutritional Status
Honeyan Liu, Yuyang Chen, Tao Feng, Pei Yu. NHRC Key Laboratory of Hormones and Development, Tianjin Key Laboratory of Metabolic Disease, Chu Hsien-I Memorial Hospital & Tianjin Institute of Endocrinology, Tianjin Medical University, Tianjin, China; Tianjin Dongli Hospital, Tianjin, China; The Second Affiliated Hospital of Baotou Medical College, Inner Mongolia University of Science and Technology, Baotou, China.

Background: The current research focuses on the effects of nutritional supplementation and exercise on dialysis patients, but whether exercise can improve outcomes in patients with different nutritional status is not clear.

Methods: The MHD patients were recruited from April 2021 to April 2022. The information of PA was obtained from the IPAQ and followed up once in 3 months. The outcomes were cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor, and all-cause death. We used COX proportional risk model to estimate the association between PA and the outcomes of MHD patients. Patients are classified into two groups based on Geriatric Nutritional Risk Index (GNRI) and classified by age, and we used COX proportional risk model to estimate the association of PA and outcomes in subgroups. ISM was used to estimate the effects of replacing LPA with MPA or VPA on risk of cardiovascular events, tumors, and all-cause death in different subgroups. The association between PA and outcomes was estimated with COX proportional risk model in different subgroups stratified according to baseline characteristics. The effects of PA on ankle-brachial index and body fat content were analyzed in different IPAQ groups.

Results: A total of 241 maintenance hemodialysis patients were included, 105 peoples developed cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor or all-cause death(43.6%). The median follow-up time was 12 months. MPA reduced the risk of outcome in MHD patients or high GNRI patients (40% vs 39%). In MHD patients who was under 65 years with high GNRI, MPA reduced cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor or all-cause death by 55%. PA reduced the risk of cardiovascular event by 65%, but did not reduce the risk of tumor and all-cause death. Replacing LPA with VPA did not improve clinical outcomes. It actually increases the risk of heart failure 0.4%.

Conclusions: MPA reduced the risk of cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor, or all-cause death in MHD patients under 65 years, while VPA had no health benefit.

FR-PO806
Prevalence and Risk Factors of Sarcopenia in ESRD Patients
Alan F. Almeida, Kiran Bijapur, Rasika Sirsatt, Aayan K. Dey, Khairwar Prasad. PD Hinduja National Hospital and Medical Research Centre, Mumbai, India.

Background: Sarcopenia is a progressive skeletal muscle disorder involving the accelerated loss of muscle mass and strength, associated with increased adverse outcomes like falls, poor quality of life, frailty, and mortality. Prevalence of sarcopenia in the dialysis population varies from 4% to 63%. However, the prevalence and risk factors in the Indian dialysis population remains uncertain.

Methods: The aim was to study the prevalence of sarcopenia, to identify associated risk factors and to assess the effect of dietary counselling on sarcopenia. It was a prospective observational study, in which, 70 adult patients on maintenance hemodialysis were enrolled and monitored for 6 months. All patients were given dietary counselling at baseline, 1, 3 and 6 months. Bio-impedance spectroscopy, a hand grip dynamometer, and a 4-meter walk test were employed to evaluate muscle mass, strength, and function, respectively. Asian Working Group for Sarcopenia criteria were used for defining sarcopenia. Univariate and multivariate analysis was done for the factors affecting sarcopenia.

Results: Seventy dialysis patients were evaluated. Age of the cohort was 55.3 ± 13.74 years old. The prevalence of probable sarcopenia, sarcopenia, and severe sarcopenia was...
11.43%, 25.71%, and 7.1% respectively. Increasing age and diabetes were potential risk factors for sarcopenia (p<0.0001 and P< 0.0093 respectively). Sarcopenia was associated with lower BMI (p<0.0006), and lower normalised protein catabolic rate (nPCR) (p=0.026). Hemoglobin, albumin, calcium, phosphorous, and high sensitivity C reactive protein (hsCRP) did not show any association with sarcopenia. Prevalence of sarcopenia at the end of 6 months was reduced to 17.46% from 25.71%. There was a significant improvement in hand grip strength. nPCR at 6 months was significantly increased in all patients as compared to baseline (p<0.05) which implies improvement in protein consumption.

Conclusions: High prevalence of sarcopenia in dialysis patients in this study emphasizes the importance of increasing clinical awareness about sarcopenia and nutritional status assessment in this group of patients. Several variables like age, BMI, diabetes mellitus and nPCR were significantly associated with sarcopenia. Detailed dietary recall and nutritional intervention can improve sarcopenia and must be actively pursued.

FR-PO807
Associations Between Submaximal Indices of Physical Function and VO2 Peak in Patients on Hemodialysis
Elliott Arroyo, Heather Burney, Drake Dillman, Syed J. Sher, Sharon L. Karp, Sharon M. Moe, Kenneth Lim. Indiana University School of Medicine, Indianapolis, IN.

Background: Cardiopulmonary exercise testing (CPET) is well-recognized as the gold standard tool for quantifying cardiovascular functional capacity (as assessed by peak oxygen uptake, VO2Peak during exercise). VO2Peak is a strong predictor of survival in patients with chronic kidney disease (CKD). It is currently unknown whether basic submaximal tests can reliably predict VO2Peak in patients with advanced CKD. Herein, we sought to compare the association between various submaximal assessments of physical function with VO2Peak in patients on hemodialysis.

Methods: We analyzed data from the ongoing, “Effects of long interdialytic intervals on Cardiovascular Functional Capacity (EUCON)” study, a randomized crossover trial of patients on hemodialysis. All participants underwent CPET and a battery of submaximal tests of physical function and mobility on a non-diary day. Multivariable step regression analysis was used to assess the association between the submaximal tests and VO2Peak.

Results: A total of 30 patients were stratified based on the median VO2Peak value of 11.2 mL/kg/min into a High group (n=15, 11 [73%] men, age=54 [11]; VO2Peak=14.4 [2.5] mL/kg/min) and a Low group (n=15, 8 [53%] men, age=56 [12]); VO2Peak=9.8 [1.3] mL/kg/min). The High group had a lower BMI (26.7 [5.9] kg/m2) compared to the Low group (33.6 [7.4] kg/m2; p=0.008). No group differences were observed in age, sex, race/ethnicity, dialysis vintage, hypertension, or diabetes (all p>0.05). The High group had a higher balance score (p=0.003), faster usual gait speed (p=0.001), faster time to complete 5 sit-to-stands (STS-5; p=0.013), longer distance walked during the 6-min walk test (p=0.003), and higher scores in the SF36-PPS (p=0.012) and PROMIS Mobility (p=0.004) questionnaires. After adjusting for age, sex, BMI, and diabetes, only STS-5 (ß [SE]=−0.51 [0.20]; p=0.008) remained significantly associated with VO2Peak.

Conclusions: Our results indicate that the STS-5, a simple submaximal test that can be completed in less than 1 minute, is superior to the 6-min walk test, usual gait speed, and SF36-PPS and PROMIS Mobility questionnaires for predicting VO2Peak in dialysis patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.

FR-PO809
Aerobic Exercise Capacity and Kidney Function Decline in Heart Failure with Preserved Ejection Fraction Patients
Jae Young Kang,2 Jung Tak Park,2 National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; 1Seoul National University College of Medicine, Seoul, Republic of Korea; 2Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

Background: Chronic kidney disease (CKD) is a complication frequently found in HFpEF patients and results in poor prognosis. However, factors related with increased risk of kidney function decline in HFpEF are not well known.

Methods: Among a total of 424 HFpEF patients with estimated glomerular filtration rate (eGFR) ≤ 60 mL/min/1.73 m², aerobic exercise capacity was assessed by the peak O2 consumption (VO2Peak) values obtained through cardiopulmonary exercise test. Primary outcome was development of incident CKD, defined as two consecutive eGFR of <60 mL/min/1.73 m² separated by a ≥90 days.

Results: The mean age of patients was 64.2 ± 10.6 years and 33.5% were male. Cardiac ejection fraction and eGFR at baseline were 67.0 ± 6.8% and 73.5 ± 12.2 mL/min/1.73 m², respectively. During 1082.8 person-years of follow-up, CKD incidence rate gradually increased in patients with lower VO2Peak levels. Multivariable Cox analyses revealed that 1-standard deviation increase in the VO2Peak level was associated with a 33% lower risk of CKD development. The adjusted HR (95% CI) of the lowest VO2Peak tertile group was 3.07 (1.51–6.23) when compared to the highest tertile group.

Conclusions: Poor aerobic exercise capacity, represented by reduced VO2Peak levels, is closely related with a higher risk of CKD development among HFpEF patients.
measured performance-based physical function outcome. All ages and any stage of CKD were included. The most common tests (defined as having 4 or more studies) are described in terms of reliability and validity.

Results: 50 studies with 21,315 participants were included, the majority were HD. Cummometric properties were reported for 22 physical function tests; the following were most common: Hand grip strength (HGS), 6 minute walk test (6MW), V02 peak, short physical performance battery (SPPB), part 1, sit to stand-test (6TST-60), timed up and go (TUG), STS-5 and incremental shuttle walk test (ISWT). Very few studies reported properties of criterion (ISWT) and responsiveness (V02 peak and 6MW).

Conclusions: The SPPB demonstrates high GRADE evidence for construct validity, reliability and measurement error. The next best tests include: 6MW and TUG with high GRADE for reliability and measurement error. This review is an important step towards standardizing a core outcome set of tools to measure physical function in research and clinical settings for CKD.

FR-PO810
Association of Myosteatosis with Poor Physical Function and Mortality in Hemodialysis Patients
Donsheng Cheng, Niansong Wang. Department of Nephrology, Shanghai Sixth People’s Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Background: Skeletal muscle area, which is measured by computed tomography (CT), can be divided into normal attenuation muscle area with little fat infiltration and low-attenuation muscle area with high fat infiltration. Herein, we aim to investigate the differential effects of normal and low-attenuation muscles at the L3 vertebra and myosteatosis on physical function and mortality in patients undergoing hemodialysis.

Methods: All patients underwent non-enhanced abdominal CT. The skeletal muscle index (SMI), normal attenuation SMI (NSMI), low attenuation SMI (LSMI), and fatty muscle fraction (FMF) at the L3 vertebra were determined (as shown in figure 1). Physical function was measured using handgrip strength, gait speed, sit-to-stand in 60 s (STS-60) test, and instrumental activities of the daily living scale.

Results: There were 101 patients on maintenance hemodialysis (mean age 52.73, 39.6% women), and 19 patients died during a median follow-up time of 26.2 months. The NSMI was moderately positively correlated with handgrip strength, gait speed, and STS-60 score (r=0.363 to 0.542; P<0.001). In contrast, the LSMI was negatively correlated with all physical function measures (r= -0.439 to -0.317; P< 0.001). In multivariate regression analyses, larger NSMI, lower LSMI, and lower FMF than SMI were significant with all physical function measures (rho: < 0.001). In multivariate regression analyses, larger NSMI, lower LSMI, and lower FMF than SMI were significant with all physical function measures (rho: < 0.001).

Conclusions: This study demonstrated distinct effects of normal and low-attenuation muscles on physical function. Moreover, it highlights the importance of myosteatosis in determining poor physical performance and predicting mortality in patients undergoing hemodialysis.

Figure 1. Muscle quality map at L3 derived from abdominal CT using region growing mode. The axial CT images at L3 were segmented into NAMA (red), LAMA (green), and IMAT (purple).

FR-PO811
Dialysis Malnutrition Score and Handgrip Strength with Quality of Life Among Patients on Maintenance Hemodialysis in Cebu City, Philippines
Jan Roslyn T. Empinado, Alexander U. Tan. Cebu Doctors’ University Hospital, Cebu City, Philippines.

Background: Malnutrition is common in hemodialysis patients and is a powerful predictor of morbidity and mortality. End stage renal disease (ESRD) has been shown to negatively affect the Quality of Life (QoL) of patients. Among Chronic Kidney Disease (CKD) patients on maintenance hemodialysis, there is a considerable effect on the functional state and QoL. Malnutrition in CKD patients is one of the factors that afflicts QoL.

Methods: One hundred eight (108) patients on maintenance hemodialysis in a tertiary hospital were assessed nutritionally by DMS and HGS while the overall perception QoL and health was assessed using World Health Organization Quality of Life - BREF (WHOQoL-BREF) questionnaire. Kendall’s tau was used to determine whether there is a correlation between DMS and HGS with quality of life scores. A p-value of <0.05 will be considered as statistically significant.

Results: Based on DMS, 87% of patients had mild to moderate malnutrition and 64.8% had renal cachexia based on HGS. Those with poor nutritional status in DMS showed significant decrease in overall perception of their quality of life p = 0.003, quality of health p = 0.026, physical p = 0.013 and environmental domains p = 0.044 of WHOQOL. Handgrip score however did not have any correlation with the overall QoL, perception of general health and on the four domains.

Conclusions: DMS and HGS are simple and accessible nutritional assessment tools to detect malnutrition among hemodialysis patients. DMS correlates with QoL with higher DMS reflecting malnutrition and the overall quality of life decreases. Early detection of malnutrition can prevent further health deterioration with nutritional interventions and therefore improve QoL in the aspects they are most affected.

Table 1. DMS and HGS on Quality of Life

FR-PO812
Effect of Leucine Supplementation and Resistance Exercise for Prevention of Sarcopenia in Patients on Maintenance Hemodialysis
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Background: Sarcopenia frequently occurs in hemodialysis patients up to 40%. We examined the effects of supplementation of leucine amino acid combined with resistance exercise on preventing sarcopenia in patients on maintenance hemodialysis (MHD).

Methods: This was a single center, prospective, single-arm pilot study. 22 non-sarcopenic patients on MHD at our hospital were enrolled. During the intervention period (first 12 weeks), participants were provided with daily 6g of leucine (3g in capsule and 3g via beverage) and a protocol for daily resistance exercise. Both interventions were stopped during following 12 weeks. Bioimpedance analysis (BIA), handgrip strength (HGS), short physical performance battery (SPPB), serum chemistry, immunophenotype of peripheral blood mononuclear cells were examined at baseline, 12 week and 24 week. Participants who expressed 5% or more improvement in each parameter were defined as responders.

Results: Among 22 patients, mean age was 55±11.8 years and hemodialysis vintage was 4.7±3.5 years. 7 patients (31.8%) were female. 21 patients (95.4%) showed improvement in at least one or more parameters. At 12 week, the number of responders was 14(63.5%) for skeletal muscle index and 7(31.8%) for grip strength. Baseline low grip strength (<35.0kg) was the strongest predictor of improvement in grip strength (AUC 0.933). Increase in grip strength was significant in females (7.6±8.2 vs -1.6±7.2%, p=0.03), in age over 60 (5.3±6.2 vs -1.4±9.1%, p=0.04), and with higher exercise adherence (6.8±7.7 vs 3.2±6.6%, p=0.004). The number of responders were 13 patients (59.1%) for gait speed and 14(63.5%) for sit-to-stand time. Baseline low hemoglobin(<10.5 g/dL) and low hematocrit lower(<30.8%) were predictors of improvement in sit-to-stand time (AUC 0.857).
Contradicted to improvement of muscle mass, muscle strength, and physical performance in certain group of non-sarcopenic hemodialysis patients. This intervention may have effect on prevention of sarcopenia in old-age, anemic, female patients on MHD with lower HGS.

Funding: Government Support - Non-U.S.

FR-PO813

Elicited Acupuncture Mimics Exercise to Ameliorate Muscle Wasting by Promoting Angiogenesis and Neurogenesis in CKD

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Background: Our previous study demonstrated that acupuncture with low frequency electrical stimulation (Acu/LFES) attenuates skeletal muscle atrophy by improving muscle progenitor cells regeneration. The present study examines whether Acu/LFES improves revascularization, innervation, and protein anabolism in muscle of chronic kidney disease (CKD) mice.

Methods: CKD was induced by the 5/6 nephrectomy. Acu/LFES was applied in hindlimbs of CKD mice. Acu/LFES points were selected by WHO Standard Acupuncture classification. Proteins from hindlimb (gastrocnemius), forelimb (triceps brachii) and back (longissimus) muscles were isolated at 0.5, 6, 24, 48 and 72 hours after Acu/LFES therapy. Protein synthesis was measured by the surface-sensing of translation (SunSET) assay. Exosomes were isolated using serial centrifugation and subjected to miRNA sequencing. The miRagenosim assay was used to determine miRNA concentration.

The microRNA library was validated using a High Sensitivity DNA chip.

Results: Protein synthesis was enhanced in the Acu/LFES-treated gnomiosin; however, in non-Acu/LFES treated muscles, triceps brachii and longissimus, protein synthesis was also significantly increased after treatment. These increases were accompanied with increased phosphorylation of mTORC1 and 4EBP-1. Myogenesis markers, Pax7, myoD and myogenin were significantly upregulated. The mRNA expression of PDGF and ENO2 were enhanced by Acu/LFES. The protein amount of Igf-1 receptor, VEGF (a protein that stimulates the formation of blood vessels), and peripherin (expressed mainly in the nervous system) were also increased by Acu/LFES.

Deep sequencing revealed that miR-150p and miR-30-5p were sharply decreased in serum exosomes of Acu/LFES mice. Using a luciferase reporter assay, we demonstrated that miR-150p directly inhibits VEGF, and miR-30-5p inhibits ENO2, which suggests a mechanism in which miRNA regulation of these genes results in expanding VEGF and ENO2 leading to accelerate revascularization and innervation.

Conclusions: Acu/LFES treatment increases myogenesis, angiogenesis and neurogenesis, as well as protein synthesis. Acu/LFES inhibits miR-150p and miR-30, resulting in increased VEGF and ENO2 contributing to these processes. Our study provides strong mechanistic insights for Acu/LFES treatment of muscle atrophy in CKD.

Funding: Private Foundation Support

FR-PO814

The Practices and Views of US and Canadian Nephrologists, Nurses, and Allied Health Professionals Regarding Exercise and Physical Activity for People Receiving Peritoneal Dialysis

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Background: Chronic kidney disease (CKD) progression is associated with deterioration of musculoskeletal health. We hypothesized that voluntary wheel running as compared to forced treadmill would preferentially impact musculoskeletal health in CKD.

Methods: We used a progressive, naturally occurring, CKD rat model (Cy/+ rat) (n=10-21/group): 1) normal littersmates (NL), 2) Cy/+ (CKD) rats, 3) CKD-treadmill (CKD-TM); 4) CKD-wheel (CKD-W). For 10 weeks treadmill rats ran 40 minutes/day, 4 days/week, for 0° grade, wheel rats had 24/7 free access; training volumes similar between the modes. Termination, and blood and tissue collection occurred at 33 weeks. Outcome measures were maximal muscle torque and fatigue, maximal running endurance, and tibia cortical bone morphology. Data analysis included one-way ANOVA with Tukey’s multiple comparisons test.

Results: Overall CKD versus NL impaired cortical bone with increased porosity (mean 0.18±0.12 NL, 20.3±1.8 CKD; p<0.05), and reduced area (mean 6.64±0.43 NL, 5.2±0.8 CKD; p<0.05). The 45° grade was maintained if in middle; and reduced if in lower 1/3. Treatments began at 22 weeks of age. There was a higher relative abundance of Firmicutes in NL compared to CKD (vs NL) with reduced maximal torque (mean 57.3±7.7 NL, 47.6±9.3 CKD; p<0.05) and increased fatigue (mean 42.8±9.9 NL, 56.5±8.7 CKD; p<0.01). Running endurance was significantly reduced in CKD (mean 24.2±3.3 NL, 20.8±4.5 CKD; p<0.05). Treadmill running increased maximal running endurance (mean 47.6±9.3 CKD, 57.1±8.8 CKD-TM; p<0.05) and running endurance (mean 20.8±4.5 CKD, 25.9±3.9 CKD-TM; p<0.05) when compared to CKD. Wheel running significantly improved maximal running endurance (mean 20.8±4.5 CKD, 24.7±3.2 kgf-cm values). However, CKD did not impact maximal muscle torque, muscle fatigue or cortical bone parameters.

Conclusions: CKD deteriorates the musculoskeletal system through cortical bone loss, and reduced muscle strength and greater muscle fatigue. To determine optimal delivery of exercise we compared treadmill to wheel running. Both methods improved maximal running endurance after 10 weeks of wheel running. Exercise professionals and structured exercise programs would benefit people receiving PD.

Funding: NIDDK Support

FR-PO815

Exercise Has Mode-Specific Effects on Musculoskeletal Health in a Rat Model of CKD-MBD

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Background: US and Canadian PD health professionals recognize the importance of exercise for people receiving PD and most programs have exercise-related policies. Even though there are few dedicated PD exercise programs in the US and Canada, most clinicians believed that exercise professionals and structured exercise programs would benefit people receiving PD.

Results: US and Canadian PD health professionals recognize the importance of exercise for people receiving PD and most programs have exercise-related policies. Even though there are few dedicated PD exercise programs in the US and Canada, most clinicians believed that exercise professionals and structured exercise programs would benefit people receiving PD.

Conclusions: US and Canadian PD health professionals recognize the importance of exercise for people receiving PD and most programs have exercise-related policies. Even though there are few dedicated PD exercise programs in the US and Canada, most clinicians believed that exercise professionals and structured exercise programs would benefit people receiving PD.

Funding: NIDDK Support

FR-PO816

Progressive Individualized Exercise Intervention Impacted the Cecal Microbiota Composition in a Rat Model of CKD

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Background: Exercise interventions are recommended to improve the musculoskeletal and cardiopulmonary health in chronic kidney disease (CKD). Exercise has been shown to impact the gut microbiome, but data in CKD is limited. We have previously shown that bone health and serum biochemistry was improved following 10 weeks of wheel running and this study hypothesized that treadmill running will improve gut microbiome in the Cy/+ rat model of CKD.

Methods: We examined the following groups (n=6-8/group): 1) Normal littersmates (NL); 2) CKD rats; 3) CKD + treadmill exercise (CKD+EX). The exercise intervention was performed for a 5° grade, 50 minutes/day, 4 days/week for 10 weeks. The running speed was progressively increased if the rat was in the upper 1/3 of the belt in the final 10 minutes of the running session. The results of the gut microbiota were analyzed using 16S rRNA gene sequencing, and Prevotella (corrected p<0.05) with exercise. Taxis whose relative abundance was lowered by the exercise intervention included Lactobacillus, Akkermansia, and Blautia.

Conclusions: A personalized progressive treadmill intervention impacted the cecal microbiota composition in a rat model of CKD.

Funding: NIDDK Support

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

Underline represents presenting author.
FR-PO817

Differences in Subjective Global Assessment Score and Mortality Risk Across Race and Ethnicity in a Prospective Hemodialysis Cohort

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Background: Protein-energy wasting is a major predictor of mortality in advanced CKD patients, and clinical guidelines endorse use of the Subjective Global Assessment (SGA) score as a validated measure of nutritional status in HD patients. We examined the relationship between SGA score and survival in a diverse HD cohort and how associations differ across race/ethnicity.

Methods: We evaluated 1084 HD patients from the prospective NIH MADRAD Study recruited across 18 dialysis clinics who underwent protocolized SGA surveys over 10/2011-12/2021. Using Cox models adjusted for expanded case-mix/laboratory covariates, we examined associations of time-dependent and baseline SGA score categorized as tertiles with all-cause mortality risk. We then examined differential SGA score—mortality associations across race/ethnicity using interaction tests.

Results: The mean±SD age of the cohort was 55±14 years, among whom 44% were female; and 53%, 27%, 10%, and 9% were Hispanic, Non-Hispanic (NH) Black, Asian, and NH White. In analyses of time-dependent SGA score, incrementally higher (worse) tertiles were associated with higher mortality (ref: Tertile 1): HRs (95%CI’s) 1.41 (1.07, 1.87) and 2.68 (2.06, 3.48), respectively, for Tertiles 2 and 3, respectively (Fig). Similar findings were observed in baseline SGA analyses. Subgroup analyses showed that Tertile 3 of time-dependent SGA scores were associated with higher mortality in all racial/ethnic groups, with the strongest point estimates observed in Hispanic and NH White patients: HRs (95%CI’s) 1.91 (1.59, 2.30), 1.47 (1.19, 1.82), 1.50 (1.01, 2.24), and 2.07 (1.29, 3.32) for Hispanic, NH Black, Asian, and NH White patients, respectively (p-interaction <0.001).

Conclusions: In a multicenter prospective HD cohort, higher (worse) SGA scores were associated with worse survival in all racial/ethnic groups. Further studies are needed to determine personalized approaches to optimizing nutritional status in diverse HD populations.

Funding: National Institute of Diabetes and Digestive and Kidney Diseases.

FR-PO818

Goal Attainment Scale as an Outcome Measure in a Randomized Controlled Trial of Lifestyle Interventions

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Background: Goal attainment scale (GAS) is a validated patient-reported outcome measure (PROM) that can be used to quantify achievement of individualised patient goals. GAS has not been assessed as a PROM in lifestyle intervention trials. We report the GAS findings of a predefined sub-analysis of the U-DECIDE study, which assessed the feasibility of digital health-assisted lifestyle interventions (DHALI) in people with kidney and liver disease.

Methods: Adults with kidney or liver disease and metabolic syndrome were randomized to either usual care (UC) or DHALI-UC. All participants received goal setting support, a wearable activity monitor, and individualized dietitian counselling. The DHALI-UC group could opt-in to receive exercise and/or dietetic video consultations; a list of targets agreed to achieve stipulated goals; and text-message education. Pre-randomization, participants were assisted by a clinician to generate up to 2 SMART (specific, measurable, attainable, realistic and timely) lifestyle goals. Possible outcomes (‘much better than expected’, ‘better than expected’, ‘as expected’, ‘worse than expected’, ‘much worse than expected’) for each goal were predetermined and quantified by the SMART criteria (0%–100% of goal achieved).

Results: We evaluated 1018 HD patients from the prospective NIH MADRAD Study recruited across 18 dialysis clinics who underwent protocolized GAS surveys 10/2011-12/2021. Using Cox models adjusted for expanded case-mix/laboratory covariates, we examined associations of time-dependent and baseline GAS score categorized as tertiles with all-cause mortality risk. We then examined differential GAS score—mortality associations across race/ethnicity using interaction tests.

Conclusions: Participants commonly selected weight loss and fitness goals. GAS is a feasible, convenient and inexpensive PROM that can be used to quantify change in patient determined lifestyle goals.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
impact disease progression were being made as early as stage 3. Decision-making was made difficult due to poor resource utilization and lack of information. Yet, the structure and nature of the medical appointment and resources served to remove challenges by assisting with enhanced communication and greater self-advocacy.

**Conclusions:** This study’s findings demonstrate the need for decision-support interventions upstream of advanced illness that train patients and caregivers to be empowered participants in answer-seeking behaviors that enhance their ability to make informed patient-centered decisions.

**Funding:** Private Foundation Support

**FR-PO821**

**Association Between the Fibrosis-4 (FIB-4) Score and ≥20% Decline in the Estimated Glomerular Filtration Rate in the General Population with Abdominal Adiposity**

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**Background:** The prevalence of chronic kidney disease is increasing in patients with non-alcoholic fatty liver disease (NAFLD), and obesity is a known risk factor for both conditions. The fibrosis index based on four factors (FIB-4) score, a non-invasive indicator, is strongly associated with liver injury and fibrosis in patients with NAFLD. The association between the FIB-4 score and the estimated glomerular filtration rate (eGFR) slope remains unclear. In this study, we investigated whether the FIB-4 score is associated with decreased eGFR decline in the general population.

**Methods:** This retrospective observational cohort study included individuals who underwent health check-ups across Japanese companies between 2009 and 2014. Participants who consumed ≥20 g of alcohol/day were excluded. An FIB-4 score of ≥1.30, which indicates moderate-to-severe liver fibrosis, was set as the cut-off value. Propensity score matching based on FIB-4 scores (<1.30, ≥1.30) was performed to eliminate biases associated with covariances across participants’ backgrounds.

**Results:** We recruited 11,296 participants at baseline; however, 5943 participants were excluded, and data of 464 participants were analyzed after propensity score matching. Participants’ mean age was 50 years, mean eGFR was 74.7 mL/min/1.73 m², and the mean waist circumference (WC) was 81.8 cm. FIB-4 scores ≥1.30 were significantly associated with ≥20% decline in the eGFR over 5-year follow-up (odds ratio [OR] 3.94, 95% confidence interval [CI] 1.29–12.06). Subgroup analysis showed that an FIB-4 score ≥1.30 was significantly associated with ≥20% decline in eGFR 5 years later in participants with WC ≥85 cm (OR 8.78, 95% CI 1.05–73.53) but not in those with WC <85 cm (OR 2.70, 95% CI 0.70–10.38).

**Conclusions:** Our findings show that an FIB-4 score ≥1.30 was associated with ≥20% decline in the eGFR 5 years later. Abdominal adiposity accompanied by an FIB-4 score ≥1.30 was a particularly important risk factor for eGFR decline.

**FR-PO822**

**Subcutaneous Fat Area Can Predict Two-Year Survival in ESRD Patients Initiating Dialysis**

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**Background:** Obesity is a risk factor for increased cardiovascular disease and diabetes in general population. However, the “obesity paradox” is observed in chronic disease such as ESRD patients. BMI does not discriminate between subcutaneous fat, visceral fat or muscle. Either overhydration or PEW state in the initial dialysis patient makes it difficult to properly assess BMI and muscle mass. The initial measurement of this modality difficult to assess the patient’s prognosis. Fat tissue can be assessed relatively accurately than muscle even in patients starting dialysis. However, obesity paradox has been described in patients with kidney disease. The association of WWI with AAC and mortality remains uncertain in hemodialysis (HD) patients.

**Methods:** This study included 161 patients on maintenance HD >3 months. WWI was determined as waist circumference divided by the square root of weight. Severity of AAC was quantified by the AAC score measured from lateral lumbar radiography.

**Results:** We found 103 HD patients who had moderate or severe AAC. During a median follow-up of 5.0 years, 50 deaths occurred. In multiple logistic regression, the highest WWI tertile was significantly associated with moderate or severe AAC. Compared to the lowest WWI category, 2nd tertile WWI (11.37 cm/m²) (HR=3.25, 95% CI: 1.18–9.83, p=0.022) was significantly associated with increased risk of all-cause mortality in multivariate-adjusted Cox analysis. Furthermore, WWI had the greatest AUC for predicting moderate or severe AAC (AUC=0.713) and all-cause mortality (AUC=0.667) when compared with body mass index, waist circumference, hip circumference, and waist-to-hip ratio.

**Conclusions:** These findings indicated that WWI may serve a valuable indicator for identifying moderate or severe AAC and predicting mortality among maintenance HD patients.
FR-PO825

Poor Vitamin K Status and Inflammation in Patients with CKD

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Background: Vitamin K is vital to cardiovascular and bone health and can mitigate inflammation. Vitamin K inhibits the activation of NF-κB, which seems related to vitamin K-dependent proteins, inhibiting the production of IL-6 by macrophages. Patients with CKD frequently present a deficiency of vitamin K. Considering the high mortality rate linked to cardiovascular disease (CVD), reduced quality of life and poor outcomes related to inflammation, it is essential to understand the relationship between vitamin K deficiency and inflammation, raising the possibility of new therapeutic targets in treating CVD. This study aimed to evaluate the correlation between vitamin K status and inflammation in patients with CKD (non-dialysis and hemodialysis - HD).

Methods: 108 patients undergoing HD (51 male, 52 yrs) and 23 non-dialysis patients (7 male, 58 yrs) were evaluated. Plasma desphospho-uncarboxylated matrix GlA-protein (dp-ucMGP), a functional vitamin K deficiency biomarker, was analysed using the IVD CE-marked chemiluminescent InaKtif MGP assay on the IDS-iSYS system. IL-6 plasma levels were evaluated by ELISA. The results were adjusted for age, sex and BMI.

Results: HD patients had significantly higher values of dp-ucMGP [728 (IQR=724) pmol/L] than non-dialysis patients [563 (IQR=296) pmol/L] (p<0.05), indicating vitamin K deficiency. Furthermore, a significant positive correlation was observed between dp-ucMGP and IL-6 levels in HD patients, which reflects elevated levels of IL-6 in patients with vitamin K deficiency (Fig. 1).

Conclusions: The results reveal a positive correlation between vitamin K deficiency and the pro-inflammatory biomarker IL-6 in patients with CKD. Vitamin K supplementation may be a strategy to mitigate inflammation in these patients.

Funding: Government Support - Non-U.S.

FR-PO824

Successful Bariatric Laparoscopic Sleeve Gastrectomy in a Home Hemodialysis Patient Led to Reduced Hemodialysis Frequency

Desiree Hemodialysis Patient Led to Reduced Hemodialysis Frequency

Successful Bariatric Laparoscopic Sleeve Gastrectomy in a Home Hemodialysis Patient Led to Reduced Hemodialysis Frequency

Introduction: Bariatric surgery (BS) is an established treatment for achieving weight loss. Patients with kidney disease and not on dialysis had a reduction in mortality compared to matched controls with vertical laparoscopic sleeve gastrectomy (LSG) being the safer option compared to Roux-en-Y gastric bypass. Use of BS in dialysis patients is not common due to fears of complications including high post-operative mortality and myocardial infarction. Furthermore, observational studies suggest a protective association of elevated BMI versus death in HD patients, although this has not been consistently observed in peritoneal dialysis patients. Our patient demonstrated that BS while on HHID is a desirable option to achieve target weight loss.

Case Description: A 36-year-old female started HHD for anuric hypertensive end stage renal disease 5.5 years before LSG. Before LSG, she did HHD 5 times a week to maintain adequacy. The renal and bariatric teams worked closely to provide a unified approach to her diet pre- and post-surgery, which included fluid diets and progression to solids. Medications and supplements were also adjusted to meet both dialysis and bariatric guidelines. Since LSG, she has exhibited progressive weight loss of 26% over 6 months (Figure), while maintaining her nutritional status. We reduced HHID frequency from five to four times weekly to mitigate intradialytic hypotension, and still maintained HD adequacy. She is more active, more energetic, takes longer walks, twice daily, and now works in her garden.

Discussion: Our HHID patient had successful bariatric surgery with 26% weight loss in 6 months and can now be listed for kidney transplant. Despite a paucity of literature on intentional approaches to weight loss in ESRD, LSG is increasingly used for patients in 6 months and can now be listed for kidney transplant. Despite a paucity of literature on intentional approaches to weight loss in ESRD, LSG is increasingly used for patients

FR-PO826

Depressive Symptoms Are Associated with Increased Hospitalization Rate in CKD Patients: A Systematic Review and Meta-Analysis of Cohort Studies

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Background: Depressive symptoms are relatively common in patients with chronic kidney disease (CKD). Recent studies showed that depressive disorders are associated with increased mortality risk in patients with CKD. However, evidence regarding the impact of depression on the risk of hospitalization in the CKD population is still limited. Therefore, we performed a systematic review and meta-analysis to explore the association between depressive symptoms and the risk of hospitalization in CKD patients.

Methods: We comprehensively searched MEDLINE, EMBASE and Cochrane Library from inception to October 2022. Included studies were cohort studies assessing the association of depressive symptoms on hospitalization rate among CKD patients, using the random-effects to calculate risk ratios (RR) and 95% confidence intervals (CIs). Six cohort studies were included in the analysis with a total of 31,259 CKD patients (7,404 patients with depressive symptoms and 4,122 patients without depressive symptoms). Subjects with depressive symptoms had an increased risk of hospitalization (pooled RR 1.139, 95% CI: 1.055–1.229, p = <0.001, I2 = 51.1%) compared to those without depressive symptoms. In subgroup analysis, depressive symptoms were associated with an increased risk of hospitalization in both CKD patients who were not receiving dialysis (pooled RR 1.432, 95% CI: 1.204-1.704, P = <0.001, I2 = 0%) and CKD patients who were receiving dialysis (pooled RR 1.088, 95% CI: 1.057-1.119, P = <0.001, I2 = 0%).

Fig 1. Correlation between dp-ucMGP and IL-6 plasma levels of HD patients. Pearson correlations were performed with residuals of linear fixed effects models, including confounders (Age, Sex, BMI, and time on dialysis).
Conclusions: Our meta-analysis demonstrated that depressive symptoms were associated with an increased risk of hospitalization. This possible association is important given the implication of depression screening to improve the quality of life in CKD patients.

FR-PO827

Hypothyroidism (HT) Rate and Testing Among Incident CKD Patients Who Transitioned to Dialysis Within Kaiser Permanente Southern California (KPSC)

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Background: HT and CKD are highly prevalent conditions with a bidirectional relationship. Among a large diverse real world CKD cohort who transitioned to dialysis, we sought to determine the rate of HT, factors associated with HT, and the overall screening rates for HT.

Methods: We conducted a cross-sectional study within KPSC during 2007-2017. Patients aged 18 years with incident CKD (defined by at least 2 consecutive eGFR less than or equal to 45 ml/min/1.73 m²) were identified, and patients who initiated outpatient dialysis (hemodialysis or peritoneal dialysis) were identified. HT was defined as TSH > 4 mIU/L and or use of thyroid replacement medication. The rate of HT and HT screening with TSH measurements were determined. HT rate ratio (RR) and its 95% confidence interval were estimated using multivariable Poisson regressions with Robust error.

Results: Among 6,812 CKD patients who transitioned to dialysis 927 (14%) had HT. 50% of incident CKD who initiated outpatient dialysis were screened with a TSH measurement in the 1 year prior to ESKD. Adjusted HT RR (95% CI) were 1.66 (1.19,2.33), 1.73 (1.53,1.95), 1.20 (1.03,1.39), and 1.54 (1.27,1.87) for age ≥ 70 years, females, atrial fibrillation, and weighted Charlson comorbidity index ≥5, respectively. Adjusted HT RR (95% CI) were 1.22 (0.81,1.42), 0.62 (0.51,0.75) and 0.75 (0.61,0.93) for non-Hispanic whites, non-Hispanic blacks and Asians, respectively. Heart failure was not associated with HT (Table 2).

Conclusions: Our study observed that 14% of CKD patients who transitioned to dialysis had HT which is higher than the ~5% described among the general population. We observed that only half of CKD patients were screened for HT prior to initiation of dialysis suggesting a potential care gap. Further studies may provide insights into understanding whether greater screening and identification of HT among CKD patients initiating dialysis will lead to improved CKD dialysis related outcomes.

FR-PO828

Poor Life Prognosis of Patients with Rapid Progression of Peripheral Artery Disease

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Background: Peripheral artery disease (PAD) is one of the major complications in patients undergoing hemodialysis (HD), leading to a higher mortality risk. As skin reperfusion pressure (SRPP) measurement is a useful screening tool for PAD early detection and prevention of progression using this tool would be important. However, only a few studies have focused on the speed of PAD progression, and its effects on life prognosis and associated factors have not been fully examined yet. We aimed to evaluate the impact of rapid progression of PAD on life prognosis and identify the factors associated with PAD progression.

Methods: We included patients undergoing HD with more than two SRPP measurements at our facility between January, 2013 and August, 2022. Patients were followed up until August, 2022. Medical data were collected at the time of the first SRPP measurement, and the associations between survival and patient backgrounds were analyzed.

Results: The study included 142 patients (71.6±9.1 years old; 59.2% men; median dialysis vintage, 58.5 months). The median observation period was 1,142.5 days (interquartile range: 680.8–1,709.8 days), and 76 patients died during the observation time. Among the participants, 17 patients underwent lower limb amputation. The patients were divided into four groups, according to the SRPP reduction rate (Q1–Q4). Log-rank test analysis showed that patients with SRPP reduction rate Q4 had a poor prognosis (p<0.001). Multivariable Cox proportional hazards analysis demonstrated that SRPP reduction rate Q4 (hazard ratio, 2.51; 95% confidence interval [CI]: 1.46–4.30; p=0.001) was significantly associated with survival. Multivariable logistic regression analysis revealed that body mass index (BMI) (odds ratio [OR]: 1.13, 95% CI: 1.00–1.28, p=0.048) and serum creatinine level (OR, 0.77, 95% CI: 0.61–0.96, p=0.02) were associated with SRPP reduction rate Q4.

Conclusions: Patients with a large SRPP reduction rate had a poor life prognosis. BMI and serum creatinine levels were associated with a large SRPP reduction rate. As serum creatinine levels in patients undergoing HD can reflect their skeletal muscle mass, sarcopenic obesity, indicated by excessive BMI and low creatinine levels, may be a risk factor for the rapid progression of PAD in our patients. Maintaining adequate body weight and muscle mass is critical in preventing PAD progression.
FR-PO830
Gastrointestinal Bleeding Types and Associated Mortality Rates in Dialysis Patients
Belen Alejos, Yue Jiao, Melanie Wolf, John W. Larkin, Anke Winter, Sheetal Chaudhuri, Manuela Stauss-Grab, Len A. Usyvat, Jeffrey L. Hynes, Franklin W. Maddux, David C. Wheeler, Peter Stenvinkel, Jürgen Flöge. On Behalf of the INSPIRE Core Group. Fresenius Medical Care, Bad Homburg, Germany; Fresenius Medical Care, Waltham, MA; Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany; University College London, London, United Kingdom; Dept of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; University Hospital RWTH Aachen, Division of Nephrology and Clinical Immunology, Aachen, Germany.

Background: The incidence of gastrointestinal bleeding (GIB) is ~7-fold higher in the dialysis vs general population. The INSPIRE collaborative group has aimed to describe mortality after a GIB episode by the type of bleed among chronic dialysis patients treated at a national provider in the United States (US).

Methods: We used data from adult dialysis patients who had ≥1 GIB episode between Jan-2018 to Mar-2021. GIB episodes were defined from ICD codes for comorbidities, or hospital discharge. We calculated crude mortality rates any time after the first GIB by type (upper or lower; Zhao et al., AHRQ 2006). GIB episodes with an unspecified location were not included in the analysis of GIB types.

Results: The incidence of a patient having ≥1 GIB episode was 7.7% (31,084/405,530). Overall, GIB was most common in patients between ages of 45-64 years (38.9%) & 65-75 years (28.7%), males (56.6%), and those of a white race (54.5%). GIB location was specified for 39.1% of the first GIB episodes. Demographics for patients with and without a specified GIB location did not differ. Crude mortality rate after the first GIB was 41.9% (n=3,392) for upper GIB and 42.3% (n=1,722) for lower GIB. Mortality rate for both GIB types was positively associated with age, and was the highest for patients with missing data on race (10.4% of cohort), followed by white race (Figure 1).

Conclusions: Mortality rate after the first GIB episode in a dialysis patient was ~40%, regardless of the location of bleeding. Age and race specific differences were consistent for upper and lower GIBs. Most GIB episodes were classified as an unspecified type, suggesting the need for improvements in evaluation/coding. Further adjusted analyses are needed to confirm these results and understand the differences by dialysis modalities, risk factors, and causes of mortality.

Funding: Commercial Support - Fresenius Medical Care

FR-PO832
Dietary Magnesium Intake and Kidney Stones: The National Health and Nutrition Examination Survey 2011-2018
Sandipan Shringi, Christina A. Raker, Jie Tang, Rhode Island Hospital, Providence, RI; Brown University Warren Alpert Medical School, Providence, RI; University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Cigarette smoking (CS) may affect the risk of kidney stone (KS) disease because it has been linked to an increased bone loss. In addition, major trace elements found in cigarette can also promote KS formation. Here, we aimed to examine the independent association between CS and prevalent KS disease defined as self-reports of any previous episode of kidney stone.

Methods: We examined The Third National Health and Nutrition Examination Survey (NHANES) 2011-2018, a large US population-based cross-sectional study, and used logistic regression analyses to determine the independent association between CS and prevalent KS disease.

Results: 19,405 participants were included for analysis, 1,895 had KS disease. 19% of stone formers (SF) versus 18% of non-stone formers (NSF) were active smokers (p=0.001), and average daily cigarettes smoked were 14 among SF vs. 12 among NSF (p=0.02). Mean serum cotinine (a major metabolite of nicotine) concentration (SCC) was 64 ng/ml among SF vs. 54 ng/ml among NSF (p=0.01). Active CS associated strongly with an increased odds of KS disease in regression analysis after adjustment for demographics, BMI, histories of hypertension, diabetes, dyslipidemia and cardiovascular disease, alcohol intake, and dietary sodium, potassium and water intakes, odds ratio (OR)=1.30, 95% confidence interval (CI)=1.05-1.50, p=0.02 (Table 1). Higher SCC also associated significantly with an increased odds of KS disease when SCC was modeled as a continuous variable (OR=1.0007, 95% CI: 1.00-1.01, p=0.003), or when comparing highest tertile of SCC to lowest tertile (OR=1.30, 95% CI: 1.10-1.50, p=0.001) (Table 1). No major interactions were found in the final regression analyses.

Conclusions: Our study showed CS had a strong independent association with an increased risk of KS disease. Future prospective studies are needed to clarify the causal relationship between CS and KS formation.

Funding: Private Foundation Support

Table 1: OR of prevalent kidney stone disease according to smoking status in the multivariate regression model.

<table>
<thead>
<tr>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active vs. non-active</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>REF</td>
</tr>
<tr>
<td>Past</td>
<td>1.10 (0.99-1.20)</td>
</tr>
<tr>
<td>Active</td>
<td>1.30 (1.15-1.46)</td>
</tr>
</tbody>
</table>

Funding: National Institutes of Health (NIH) [P01DK033186, R01DK090574], Patient-Centered Outcomes Research Institute (PCORI) [PI130106], and a Richard W. & Lillian D. Thomas Foundation grant.
FR-PO833

Diet-Induced Oxalate Nephropathy: Eating Too Much “Healthy” Food

Alexandre P. Landry, Jefferson L. Triozzi, Agnes B. Fogo, Natalie N. McColl. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Oxalate nephropathy is an intrinsic kidney disease characterized by kidney tubular injury via the deposition of calcium oxalate crystals with initial acute tubular injury that can progress to scarring and eventually to end-stage kidney disease. This condition may be caused by primary hyperoxaluria (genetic), enteric hyperoxaluria (in setting of fat malabsorption), and ingested foods high in oxalate (e.g., spinach, pine nuts holding the highest oxalate content). Finally, high protein intake may increase oxalate excretion in the urine. Patients with acute oxalate nephropathy typically recover with acute kidney injury. He reported a diet consisting of obsessive compulsive eating behavior. He reported heavy ingestion of foods presumed to be healthy, including oranges, assorted nuts, turkey, and up to 5 protein bars at a time. Vital signs and physical exam were unremarkable. Serum creatinine was 2.1 mg/dL (baseline 1.2 mg/dL) with a bland urinalysis without hematuria or proteinuria. Serologic work-up was unremarkable.

A kidney biopsy revealed numerous calcium oxalate crystals associated with diffuse acute tubular injury, diagnostic of oxalate nephropathy.

Discussion: Oxalate nephropathy is an intrinsic kidney disease characterized by deposition of calcium oxalate crystals in the kidney tubules. Excessive consumption of foods high in oxalate or its precursors can cause acute or chronic kidney disease. In this case, the ingestion of oranges, nuts, turkey slices, and protein bars may have led to oxalate nephropathy. Vitamin C (ascorbic acid) found in citrus fruits is a precursor to oxalate. However, vitamin C supplementation is more commonly reported as a cause because it is more bioavailable. Nuts are also a high oxalate food, with almonds, Brazil nuts, and pine nuts holding the highest oxalate content. Finally, high protein intake may increase oxalate excretion in the urine. Patients with acute oxalate nephropathy typically recover kidney function and have a better prognosis than those with chronic disease. In this case, the patient reduced his intake of high oxalate foods and increased fluid intake to 2 liters of water daily. Thereafter he had progressive improvement of kidney function back to baseline.

FR-PO834

Coexposure of Melamine and Di-2-Ethylhexylphthalate Changes Mitochondrial Dynamics and Accelerates Kidney Injury in Adenine Diet-Induced CKD Mice

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Background: Environmental chemical exposures have shown to be risk factors for chronic kidney disease (CKD). Even though the 2008 event of melamine-added formula milk was over, environmental melamine exposure still occurs due to the contamination in daily food products and widely uses of melamine-made tableware. Our previous study found that environmental melamine increased oxidative stress and early kidney injury in adults. Bis-2-ethylhexylphthalate (DEHP) is presented widely in plastic products and in daily food products and widely uses of melamine-made tableware. Our previous study are to clarify the nephrotoxicity of melamine and DEHP coexposure and to investigate the role of mitochondrial oxidative stress in the pathological mechanisms using a mouse model based on the US-FDA suggested human tolerable daily intake (TDI) levels of melamine and DEHP.

Methods: An adenine-rich diet induced CKD model was conducted in male and female ICR mice with the coexposure of TDI levels of melamine and DEHP for 4 weeks. Urine albumin-creatinine ratio (uACR) was used to monitor kidney function. Kidney injury molecule (KIM-1) immunohistochemistry, Sirius-red staining and TUNEL assay were applied to observe kidney injury, fibrosis, and apoptosis. We used Western blotting to detect target proteins, real-time PCR to measure mitochondrial DNA (mtDNA) and MitoSOX staining to detect mitochondrial ROS.

Results: Our results showed that melamine and/or DEHP exposure increased uACR, indicating a decline of kidney function. Fibrosis, apoptotic cells and KIM-1 were increased in the kidney sections of CKD mice exposed to melamine and/or DEHP. Biomarkers of oxidative stress (MDA, 4-HNE), inflammation (NF-kB) and fibrosis (TGF-β, collagen IV) were also elevated. Melamine and DEHP increased mitochondrial ROS and changed mtDNA and mitochondrial dynamic proteins (pink1, Parkin, Min2, Dlp1, Fisl) in the kidney of CKD mice.

Conclusions: Our findings suggest that melamine and/or DEHP exposure accelerates a progression of kidney injury in CKD, which may be mediated by changes in mitochondrial dynamics. Avoiding exposure of environmental melamine and DEHP should be advised in patients with CKD.

Funding: Government Support - Non-U.S.

FR-PO835

The Vitamin D Metabolite Ratio and Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis

Jonathan Cheng,1,2 Andrew N. Hoofnagle,3 Ronit Katz,3 Simon Hsu,4 Deborah M. Kado,4,5 Matthew J. Budoff,6,7 Bryan R. Kestenbaum,8 Erin D. Michos,5 Lindsay M. Miller,1 Joachim H. Ix,1,2 Ian H. de Boer,3 Charles Ginsberg,9 1University of California San Diego, La Jolla, CA; 2VA San Diego Healthcare System, San Diego, CA; 3University of Washington, Seattle, WA; 4Stanford Medicine, Stanford, CA; 5VA Palo Alto Geriatric Research Education and Clinical Center, Palo Alto, CA; 6University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA; 7Johns Hopkins Medicine, Baltimore, MD; 8Harbor-UCLA Medical Center, Torrance, CA.

Background: Vitamin D deficiency has been linked to cardiovascular disease (CVD) with mixed results. The vitamin D metabolite ratio (VMR), the ratio of 24,25(OH)D to 25(OH)D, has shown stronger associations with bone health and mortality than 25(OH)D alone. Our study assessed the association between the VMR and CVD outcomes.

Methods: We evaluated 6,313 Multi-Ethnic Study of Atherosclerosis (MESA) participants without CVD using Cox regression to test the associations of both VMR and 25(OH)D with incident CVD (including myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death, and stroke death), heart failure (HF), and cardiovascular mortality. We adjusted models for age, gender, race, physical activity, BMI, smoking, diabetes, blood pressure condition and medication use, C-reactive protein, cholesterol levels and medication use, triglycerides, kidney function, parathyroid hormone, fibroblast growth factor 23, calcium, and phosphate.

Results: The study participants had a mean age of 62, with 53% of them being female. The cohort was 38% White, 28% Black, 22% Hispanic, and 12% Chinese. The mean (SD) 25(OH)D level was 22.7 (11.0) ng/mL, and the mean VMR was 15.2 (5.0). In fully adjusted models, a two-fold increase in VMR was associated with a 24% reduction in incident CVD (HR: 0.76, 95% CI: 0.65-0.88). However, there was no association between the VMR and HF (0.98, 0.78-1.24), or cardiovascular mortality (0.96, 0.77-1.21). 25(OH)D was not significantly associated with any CVD outcome.

Conclusions: In a multi-ethnic cohort, VMR was significantly associated with reduced incident CVD, but not HF or cardiovascular mortality over 15 years of follow-up. The results suggest that VMR may provide greater insight into vitamin D metabolism compared with 25(OH)D levels alone.

Funding: NIDDK Support, Veterans Affairs Support

Association of VMR and 25(OH)D with Cardiovascular Outcomes: Fully Adjusted Model

<table>
<thead>
<tr>
<th>Outcome</th>
<th>H.R. (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD</td>
<td>0.76 (0.65, 0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>HF</td>
<td>0.98 (0.78, 1.24)</td>
<td>0.81</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>0.76 (0.65, 0.88)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*Per two-fold increase
FR-PO836
Paradoxical Association of Vitamin D Supplementation with Elevated Blood Pressure in Individuals Without Vitamin D Deficiency

Manasawee Tanaritkulak,1 Chinnawat Arayangkool,1,2 Thirastest Leesutipornchai,1,3 Noppawat Aiumtrakul,1,3 Mohammad I. Khan,1,3 Ekamol Tantisattamo,1 University of Hawai’i at Manoa John A Burns School of Medicine, Honolulu, HI; 2Division of Nephrology, Hypertension and Kidney Transplantation, Department of Medicine, University of California Irvine School of Medicine, Orange, CA; 3Hawaii Residency Programs Inc, Honolulu, HI.

Background: While vitamin D (Vitamin D) deficiency (def) is associated with high blood pressure (BP), potential effects of supplemental Vitamin D intake in individuals without Vitamin D def is unknown. This study aims to examine the association of the amount of Vitamin D intake with BP in individuals with and without Vitamin D def.

Methods: This cross-sectional study utilized data from the 2017-2018 Continuous NHANES. Participants’ average daily Vitamin D intake over a 30-day period and their BP were collected through questionnaires and examinations. The study included individuals with more or less Vitamin D intake (>800 or <300IU/day). Difference in systolic and diastolic BP (SBP and DBP) between two groups stratified by presence and absence of Vitamin D def defined by Vitamin D level <30 and >30 nmol/L, respectively was evaluated by an independent sample t-test.

Results: Among participants without Vitamin D def, 1068 had more and 837 had less Vitamin D intake. SBP in the former group were greater than those of the latter group (SBPmore vs less 129.5 ± 12.8 vs 126.5 ± 12.7 mmHg; mean ± SEM, p < 0.001). Similarly, DBP was higher in the more Vitamin D intake group (DBPmore vs less 76.2 ± 7.2 vs 73.5 ± 6.9 mmHg; mean ± SEM, p < 0.001). Of 90 participants with Vitamin D def (34 and 56 with more and less Vitamin D intake), both SBP and DBP remained higher in the more Vitamin D intake group but there was no statistical significance (SBPmore vs less 128.9 ± 13.2 vs 125.7 ± 13.5 mmHg; mean ± SEM, p = 0.163; DBPmore vs less 70.7 ± 7.1 vs 67.8 ± 7.2 mmHg; mean ± SEM, p = 0.051).

Conclusions: Although Vitamin D supplementation is associated with lowering BP in individuals with Vitamin D def, supplemental Vitamin D intake greater than 800 IU/day is paradoxically associated with higher BP in individuals without Vitamin D def compared to less Vitamin D intake. The absence of Vitamin D def, whether Vitamin D supplementation causes an imbalance of mineral and bone metabolism related to vascular calcification leading to elevated BP requires further studies.

FR-PO837
A Randomized Controlled Trial Comparing Between Fixed Dose and Serum Level-Based Titration Regimen of Vitamin D Supplementation on Sarcopenia Outcomes Among Dialysis Patients

Saranchana Jampochanan,1 Piyatida Chuengsaman,2 Yingyos Avihingsanon,1 Somchai Eiam-Ong,3 Piyawat Kittisuklum,3 King Chulalongkorn Memorial Hospital, Bangkok, Thailand; 2Banphao-Charonkruong Peritoneal Dialysis Center, Banphao Dialysis Group, Banphao Hospital, Bangkok, Thailand.

Background: Low vitamin D status is associated with either low muscle mass or impaired muscle function in dialysis patients. However, there is no consensus on how best to correct vitamin D deficiency in patients with end-stage kidney disease (ESKD). We investigated the effect of different vitamin D supplementation regimens on sarcopenia outcomes in ESKD patients.

Methods: This was a randomized controlled trial (ClinicalTriail.gov NCT05434377). ESKD patients treated with maintenance hemodialysis or peritoneal dialysis with low vitamin D status, defined as serum 25-hydroxyvitamin D (25-OH D) level <30 ng/mL were randomized to either receive oral ergocalciferol using a fixed dose regimen of 20,000 IU/week or utilizing serum 25-OH D level-based titration of dosage adjustment as per formula: dosage = 500×(serum 25-OH D level-<30 ng/mL) (mg/day). The changes in serum total muscle mass measured by bioimpedance spectroscopy, muscle strength using a hand grip dynamometer, and physical performance measured by gait speed were determined. Baseline data after 6 months of supplementation were compared between groups.

Results: A total of 76 dialysis patients were enrolled (HD=43%). Baseline characteristics including age, diabetes mellitus, muscle parameters, and dialysis vintage were similar. After supplementation, the average serum 25-OH D levels in the fixed dose and titration groups were significantly elevated from 14.9 ± 6.4 to 28.8 ± 11.5 ng/mL, p < 0.001 and from 10.0 ± 7.1 to 26.9 ± 13.2 ng/mL, p < 0.001, respectively, but did not differ between groups at 6 months (p = 0.52). Despite comparable energy and protein intake, the mean BIS-derived total-body muscle mass normalized to height squared was significantly increased at 6 months in the fixed dose group (14.4 ± 3.4 vs 15.3 ± 3.0 kg/m², p < 0.001). Visceral hypercalcemia nor hyperphosphatemia was found throughout the study.

Conclusions: Increased muscle mass among patients receiving maintenance dialysis. Vitamin D supplementation appears to be a promising treatment of sarcopenia among dialysis population.

Funding: Private Foundation Support

FR-PO838
Effects of Two-Month Low-Sodium (Na+) Diet on Muscle Na+, Fat, and Function in Hemodialysis (HD) Patients


Background: Higher muscle sodium concentration ([Na+]m) in HD patients is linked with muscle metabolic disturbances. We aimed to test if a 2-month low-Na+ diet would reduce muscle [Na+], thereby improving muscle structure or function in HD patients.

Methods: Eleven HD patients (56±13 y) received 2 and 1-low-Na+ meal(s)/day during the first and second months of intervention, respectively, along with dietary counseling. The [Na+]m and fat fraction (FF) in muscles were measured by 3T 31Na- and 1H-MRI at pre- and post-intervention in 6 muscles: tibialis anterior (TA), extensor digitorum longus (EDL), peroneus (PER), soleus (SOL), and lateral (LG) and medial (MG) gastrocnemius. Lower-limb muscle function was assessed using the 30s sit-to-stand (STS) test after MRI. Data were analyzed using the paired t test and Pearson’s or Spearman’s correlation.

Results: At baseline, muscle [Na+]m was inversely correlated with STS score in all muscles except SOL (Fig. 1) and tended to positively correlate with FF in MG (r=0.60, p=0.05). There were no significant changes in muscle [Na+]m or FF post-intervention in each muscle studied (all P>0.05), with no improvement seen in STS score (P=0.34). An increase in muscle [Na+]m from pre- to post-intervention was associated with a decrease in STS score in all muscles except SOL (Fig. 2). There was no correlation between pre- to post-intervention changes in muscle FF and changes in STS score for each muscle (all P>0.05).

Conclusions: Two-months of a low-Na+ diet did not reduce muscle [Na+]m in HD patients. However, the inverse correlations between baseline muscle [Na+]m and STS score and the changes in muscle [Na+]m and STS score, may serve as a rationale for developing new interventions to mitigate muscle dysfunction in HD patients by controlling muscle [Na+]m.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO840

Involvement of Type I Interferon-Responsive Myeloid Cells in Renal Inflammation in a Lupus Mouse Model
Lindsey Han, Cleveland Clinic Lerner Research Institute, Cleveland, OH.

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that damages multiple organs, including the kidneys in Lupus Nephritis (LN). Current treatments for SLE/LN are limited to conventional disease-modifying anti-rheumatic drugs and corticosteroid therapy. A more targeted therapy is necessary to address the unique disease-related symptoms aggression. Type I interferon (IFN-I) and its receptor (IFNAR) are known to play a significant role in the progression of SLE/LN, making them a major focus of research and therapy.

Methods: 3 female mice strains were used to investigate whether deficiency of IFNAR on myeloid cells can prevent or reduce disease progression in SLE/LN. The study mice were LysM cre/cre, IFNAR flx/flx B6.Nba2 (n=16) with knockout of IFNAR on myeloid cells (cKO). We also used B6.Nb2 (WT) mice that develop lupus-like disease (n=18) and B6 (C57Bl/6) healthy mice (n=4). The tests performed include flow cytometry on 9 month (9mo) kidney cells, spleen multi-cytokine array of pro-inflammatory cytokines and chemokines, and ELISA of urine biomarkers S100a8, VCAM-1, and PF4.

Results: Kidney 9mo flow data revealed elevated neutrophil and decreased monocytic infiltration in the WT, but normalized levels in cKO, as well as specifically reduced levels of B cells in cKO. CD4+ T cells were specifically reduced, CD8+ T cells were specifically elevated, and Double positive (DP) T cells were normalized in 9mo cKO kidneys. Furthermore, we found that urinary biomarkers S100a8 and PF4 were decreased in 9mo cKO compared to the WT. 9mo spleen IL-21, IL-10, IL-6, IFN-γ, and TNF-α were reduced in cKO, and cKO mice developed accelerated Splemonomegaly at 2 months, followed by Nephromegaly at 9mo.

Conclusions: In essence, we observed reduced levels of neutrophilic, B cells, CD4+ T cells and DP T cells associated with reduced levels of urine biomarkers and that lack of type I interferon expression on myeloid cells affects the trafficking pattern of both mononuclear and myeloid cells. Thus, our hypothesis for LN development follows: IFNAR facilitates the infiltration of neutrophilic cells, leading to the release of chemokines and the recruitment of inflammatory lymphocytes, and ultimately resulting in renal cell damage and the development of LN. Future directions include further analyses of renal inflammas and additional urinary biomarkers.

FR-PO841

Healthy Women Have Higher Systemic Uromodulin Levels: Identification of a New Extragonadal Estrogen Response Gene
Azuma Nanamatsu, Radmila Micanovic, Shelnaz Khan, Tarek M. El-Achkar, Katie A. LaFavers, Indiana University School of Medicine, Indianapolis, IN.

Background: Urinary and serum uromodulin (gene: UMOD), secreted by the kidney, gained attention as potential biomarkers for kidney function in the context of acute and chronic kidney diseases and as an overall marker of health. However, there are few analyses focusing on a large number of healthy subjects, the ranges and physiological regulation of serum uromodulin have not been well established.

Methods: We determined serum uromodulin levels of healthy human subjects (n = 380) available from the Indiana University Biobank. To identify predictors of levels, we performed automated linear modeling in SPSS using relevant predictor variables extracted from deidentified patient charts (age, sex, body mass index, race, serum creatinine, eGFR, prescription drug usage). We also measured serum uromodulin in mice using ELISA. To identify a potential mechanism for increased serum uromodulin levels in females, mouse kidney thick ascending limb (MKTAL) cells were treated with 17β-estradiol, and uromodulin mRNA and protein expression were evaluated by RT-qPCR and Western blotting, respectively.

Results: Healthy subjects showed a wide range of serum uromodulin levels. Automated linear modeling in SPSS identified sex and body mass index (BMI) as significant (p<0.05) predictors of serum uromodulin level. Serum uromodulin levels are upregulated in female MKTAL cells, not male rats. To identify a potential mechanism for increased serum uromodulin levels in females, we analyzed the UMOD locus in H. sapiens and M. musculus. We found two non-canonical estrogen response elements (ERE) and 29 canonical half-EREs in the H. sapiens sequence and 45 canonical half-EREs in the M. musculus sequence. Consistent with this, serum uromodulin levels normalized to weight are higher in female mice. Additionally, treatment with 10 µM - 1 nM of 17β-estradiol increases uromodulin expression in the mRNA and protein levels in MKTAL cells.

Conclusions: Healthy females have higher serum uromodulin levels, likely due to the estrogenic environment of the female reproductive tract. Since estrogen reduces glomerular filtration rate and is protective against acute kidney injury, estrogen-responsive increases in serum uromodulin might partially explain sex-specific susceptibility to infection and kidney injury.

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

FR-PO843

Sex-Based Differences in Proximal Tubule Recovery of Filtered Proteins
Katherine E. Shipman,1 Catherine J. Baty,1 Elyonna B. Youm,2 Aurelie Edwards,2 Ora A. Weiss,1 1University of Pittsburgh School of Medicine, Pittsburgh, PA; 2Boston University, Boston, MA.

Background: The proximal tubule (PT) efficiently reclaims albumin and other proteins that escape the glomerular barrier to maintain protein free urine. The recovery of filtered proteins occurs via receptor-mediated endocytosis facilitated by the multiligand receptors megalin and cubulin. PT health is impacted by excess albumin uptake that occurs when the glomerular barrier is breached and by nephrotic drugs that enter cells in a megalin/cubulin dependent manner. Transcriptomic and genomic studies in male rodents have demonstrated differences in the expression of megalin and cubulin across the S1, S2, and S3 sub-segments that comprise the PT. Based on this, we previously developed an axial model of protein uptake in mice which predicts that most uptake under normal conditions exists in S1, with S2 providing excess uptake capacity under nephrotic conditions. Multiple studies have shown that females are more protected from renal injury than males, however, the mechanisms underlying this difference in protection from renal injury are unknown.

Methods: To determine if there are sex-based differences in baseline PT recovery of filtered proteins, urine and kidneys were collected from five male and five female 13-week-old C57BL/6 mice. Urinary albumin was quantified by ELISA. Kidneys were processed for Western blotting and immunofluorescence staining. We used imaging-based approaches to quantify the expression and distribution of megalin and cubulin in SGLT2- positive S1 and SGLT2-negative S2 segments.

Results: Compared to males, female mice had lower levels of urinary albumin excretion when normalized to creatinine at baseline. Female mice had greater expression of total megalin and cubulin and decreased expression of NHE3 in the kidney cortex. Male and female mice had similar levels of megalin expression and surface localization in S1, whereas female mice had greater expression and surface localization of megalin in S2. A greater fraction of total cubulin localized to the apical surface compared to megalin along the length of PT.

Conclusions: Our data suggest differences in the capacity of the PT to recover filtered proteins between male and female mice which could be especially relevant under nephrotic conditions. Current studies are focused on incorporating these sex-based differences into a mathematical model of protein uptake along the length of the PT.

Funding: NIDDK Support

FR-PO845

Sex Differences in Regional Distribution of Key Steroidogenic Enzymes in the Rat Kidney
Leah B. Shelton,1 Victoria L. Naczi,2 Ravneet Singh,1 Erman Y. Gohar,2 Eastern Virginia Medical School, Norfolk, VA; 2Vanderbilt University Medical Center, Nashville, TN.

Background: Extragonadal estrogen (E2) synthesis has been demonstrated in tissues such as brain, bone, and adipose tissue. We recently demonstrated a decrease in E2 production in an intrarenal E1 synthesis in the outer medulla (OM) of Sprague Dawley rats. Measurement of renal E1 showed higher E1 levels in female inner medulla (IM) compared to male rats. Thus, we aimed to investigate regional sex differences in renal E1-synthesizing enzymes that underlie these differences in E1 levels.

Methods: Kidneys from male and female Sprague Dawley rats (n=8/group) were flushed, dissected into cortex (CTX), OM, and IM regions, and assessed for mRNA expression or protein abundance of enzymes in the E1 biosynthesis pathway.

Results: mRNA expression of 3-hydroxy-3methylglutaryl-CoA reductase (HMGR), the key enzyme in cholesterol synthesis (the first substrate in steroidogenesis), was higher in female OM compared to males (100.0 ± 14.4 vs 254.4 ± 50.5 relative expression, p=0.0148), while no sex difference in HMGR mRNA was observed in CTX or IM. Protein abundance was measured by Western blotting. We found higher E1 mRNA expression in female CTX and OM, while males expressed higher levels in IM (CTX: 100.0 ± 34.7 vs 204.0 ± 71.1, p=0.0120; OM: 100.0 ± 41.0 vs 228.9 ± 78.0, p=0.0017; IM: 100.0 ± 37.5 vs 36.3 ± 15.2, p=0.0010). We also assessed mRNA expression of 3-hydroxy-3methylglutaryl-CoA dehydrogenase (HSD17B) 1, 2 and 3 which interconvert androgens and estrogens. HSD17B1 was higher in male CTX and OM (CTX: 100.0 ± 46.5 vs 7.6 ± 1.3, p=0.0003; OM: 100.0 ± 52.6 vs 10.1 ± 2.4, p=0.0005), while HSD17B2 and 3 were higher in female CTX and OM (CTX: 100.0 ± 43.8 vs 541.4 ± 271.1, p=0.0042, IM: 100.0 ± 119.8 ± 7.6 ± 1.3, p<0.0001). Measurements showed that male rats had higher E1 levels in IM, compared to females. Region-specific differences in enzyme levels may contribute to renoprotective effects.

Conclusions: Our data indicate sex- and region-specific differences in expression of key enzymes in the biosynthesis pathway within the rat kidney. HMGCR, CYP17A1, and HSD17B2 and 3 were upregulated within the female rat renal cortex and/or OM, but not IM, compared to males. Regional-specific upregulation of these enzymes in females may contribute to renoprotective effects.

Funding: Other NIH Support - ASN Carl Gottschalk Research Scholar Grant to EVG; ORAU Short Term Research Training Program for Medical Students (NIH grant DK07383)
FR-PO844

Multiple Pregnancy Can Induce Preeclampsia-Like Changes in Complement Factor H Point Mutation Mice
Feifei Chen, Ying Tan. Peking University First Hospital, Beijing, China.

Background: Preeclampsia is a severe placenta-related pregnancy disorder, its pathogenesis has still not been fully elucidated. Studies suggested a link between complement activation and preeclampsia. In view of that normal pregnancy can induce appropriate activation of the complement system, we assumed that patients with preeclampsia may have increasing genetic susceptibility to overactivation of complement system, and under the burden of pregnancy, overactivation of the complement system occurs, in turn leading to the occurrence of preeclampsia.

Methods: We mated the female and male mice with heterozygous mutations in complement factor H through five times and assessed clinicopathological indicators of preeclampsia.

Results: Along with complement activation, multiple pregnant heterozygous complement H mutated the key features of human preeclampsia, such as hypertension, proteinuria, elevated blood urea nitrogen, lactic dehydrogenase, reduced placental weight, restricted fetal growth, typical histology change in placenta and kidney of preeclampsia, placental imbalance of angiogenesis and renal endothelial cell injury.

Conclusions: This study provided direct evidence that pregnant status can induce overactivation of complement system in mice with mutation in complement regulator gene, which could lead to the development of preeclampsia. This model provided a new option for the investigation of the pathogenesis of preeclampsia.

FR-PO845

Screening Fabry Disease in Women Combining Enzyme Activity with Lyso-GL3: Results of a Brazilian Study
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Background: Fabry disease (FD) is a rare X-linked lysosomal storage disease that can affect multiple organs, including the kidneys. The main objective of this study was to evaluate the effectiveness of a combination of α-GAL enzyme activity and plasma levels of lyso-GL3 for screening FD in women with chronic kidney disease (CKD).

Methods: Women with CKD, stages 3 to 5, in regular nephrological follow-up were selected from renal centers in all regions of Brazil. Exclusion criteria: under 18 years old, α-GAL enzyme activity was below and/or lyso-GL3 levels were above the reference range. α-GAL gene sequencing was performed if selected from renal centers in all regions of Brazil. Exclusion criteria: under 18 years old, α-GAL enzyme activity and plasma levels of lyso-GL3. GLA gene sequencing was performed if patients with preeclampsia may have increasing genetic susceptibility to overactivation of complement system, and under the burden of pregnancy, overactivation of the complement system occurs, in turn leading to the occurrence of preeclampsia.

Results: The mean age was 53 [42 – 64] years. All cases of low α-GAL and/or increased lyso-GL3 were submitted to genetic analysis, and 6 positive cases were found. Among genetic variants, four patients have R118C, one A143T and other with T430G, all considered variants of uncertain significance (VUS). The sensitivity and specificity of α-GAL reduction for the detection of FD was 83.3% and 97.6%, respectively. As for the increase in lyso-GL3, the values were 16.6% and 93.9%, respectively. There were no cases that presented a concomitant increase in lyso-GL3 and a reduction in enzymatic activity.

Conclusions: Preliminary results suggest that the combination of α-GAL enzymatic activity with lyso-GL3 measurement may be a good alternative for screening FD in women with CKD. A thorough medical evaluation is required to determine the pathogenicity of variants in these patients.

Funding: Commercial Support - Sanofi-Genzyme

FR-PO846

Sexual Function, Activity, and Satisfaction Among Young Females with CKD
Kathryn Corbet,1,2 Victoria J. Riehl-Tonn,1,2 Danica H. Chang,3 Sofia B. Ahmed,3,4 Sandi M. Dumasinski,3,4 University of Calgary, Calgary, AB, Canada; 5Libin Cardiovascular Institute of Alberta, Calgary, AB, Canada; 6University of Alberta, Edmonton, AB, Canada.

Background: Up to 80% of women with chronic kidney disease (CKD) experience sexual dysfunction, though its link with sexual activity and sexual satisfaction is not known. Recent literature demonstrates that among older women with kidney failure treated with dialysis, the majority report sexual inactivity, few describe sexual dysfunction and most report high sexual satisfaction. Whether this applies to young females with CKD has not been described. Our objectives were to determine the incidence of sexual activity, sexual dysfunction and sexual satisfaction among young females with CKD.

Methods: Females < 51 years old with CKD were recruited from nephrology clinics in Calgary, Alberta, Canada. Participants completed a modified version of the Female Sexual Function Index, a validated tool to assess sexual function.

Results: Thirty-six females with CKD (6% hemodialysis, 14% peritoneal dialysis, 14% stage G5-5 CKD, 11% transplant) participated. The median age was 37 years old (IQR 32, 43) and all participants identified as cis-gender. Eighteen participants (51%) reported sexual activity, and 82% of these individuals met criteria for sexual dysfunction. Among all participants, only 23% reported satisfaction with their sex life, while 57% reported moderate to severe dissatisfaction. Sexual dissatisfaction was more common among women experiencing sexual dysfunction (p = 0.003).

Conclusions: Young females with CKD are sexually active and experience a high incidence of both sexual dysfunction and dissatisfaction. These findings emphasize the importance of screening for sexual dysfunction and providing effective treatment options.

FR-PO847

Albuminuria and Vascular Health in Females with CKD
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Background: Cardiovascular (CV) disease is the leading cause of death in chronic kidney disease (CKD), and elevated CV risk occurs earlier in the CKD disease course in females compared to males. Albuminuria, a marker of CKD severity, has been independently associated with CV disease in females, however the mechanism of this association is not yet understood. This study aimed to determine the association between albuminuria and markers of vascular health, including mean arterial pressure (MAP) and arterial stiffness, as measured by aortic augmentation index (AIX) and pulse-wave velocity (PWV), in females with CKD.

Methods: An exploratory cross-sectional study recruited 54 females with CKD from nephrology clinics in Calgary, Alberta. Albuminuria was quantified by collection of a midstream urine and measurement of urine albumin-to-creatinine ratio (ACR). Using standardized protocols, blood pressure and arterial stiffness were measured. Multiple linear regression analysis was used to estimate the association between urine ACR and CV disease in females, however the mechanism of this association is not yet understood. This study aimed to determine the association between albuminuria and markers of vascular health, including mean arterial pressure (MAP) and arterial stiffness, as measured by aortic augmentation index (AIX) and pulse-wave velocity (PWV), in females with CKD.

Results: Among all participants, only 23% reported satisfaction with their sex life, while 57% reported moderate to severe dissatisfaction. Sexual dissatisfaction was more common among women experiencing sexual dysfunction (p = 0.003).

Conclusions: Young females with CKD are sexually active and experience a high incidence of both sexual dysfunction and dissatisfaction. These findings emphasize the importance of screening for sexual dysfunction and providing effective treatment options.
FR-P0848
To Assess Serum Prolactin Levels in Female Patients of CKD on Maintenance Haemodialysis
Anuja P. Makan, Tushar A. Dighe, Charan B. Bale, Pavan Wakhare, Nilesh Shinde, Akash R. Kulkarni, Abhijit S. Chavan, Deapabirya Saha, Chetan U. Phadke, Shreerachad Godbole, Atul Sajgure. DY Patil University Deemed to be University School of Medicine, Pune, India.

Background: Kidneys play an important role in endocrine regulation, not only producing hormones such as erythropoietin and renin but also acting on the metabolism of others such as insulin, cortisol and prolactin. Therefore, CKD patients have numerous endocrine dysfunctions, with changes in feedback loops, reduced transport of protein-bound hormones, and reduced metabolism and hormone elimination. Hyperprolactinemia occurs by several mechanisms of which reduction in metabolism is one of the main mechanisms. The other is increased prolactin secretion by lactotrophs in the ucemic state – reduced availability of dopamine in the brain directly stimulates prolactin secretion as also increased autonomic production state. As a result of hyperprolactinemia, normal cyclic GnRH secretion decreases, resulting in the loss of pulsatile LH and FSH release.

Methods: Observational prospective study with a sample size of 30 patients in the age group of 15 to 45 years. Results: In our study of 30 patients, prolactin was high in 16 patients (53%) of end stage renal disease on dialysis.

Conclusions: To summarise, serum prolactin concentrations were high in a large majority of patients with ESRD. Even with a greatly increased prevalence in CKD, the clinical diagnosis of hyperprolactinemia in this population is difficult. Signs and symptoms of hyperprolactinemia are confused with some manifestations of CKD itself such as oligomenorrhea, amenorrhea, decreased libido, erectile dysfunction, infertility and osteoporosis.

FR-P0849
Bilateral Ureteral Obstruction: Cause of AKI in Pregnancy
Roland Ngum Kum, Kundana R. Thimananagai, Heather R. Lefkowitz. Newark Beth Israel Medical Center, Newark, NJ.

Introduction: Pregnancy-related acute kidney injury (PR-AKI) has an incidence of about 2% (1). The incidence has decreased significantly over the past years in developed countries and this is attributed to improved antenatal care (2). A rare cause of PR-AKI is bilateral ureteral obstruction, which has been reported in only a few studies. We report the case of a patient with bilateral ureteral obstruction, which has been reported in only a few studies. We report the case of a patient with severe hypokalemia and hypertension in recurrent pregnancies. Careful history taking, in this case however, revealed a unique cause of her symptoms.

Case Description: A 32-year-old woman was referred for hypertension (180/108 mmHg) and massive proteinuria (7.3 g/gCr) at 34 weeks gestation. Despite well controlled blood pressure, renal biopsy was performed for definitive diagnosis. Histological findings showed focal endothelial hyperplasia of the mesangial and double contour. Immunofluorescence showed remarkable glomerular deposition. Reticulation of endothelial cell and duplication of GBM were detected by electron microscopy. Histological interpretation lead to definitive diagnosis as PE and to appropriate treatment, resulted in diminish of proteinuria. In present case, histological implication lead to appropriate diagnosis as PE and to appropriate treatment, resulted in diminish of proteinuria.

Discussion: Analysis of RETNEXT in female patients with PE and renal biopsy, showed that the RET gene in the patients with PE and renal biopsy, showed that the RET gene is not a major cause of PE and renal biopsy.

FR-P0850
Rare Case of Recurrent Hypokalemia in Pregnancy: Broaden Your Differentials
Mozammul M. Cheema, Laith Alzyood, Roy Lee, Wei Chen, Maureen Brogan, Sonali Gupta. Montefiore Medical Center, Bronx, NY.

Introduction: Geller’s syndrome is in the differential diagnosis when a pregnant woman presents with hypertension and severe hypokalemia. Here, we present a case of a patient with severe hypokalemia and hypertension in recurrent pregnancies. Careful history taking, in this case however, revealed a unique cause of her symptoms.

Case Description: A 30 year-old, G3P3013 presented at 39 weeks 5 days gestation in labor and was diagnosed to have severe preeclampsia and HTN. Labs notable for K < 2.0 mg/dL, Mg 1.6 mg/dL, calcium 9.1 mg/dL (corrected), phosphorus 4.2 mg/dl and Cr 0.67 mg/dL. EKG noted U-waves. She required aggressive replacement of potassium (IV and PO for 2 days). She had history of severe hypokalemia requiring aggressive potassium repletion in her two previous pregnancies except for third pregnancy. She first presented with AKI and bilateral ureteral obstruction, which has been reported in only a few studies. We report the case of a patient with severe hypokalemia and hypertension in recurrent pregnancies. Careful history taking, in this case however, revealed a unique cause of her symptoms.
Ultrasound of transplanted kidney at 24 weeks (A), 36 weeks (B) with fetal head compressing renal hilum (white arrow), and 2 days postpartum (C).

FR-PO853
Renal Artery Stenosis in Early High-Risk Pregnancy
Marielle Ilamas, Tyler Andrea. Samaritan Health Services, Corvallis, OR

Introduction: Renovascular hypertension is an uncommon cause of hypertension in pregnancy.1 Renovascular hypertension management is complicated by contraindication in pregnancy to established first line treatment of ACE-I and ARBs due to teratogenicity. The potential teratogenic risks of radio logical intervention using fluoroscopy limits diagnostic options.2 Previous cases of pregnancy patients presenting with new onset or superimposed preeclampsia secondary to renovascular hypertension have been rarely reported.2 We present a case report of renovascular hypertension in a pregnant patient who was at 17 weeks gestation at the time of diagnosis.

Case Description: 38-year-old pregnant female presenting for routine prenatal care. Pre-existing diagnoses of insulin-dependent T2DM complicated by diabetic neuropathy, combined systolic/diastolic heart failure, history of methamphetamine use in remission, prior stroke x2 with residual left-sided deficits (2020), and poorly controlled hypertension. Confirmatory 24-hour urine protein: 7.410 mg/24h 24h BP monitor: average reading of 185/87 Aldosterone/renin activity ratio: normal Regularly scheduled visits with her obstetrician soon revealed difficulties with hypertension control, resulting in an increase of 20 mg of her labetalol dose to 300 mg twice daily. At 17 weeks gestation, duplex ultrasound of the renal arteries confirmed high-grade stenosis of the right kidney artery greater than 70%. Patient was promptly admitted for renal revascularization with renal artery stenting.

Discussion: Diagnosis of RAS can be done through duplex ultrasound imaging, CTA scan, or MRA. A catheter angiogram, which requires contrast to be injected via a catheter threaded through the renal artery is considered the gold standard diagnostic tool. However, it is not widely used during pregnancy due to radiation effects.3 While extra-abdominal radiologic examinations render insignificant exposures to the pregnant uterus, high quality tools such as, fluoroscopically- or CT-guided interventional procedures (such as renal artery angioplasty) should be carefully considered during pregnancy.4 The management of hypertension in early pregnancy should involve screening for RAS, especially in the setting of resistance to antihypertensive medications.5 The benefits of early diagnosis of renal artery stenosis in pregnancy must be balanced with the risks of diagnostic imaging, interventional procedures, and its teratogenic risks.

FR-PO854
Neither Infantine nor Idiopathic: A Challenging Case of Hypercalcemia During Pregnancy
Eric Magliulo, Saher Aslam, Jay L. Hawkins. University of Nebraska Medical Center, Omaha, NE

Introduction: Idiopathic Infantile Hypercalcemia (IIH) Type I is a rare cause of hypercalcemia presents both in infancy and in adulthood. Autosomal recessive mutations in the CYP24A1 gene, which encodes for the 24-hydroxylase enzyme, were recently identified in patients diagnosed with IIH Type I. A deficiency or loss of function in this enzyme leads to reduced metabolism of activated vitamin D. Here we present a case of a patient presenting with hypercalcemia, hypertension, and nephrocalcinosis during pregnancy.

Case Description: A 34 year old woman G3P003 with a history of three pregnancies complicated by hypercalcemia and pre-eclampsia with severe features was referred to Nephrology for evaluation of persistent post-partum hypercalcemia. During her most recent pregnancy, she was hypertensive with a total serum calcium ranged from 9.9 - 12.7 mg/dL. Post-partum, she was initiated on nifedipine, hydralazine, and enalapril. Initial labs were consistent with PTH-independent hypercalcemia with an inappropriately normal serum 1,25 dihydroxy vitamin D. Work up for a granulomatous disease process was negative. Imaging revealed bilateral medullary calcinosis. 24 hour stone analysis showed an increased risk for formation of calcium phosphate stones. A 25 Hydroxyvitamin D24,25 Dihydroxy-vitamin D ratio could not be calculated at 24,25-Dihydroxy-vitamin D was below the limit of quantification. Genetic testing confirmed the presence of compound heterozygous mutations in the CYP24A1 gene.

Discussion: A deficiency in the 24-hydroxylase enzyme can manifest in adulthood as hypercalcemia, hypertension, and nephrocalcinosis, often in the setting of pregnancy. Given the rarity of this genetic disease, diagnosis is often delayed. Initial laboratory work up often reveals hypercalcemia, suppressed parathyroid hormone, and normal to mildly elevated 1,25 dihydroxy-vitamin D. Diagnosis requires either genetic testing or an elevated 25 Hydroxvitamin D24,25 Dihydroxy-vitamin D ratio, often greater than 80. In our case, the patient developed recurrent gestational hypercalcemia and hypertension. As a result of a delayed diagnosis, measures had not been taken to avoid excess vitamin D and calcium supplementation. This case highlights the importance of pursuing the diagnosis of 24 hydroxylase deficiency in patients that present with hypercalcemia and hypertension in the setting of pregnancy.

FR-PO855
Observational Cohort with Embedded Randomised Controlled Trials to Study Pregnancy-Associated Progression of Renal Disease (ORCHARD)
Priscilla Smith,1 Kathryn Dalrymple,1 Katherine R. Clark,1 Yanzhong Wang,1 Tess M. Harris,2 Andrew J. Webb,1 Lucy C. Chappell,1 Kate Bramham.1
1King's College London, London, United Kingdom; 2The PKD Charity, London, United Kingdom.

Background: 46% of women with moderate-severe chronic kidney disease (CKD) will require dialysis or lose at least 25% of kidney function within six months of delivery with no development of preventative treatments.

Methods: Biological samples, longitudinal and outcome data will be collected in a prospective cohort and eligible women identified to participate in ORCHARD-BET randomised controlled feasibility trial. Inclusion criteria: single pregnancies; 24 weeks or less; CKD (pre-pregnancy eGFR <90mls/min/m²) or pregnancy Cr-70µmol/l). Randomisation: 1 to 1. Standard care or daily beetroot juice supplement (nitrate 400mg). Primary outcome: recruitment rate; secondary outcomes: tolerability, acceptability, eGFR change at 6 months postpartum.

Results: 118 women consented to participate in the cohort and 104 were randomised to ORCHARD-BET trial. 65% of eligible participants approached consented to be enrolled in the trial. Cohort maternal baseline characteristics are presented in Table 1. Trial results will be reported in 2024 once follow up complete.

Conclusions: To our knowledge this is the largest prospective cohort study with embedded pragmatic feasibility trial with concurrent biobanking of pregnant participants which is representative of women with moderate and severe CKD. Findings will be used to inform future intervention trials to prevent pregnancy associated progression of kidney disease. ISRCTN 91211980.

Funding: Private Foundation Support

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Renal Function Characteristics</th>
<th>Cohort (N=118)</th>
<th>Mean (SD)/Median (IQR)/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34.5 (± 5.3)</td>
<td>32 (26-39)</td>
</tr>
<tr>
<td>Stroke</td>
<td>6 (5.1%)</td>
<td>6 (5.1%)</td>
</tr>
<tr>
<td>Newborns</td>
<td>38 (32.7%)</td>
<td>38 (32.7%)</td>
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<tr>
<td>Native white ethnicity</td>
<td>51 (43.7%)</td>
<td>51 (43.7%)</td>
</tr>
<tr>
<td>Gestation weeks at recruitment</td>
<td>33 (2,21)</td>
<td>33 (2,21)</td>
</tr>
<tr>
<td>BMI</td>
<td>25.6 (± 5.7)</td>
<td>25 (21-29)</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>53 (45.9%)</td>
<td>53 (45.9%)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>137 (± 20.7)</td>
<td>137 (± 20.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>84 (± 9)</td>
<td>84 (± 9)</td>
</tr>
<tr>
<td>Pre-pregnancy eGFR (ml/min/1.73m²)</td>
<td>70 (± 18.8)</td>
<td>70 (± 18.8)</td>
</tr>
<tr>
<td>Pre-pregnancy eGFR (ml/min/1.73m²)</td>
<td>70 (± 18.8)</td>
<td>70 (± 18.8)</td>
</tr>
<tr>
<td>Primary cause of renal disease</td>
<td>Polyvinyl Kidney Disease</td>
<td>108 (90.5%)</td>
</tr>
<tr>
<td>Glomerular</td>
<td>13 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Renal neoplasms</td>
<td>13 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Renal transplantation</td>
<td>3 (2.6%)</td>
<td></td>
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<tr>
<td>Congenital/identical</td>
<td>3 (2.6%)</td>
<td></td>
</tr>
<tr>
<td>Renal trauma</td>
<td>3 (2.6%)</td>
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<tr>
<td>Urinary causes/other</td>
<td>4 (3.4%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 (15.9%)</td>
<td></td>
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<tr>
<td>Chronic hypertension</td>
<td>3 (2.5%)</td>
<td></td>
</tr>
</tbody>
</table>

* Index of Multiple Deprivation UK 2019

FR-PO856
Maternal Outcomes Following Nephrology Review in Pregnancy
Sinead Stoneman,1,2 Hadis Miremberg,2 Blathnadh O’Connell,3 Cliona Cowhig,4 Fiona P. Daly,5 Michael Clarkson,6,7 Nööri Russell,2,7 Louise Kenny,6 Liam Plant,2 Sarah M. Moran,4,8 Cork University Hospital, Ireland; Cork University Maternity Hospital, Cork, Ireland; University College Cork, Cork, Ireland; University of Liverpool, Liverpool, United Kingdom.

Background: Chronic kidney disease (CKD) is estimated to affect 3% of pregnant women. Dialysis-requiring pregnancy-associated acute kidney injury [PRAKI] is increasing in incidence, however accurate definitions for non-dialysis requiring PRAKI are lacking.

Methods: We conducted a retrospective cohort study of women who were reviewed by our Obstetric Nephrology Service from January 1st 2007 to March 31st 2023. Maternal and fetal outcomes were collected. Ethical approval was provided by the institution’s ethics committee. Statistical analysis was performed with GraphPad version 7 and R. Results: 459 women met inclusion criteria. We report the incidence analysis of 154 pregnancies in 128 women. Mean maternal age at conception was 32.9 ± 5.3 years. 30% of mothers were nulliparous and 25% had hypertension pre-pregnancy. Indication
for review was pre-existing CKD (57%), acute kidney injury and/or new proteinuria/hematuria (20%) and newly diagnosed CKD in the index pregnancy (9%). CKD was attributed to urological causes in 44%, glomerulonephritis in 29% and polycystic kidney disease in 15% of the cohort. In women with newly detected CKD in pregnancy, 26% underwent subsequent kidney biopsy. In women with CKD, serum creatinine (sCr) preconception was 73 µmol/L (63-138) and in trimester 2 during pregnancy was 56µmol/L. Follow-up sCr at 1 yr was 73 µmol/L (65-94), 3 yrs was 76 µmol/L (65-94), 10 yrs was 87 µmol/L (66-250) and at 15 years was 150 µmol/L (88-850µmol/L). 3% of all women developed ESKD during follow up.

Conclusions: Results from this single-center study provide longitudinal kidney and maternal outcomes from a large cohort of women who received obstetric nephrology care.

Serial serum creatinine measurements (µmol/L) from pre-conception to 15 years of follow up.

FR-PO857
Adverse Maternal-Fetal Outcomes in Pregnant Women with CKD on Hemodialysis: A Single-Center Experience

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Background: Chronic kidney disease (CKD) pregnant women are at high risk of adverse maternal and fetal outcomes (AMAFO). 4% of women of childbearing age suffer from CKD, an independent risk factor for prematurity, low birth weight, neonatal death, and preeclampsia. Objective: To determine the incidence of AMAFO in pregnant women with CKD in hemodialysis (HD).

Methods: Observational retrospective study of 30 patients with CKD on HD and pregnancy from Aug 2017 to Dec 2021. Sociodemographic data, comorbidities, and AMAFO were recorded and analyzed.

Results: The incidence of adverse maternal events was 33%, the most frequent was preeclampsia with severe features (17%), followed by preeclampsia (7 %), HELLP syndrome (3%), gestational diabetes (3%), and placental abruption (3%). Neither patient died during the follow-up. 90% of the newborns present with adverse fetal outcomes, 90% with low birth weight, 40% with prematurity, 13 % with transient tachypnea of the newborn, 7% with premature rupture of the membranes, 7% with fetal distress, and 17% died.

Conclusions: There was a 33% incidence of adverse maternal events and 90% of adverse fetal outcomes in pregnant women with CKD in HD, with only 10% of pregnancies without AMAFO.

FR-PO858
Characteristics and Outcomes of Patients with Pregnancy-Related ESKD

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Background: The incidence of pregnancy-related AKI is increasing and associated with morbidity including progression to ESKD. We aimed to examine characteristics and clinical outcomes of patients with a pregnancy-related primary cause of ESKD (PR-ESKD).

Methods: We studied 183,640 reproductive-aged females with incident ESKD, 341 with PR-ESKD, from Jan 2000-Nov 2020 in USRDS. We compared baseline characteristics of those with PR-ESKD to the US birthing population using CDC natality data. We built multivariable Cox/competing risk models to examine 1) mortality, 2) access to kidney transplant (KT), and 3) time to KT after joining the waitlist between those with PR-ESKD and reproductive-age women with other causes of ESKD.

Results: Versus the general US birthing population, Black patients were overrepresented in PR-ESKD (51.9% vs. 16.7%). PR-ESKD had similar/lower hazards of mortality but significantly less access to KT vs other causes of ESKD (Figure); this persisted in adjusted analyses (Table). Those with PR-ESKD were less likely to have nephrology care prior to ESKD-onset (aHR=0.47, 95% CI 0.40-0.56).

Conclusions: Black patients are disproportionately affected by pregnancy-related ESKD. Our finding of reduced access to KT and pre-ESKD care highlight the need for improved postpartum and long-term support.
Acute Starvation Ketoacidosis in Pregnancy: Too Fast, Too Furious

Introduction: Starvation ketoacidosis in pregnancy is rare and potentially lethal. Maternal mortality rates up to 35% and fetal mortality rates up to 85% have been reported. Moreover, maternal acidosis is associated with detrimental fetal neural development. Majority of previously reported cases were in setting of pre-existing diabetes mellitus and required emergent caesarean section. This case demonstrates a distinctive presentation characterized by severe ketoacidosis in the context of acute starvation, absence of diabetes, and positive fetomaternal outcomes.

Case Description: 26-year-old female G4P2103 at 35 weeks of gestation with a history of anemia presented to labor unit with intractable vomiting for around 24 hours. Further history was significant for acetaminophen use for a month. Vitals were significant for pulse 115/min, respiratory rate 20/min, BP 106/63 mm Hg. Blood chemistry showed Hartree ratios showed severe cause of renal failure, so should be interpreted as the hazard for patients with pregnancy-related ESKD compared to each of the other causes. Models adjusted for potential confounders including race, Hispanic Ethnicity, insurance type, current employment, and comorbidities including congestive heart failure, COPD, cerebrovascular disease, alcohol dependence, hypertension, hyperlipidemia, to stubborn ratio.

Discussion: In healthy individuals, it takes a minimum of 14 days for starvation to reach its peak severity, characterized by a pH value typically above 7.3 while in pregnancy, starvation ketoacidosis can develop within a few days. In pregnancy, heightened levels of estrogen, progesterone, and human placental lactogen cause insulin resistance, hindering cellular glucose uptake. Consequently, increased lipolysis and free fatty acids lead to ketosis. Management primarily includes bicarbonate and dextrose infusion along with fetal monitoring. Insulin does not play a role in starvation ketoacidosis as opposed to diabetic ketoacidosis.

FR-PO860

Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Marker of Disease Activity and Pregnancy-Related Adverse Outcomes in Pregnant Women with Inflammatory Bowel Disease

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Background: Control of disease activity in pregnant women with inflammatory bowel disease (IBD) is crucial as an uncontrolled disease is associated with higher risks of adverse pregnancy outcomes for both the mother and newborn. Human neutrophil gelatinase-associated lipocalin (NGAL) is an acceptable biomarker in some pathological conditions such as acute and chronic kidney injuries and high levels of NGAL were observed in the colon, serum, and stool of patients with IBD. In pregnancy, first-trimester NGAL was found to be an early marker of late-onset preeclampsia. However, no data exists on urinary NGAL in pregnant women with IBD.

Methods: The study recruited women with (IBD) who attended the IBDMOM clinic for antenatal and postnatal follow-up. The correlation of urinary NGAL levels with baseline clinical characteristics and its predictive capacity for pregnancy-related adverse outcomes such as preterm birth, preeclampsia, stillbirth, low-birth weight, and IBD flares were assessed by univariate and multivariate stepwise regression analyses.

Results: The median age of patients was 28 years and the median duration of IBD at the time of conception was 6 years. A total of 252 urine samples (172 samples from patients with Crohn’s disease, 77 with ulcerative colitis, and 3 with unclassified IBD) were examined. Urinary NGAL measurements were obtained from 192 pregnancies, throughout the different gestational periods (1st trimester n = 90; 2nd trimester n = 111; 3rd trimester n = 92). Urinary NGAL levels were not significantly higher in patients with active IBD compared with inactive IBD (median 47.4 ± 4.7 ng/mL vs. 52.8 ± 3.98 ng/mL, p = 0.242). Forty-nine patients reached secondary outcomes (27, 8 and 14 had preterm deliveries, abortions, and either preeclampsia, IUGR, and stillbirth, respectively). There was no statically significant correlation between urinary NGAL levels and obstetric adverse outcomes. However, the incidence of cesarean sections, treatment regimen changes and hospital admissions during pregnancy were significantly higher in patients with active IBD (p = 0.001).

Conclusions: Our data suggest limited predictive capacity of urinary NGAL levels for predicting disease flares or obstetric adverse outcomes in pregnant women with IBD. However, the role of serum NGAL in this patients population remains to be elucidated.

Funding: Private Foundation Support

FR-PO861

Maternal and Foetal Outcomes in ANCA Vasculitis: A Review of the Literature

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Background: Limited data exists on the effects of ANCA-associated vasculitis (AAV) on maternal and foetal outcomes. Although historically rare in pregnancy and primarily affecting individuals <65 yrs, the incidence of AAV in younger women is increasing. This highlights the significant impact of AAV on fertility and the need for increased healthcare provision and interdisciplinary approach to management. There is however a lack of literature guiding healthcare professionals in managing AAV patients throughout the pre-conception, prenatal and postnatal periods. This review examines maternal and foetal outcomes associated with AAV, compares outcomes with the general population and explores the effectiveness of AAV treatments during pregnancy.

Methods: A literature search using PubMed, Cochrane and WoS was conducted, to identify all published studies that included pregnant women with a diagnosis of AAV. Two reviewers screened the papers and studies were assessed for quality.

Results: Five papers were included with a total of 60 women and 84 pregnancies. Results showed an increased risk of pre-eclampsia, pre-term delivery, low birth weight and high rates of caesarean delivery compared to the general population (Fig.1). Risks associated with organ involvement with patients who had multi-system involvement at highest risk of adverse outcomes. The majority of patients received prednisolone and azathioprine treatment during their pregnancy and >30% received no treatment at all. Pregnancies in women with disease remission had favourable outcomes.

Conclusions: Data on pregnancy outcomes in AAV is limited and there is a lack of guidance regarding patient management in the pre-conception, prenatal and postnatal periods. The literature suggests adverse outcomes in pregnant patients with AAV, emphasizing the need for additional support and further research looking at maternal health risks, the impact of disease relapse and the role of data registries.
Maternal and foetal outcomes in aAV compared to the health population averages

FR-PO862

The Effect of Pregnancy and Delivery on Renal Prognosis in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a frequently inherited renal disease, which is caused by PKD1 and PKD2 gene abnormalities, and results in the progressive development and enlargement of numerous cysts in the bilateral kidneys, leading to progressive deterioration of renal function and end-stage renal failure. It has been reported that the pregnancy and delivery rates of women with ADPKD are similar to those without it in terms of fertility, miscarriage, stillbirth, and fetal complications. On the other hand, it has also been reported that the hypertensive disorders of pregnancy (HDP) are higher and the risk of renal failure is higher in women with ADPKD. This result may lead ADPKD women who wish to have a baby to hesitate in pregnancy and delivery. This study aims to determine whether the development of HDP affects renal function after delivery in women with ADPKD.

Methods: We performed a questionnaire on pregnancy and delivery to obtain clinical data and circumstances around women with ADPKD. The primary outcome was renal failure, with or without induction of dialysis. Survival analysis was performed to evaluate whether the primary endpoint is HDF with Cox proportional hazards analysis. Factors associated with the risk of the primary outcome will be evaluated using univariate and multivariate logistic analysis.

Results: One hundred eighty-three ADPKD women (including 100 patients on hemodialysis) were enrolled in this study. The median age was 58.6 years. The mean age at first delivery was 26.9 years. The average number of births was 2.5. The mean duration from the first delivery to dialysis was 31.7 years. The age of induction of dialysis was 54.4 years. Eighteen percent of the patients developed HDF at the time of first delivery, and 71.4% of the women with a history of HDF developed HDF at the time of second delivery. Although the incidence of HDF was higher than that of the general population, there was no difference in cumulative renal survival between patients with HDF (n=28) and those without (n=140) (p=0.27, Log-rank test). Multivariate analysis also showed that the presence of diabetes and HDF was not a risk for poor renal prognosis.

Conclusions: In female patients with ADPKD, the presence of HDF does not affect renal prognosis and accelerate renal failure.

FR-PO863

Native Renal Biopsy D4 Postpartum

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Introduction: aHUS is a thrombotic microangiopathy caused by overactivation of the alternative pathway of complement activation. aHUS can be diagnosed on renal biopsy, and treatment with eculizumab should begin as soon as possible in order to prevent progression to ESRD. This study aimed to determine whether the development of HDF affects renal function after delivery in women with ADPKD.

Methods: We performed a questionnaire on pregnancy and delivery to obtain clinical data and circumstances around women with ADPKD. The primary outcome was renal failure, with or without induction of dialysis. Survival analysis was performed to evaluate whether the primary endpoint is HDF with Cox proportional hazards analysis. Factors associated with the risk of the primary outcome will be evaluated using univariate and multivariate logistic analysis.

Results: One hundred eighty-three ADPKD women (including 100 patients on hemodialysis) were enrolled in this study. The median age was 58.6 years. The mean age at first delivery was 26.9 years. The average number of births was 2.5. The mean duration from the first delivery to dialysis was 31.7 years. The age of induction of dialysis was 54.4 years. Eighteen percent of the patients developed HDF at the time of first delivery, and 71.4% of the women with a history of HDF developed HDF at the time of second delivery. Although the incidence of HDF was higher than that of the general population, there was no difference in cumulative renal survival between patients with HDF (n=28) and those without (n=140) (p=0.27, Log-rank test). Multivariate analysis also showed that the presence of diabetes and HDF was not a risk for poor renal prognosis.

Conclusions: In female patients with ADPKD, the presence of HDF does not affect renal prognosis and accelerate renal failure.
FR-PO866
Temporal Trends in Pregnant CKD Patients
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Background: Chronic kidney disease (CKD) during pregnancy significantly increases both maternal and perinatal morbidity and mortality and the incidence of CKD is increasing in persons of childbearing age. In this study, we aimed to identify changes in demographics and comorbidities over time in people with CKD and pregnancy in our tertiary care practice.

Methods: We identified pregnancies delivered at Mayo Clinic in Rochester, MN from 2010 to 2022 and screened the population for ICD-9/10 codes for CKD present prior to the date of delivery. If more than 1 pregnancy occurred in the study period, we evaluated the first pregnancy with pre-existing CKD. We abstracted data on demographics, comorbidities, body-mass index, etiology and stage of CKD. Maternal and perinatal outcomes were evaluated. We compared characteristics by era – 2010 to 2016 vs. 2016 to 2022 – using Fischer’s exact test for categorical variables and Kruskal-Wallis test for continuous variables. Correlations were evaluated by Spearman’s correlations.

Results: We identified 67 deliveries in patients with pre-existing CKD. Median (interquartile range (IQR)) pre-pregnancy BMI was lower prior to 2016 than after (24 (22-23) vs. 30.5 (24-34.5), p=0.048). There was also a significant trend toward increasing BMI by year of delivery (p = 0.27, p = 0.04). Consistent with this trend was the increasing incidence of CKD due to diabetes (14.8% to 27.3%, before vs. after 2016), though this was not statistically significant. Six patients had biopsies during pregnancy, between 11 and 24 weeks gestation, that established the cause of CKD and had no complications. There was no increase in the incidence of pre-eclampsia, preterm delivery or maternal ICU stays by era. The eGFR at baseline was significantly associated with gestational age at delivery (p = 0.32, p = 0.01) and birth weight (p = 0.30, p = 0.02).

Conclusions: We found that pre-pregnancy BMI has been increasing over time in patients with CKD. Additionally, worse baseline kidney function was associated with earlier gestational age at delivery and lower birth weight in infants. Given that obesity impacts both pregnancy and CKD health and that there are more obesity treatments available, more investigations should be done to understand whether treatment of obesity prior to conception could impact outcomes of pregnancy in patients with CKD.

FR-PO867
Uric Acid and Risk of Preeclampsia: A Mendelian Randomization Study
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Background: Maternal serum uric acid (UA) is observationally associated with preeclampsia. However, whether elevated uric acid is a marker of the disease or a causal factor remains unknown. We conducted a two-sample Mendelian randomization (MR) analysis to explore the potential causal effect of UA on preeclampsia.

Methods: Summary statistics for UA were from a meta-analysis of genome-wide association studies involving 288,649 individuals of European ancestry, while summary statistics for preeclampsia or eclampsia (PE) were from the FinnGen consortium with 4,636 cases and 176,113 controls. Independent SNPs strongly associated with UA were selected as instrumental variables in causal inference, removing the confounders and/or Department of Obstetrics in Kanazawa University between 2004 and 2018. The association between kidney function, especially hyperfiltration during pregnancy and adverse pregnancy outcome was evaluated.

Results: The patients without adverse pregnancy complication showed higher eGFR than those with complication during pregnancy period. The increase of estimated glomerular filtration rate (eGFR) during pregnancy is associated with good pregnancy outcome in CKD patients(Fig.1). Even in patients with high eGFR in pre-pregnancy, the absence of increase of eGFR during pregnancy is associated with adverse pregnancy events.

Conclusions: The increase of eGFR during pregnancy was associated with good outcome in CKD patients. Further studies may raise the possibility that assessment of kidney function during pregnancy may be useful marker for the prediction of the pregnancy outcome in CKD patients.

FR-PO869
Kidney Hyperfiltration Is Associated with Pregnancy Outcome in Patients with CKD
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Background: While major population of chronic kidney disease (CKD) is older patients, some population of younger patients are also suffered from CKD. The increased risks of adverse pregnancy outcomes were reported in CKD patients. In fact, the frequency of adverse pregnancy outcome is increased in accordance with the severity of kidney dysfunction. In healthy kidney, hemodynamics shifts to hyper-dynamic state during pregnancy. However, details of hemodynamics during pregnancy and its effects for pregnancy outcome are not clear in CKD patients. Therefore, we explored the association between kidney function and pregnancy outcome in CKD patients in this study.

Methods: We retrospectively enrolled 21 CKD patients with pregnancy. The patients visited or were admitted to the Department of Nephrology and Laboratory Medicine and/or Department of Obstetrics in Kanazawa University between 2004 and 2018. The association between kidney function, especially hyperfiltration during pregnancy and adverse pregnancy outcome was evaluated.

Results: The patients without adverse pregnancy complication showed higher eGFR than those with complication during pregnancy period. The increase of estimated glomerular filtration rate (eGFR) during pregnancy is associated with good pregnancy outcome in CKD patients(Fig.1). Even in patients with high eGFR in pre-pregnancy, the absence of increase of eGFR during pregnancy is associated with adverse pregnancy events.

Conclusions: The increase of eGFR during pregnancy was associated with good outcome in CKD patients. Further studies may raise the possibility that assessment of kidney function during pregnancy may be useful marker for the prediction of the pregnancy outcome in CKD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
identified 5268 patients with a 2nd trimester creatinine, only 22% of patients receiving care in the 2nd trimester. Patients who received 1st trimester creatinine measurements were more likely to be ≥35 years old, Black and from disadvantaged areas. Patients with eGFR <90 ml/min/1.73 m² in the 1st and 2nd trimesters of pregnancy had the highest rates of preterm birth. Patients with eGFR>150 ml/min/1.73 m² had the highest rates of adverse outcomes, though a very small portion of the population.

Conclusions: Less than 1 in 3 patients had serum creatinine measurements available during the 1st and 2nd trimesters of pregnancy. More data is needed to evaluate the utility of creatinine measurements in pregnancy.

Funding: Private Foundation Support

FR-PO870
Maternal Exposure to Tetrahydrocannabinol (THC) During Pregnancy Increases Kidney Damage in Mouse Offspring
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Background: Maternal use of cannabis during pregnancy has been associated with adverse effects on fetal development. However, little is known about the impact of maternal cannabis use on kidney development in offspring. In this study, we investigated the effects of maternal exposure to placebo, CBD, and THC inhalers on kidney damage in mouse offspring.

Methods: Pregnant mice were randomly assigned to receive either a placebo, CBD, or THC inhaler throughout pregnancy. Offspring kidneys were collected at birth and evaluated for kidney damage using the Kim-1 antibody. The percentage of Kim-1 was measured using flow cytometry.

Results: Kim-1 expression was higher in THC treated group compared to the placebo and CBD groups, suggesting more kidney injuries in THC treated animals.

Conclusions: Our findings suggest that maternal exposure to THC during pregnancy may increase the risk of kidney damage in offspring. These results highlight the need for further research on the potential long-term effects of cannabis use during pregnancy.

FR-PO871
Practice Patterns of Nephrologists Who Care for Pregnant Patients with CKD
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Background: Chronic kidney disease (CKD) increases adverse pregnancy events such as pre-eclampsia, preterm delivery, and progression of maternal CKD. While live birth rates among pregnant people with kidney disease have increased, these pregnancies remain a high risk, emphasizing the critical need for advanced understanding and management strategies. Data on Canadian nephrologist practice patterns and center-specific strategies to improve outcomes for pregnant people with CKD are limited. This study used survey methodology to assess practice patterns and policies in this area.

Methods: We conducted a national, cross-sectional survey to assess the practice patterns of Canadian nephrologists caring for pregnant people with CKD. Following literature review, we developed a list of items covering key aspects of CKD management in people who are pregnant, including pre-conception counseling, multispecialty team collaboration and post-transplant care. Items were refined and deduplicated through iterative review by team members. The survey was distributed through professional networks. The responses were analyzed descriptively and key findings were presented as percentages. Additionally, the results for each aspect of the questionnaire were evaluated in light of existing recommendations.

Results: The survey response rate was 71% (25/35). Of the responding nephrologists, 76% identified as women, and 52% had been in practice between 10 and 19 years. Regarding multispecialty care, 36% reported having a full team, 40% had some team elements, and 24% had no team. Individualization of patient care was the most common practice, as opposed to a conventional or standardized approach. This preference for individualization extended to offering pre-natal genetic counseling, antenatal kidney biopsy and antibiotic prophylaxis, and post-partum ACE inhibitor re-initiation.

Conclusions: Our study is the first to assess the practice patterns and policies of Canadian nephrologists caring for pregnant people with CKD. We found important variations in obstetric nephrology care, and that the majority of programs did not have a full multispecialty team. These results emphasize an opportunity to improve care through the creation of formal multidisciplinary teams and the consistent adoption of evidence-based policies.

Can ChatGPT Keep up with Obstetric and Gynecologic Nephrology? Assessing Its Proficiency in Key Concepts

Background: ChatGPT is a language model known for its ability to generate responses similar to those of humans across a variety of tasks. Despite ongoing discussions about the potential of ChatGPT to replace clinicians in clinical contexts, its ability to address essential concepts in a multidisciplinary field, such as obstetric and gynecologic nephrology, has not been thoroughly evaluated. The purpose of this study is to evaluate ChatGPT’s proficiency in addressing fundamental questions related to the diagnosis, treatment, and management of hypertension in pregnancy.

Methods: Using the Nephrology Self-Assessment Program (NephSAP) issues V15N2 and V21N4 (questions 25-30), we conducted a study of ChatGPT’s accuracy in answering fundamental questions related to obstetric and gynecologic nephrology. Questions with images were excluded. Analysis included 30 questions. Each question set was run 3 times using ChatGPT (version Mar 14, OpenAI), and we evaluated the agreement between the initial and subsequent runs, which were conducted 2 weeks apart.

Results: ChatGPT had accuracies of 66.6% on the 1st, 80% on the 2nd and 3rd runs for the NephSAP questions. We found that ChatGPT demonstrated a higher level of agreement for correct answers than for incorrect ones. However, it is important to note that the accuracy rates of 66.6% and 80% may still have room for improvement, particularly when dealing with complex and specialized medical topics like obstetric and gynecologic nephrology. ChatGPT itself acknowledged these results (Figure 1).

Conclusions: ChatGPT’s proficiency in addressing fundamental queries related to obstetric and gynecologic nephrology management is below the minimum passing threshold of 75% set by the ASN for nephrologists in its 1st attempt, with an accuracy rate of 66.6%. While ChatGPT can provide some useful information, it may not be as reliable or comprehensive as a human expert in this specific field.
FR-PO873
Terminal Complement Activation and Regulation in Placentas of Women with Kidney Transplantation and CKD

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Background: Women with chronic kidney disease (CKD) or kidney transplant (KTX) are at increased risk of adverse pregnancy outcomes, including pre-eclampsia, intrauterine growth restriction and premature birth. The role of the complement and its relation to placental histopathology has not been studied in this group. We evaluated terminal complement activation and regulation in KTX, CKD and control placentas.

Methods: We retrospectively included 92 placentas, with 33 placentas from KCD, 18 from KTX women and 41 placentas from healthy pregnancies. Histopathological reports were systematically re-evaluated for lesions scores. Immunohistochemical analysis for terminal complement C5b-9 and its corresponding regulator CD59 were performed in consecutive tissue slides.

Results: C5b-9 expression was pronounced in the villi area of KTX and CKD placentas (p<0.01) with localization of C5b-9 in areas of villous fibrinoids (2). In eight placentas, we noted a unique expression of C5b-9 along the syncytiotrophoblastic layer (3). All of these eight placentas were derived from KTX/CKD women, who were more often treated with tacrolimus during pregnancy (p<0.05), and had higher overall expression of C5b-9 in the villous region (p<0.05). C5b-9 expression was higher in the CKD group in the decidual (p<0.01), and linked to low birth weight (p=0.03) and prematurity (p=0.049). Local C5b-9, CD59, and CD59/C5b9 ratio were not linked to lesions scores.

Conclusions: Terminal complement activation in the placental villi of women with KTX or CKD is increased, without corresponding alternations in complement regulation. Altered decidual complement regulation might potentially interfere with placentaion, possibly accounting for low birth weight and intrauterine growth restriction. Syncytiotrophoblastic C5b-9 in a subgroup of KTX and CKD women might be of clinical relevance and needs further investigation in a larger cohort.

FR-PO874
Multi-Omics of Sex-Based Differences in Nephrotic Syndrome Nephritis

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Background: Sex-based differences have been observed in the incidence and clinical course of acute kidney injury as well as chronic kidney disease. Compared to males, female patients are more protected from kidney injury and disease progression. Prior studies have identified sexual dimorphism in kidney development and ischemic response, but the mechanisms by which inflammatory stimuli contribute to kidney sex-based differences have not been fully elucidated.

Methods: To examine these differences, we induced nephrotic syndrome (NTS) nephritis in female and male C57BL/6 mice of either 8-12 weeks or 18 months of age. Changes in urine and serum markers were measured, and differences in fibrosis were quantified. Kidneys were harvested on Day 10. Multi-omics data from matched single nucleus RNA-seq (snRNA-seq) and single nucleus ATAC-seq (snATAC-seq) were generated from those kidneys, with 66,430 nuclei examined.

Results: GSEA of RNA-seq and ATAC-seq data revealed major NTS-induced differences in metabolic programs in young males vs. females differentiated accessible chromatin regions in young females were not enriched in motifs containing estrogen responsive elements, suggesting that cis-regulation by ESR1 is not the direct driver of sex-based differences in NTS nephritis.

Conclusions: Sexual dimorphism in NTS nephritis is characterized by more severe albuminuria in young male mice, likely due to sex-based differences in metabolic pathways in different cell populations rather than direct cis-regulatory function of estrogen receptor binding activity.

Funding: NIDDK Support

FR-PO875
Targeting Interleukin-6/Glycoprotein130 Signaling Ameliorates Renal Injury in Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS) usually presents with hyperandrogenism, chronic low-grade systemic inflammation, and renal injury. The inflammatory cytokine Interleukin-6 (IL-6) is involved in the pathogenesis of several renal injury models by activating its soluble receptor (sILR4) and a membrane-bounded glycoprotein130 (gp130); however, its role in PCOS-mediated renal damage is unknown.

We aimed to test the hypothesis that the increases in systemic and renal IL-6 levels, mediate renal injury in PCOS via IL-6/gp130 signaling activation.

Methods: PCOS was induced in three-week-old female mice using dihydrotestosterone (DHT) differentiated tubules (8 mg SC) or vehicle for 12 weeks. Eight weeks post-induction, the animals were treated with the IL-6/gp130 signaling inhibitor SC144 (10 mg/kg, SC, 3x/week) or its vehicle for 4 weeks. Body weight, fat mass (EchoMRI), kidney weight, the glomerular filtration rate (GFR), transcutaneous fluorescence, as well as the renal injury markers urinary albumin to creatinine ratio (UACR, clinical chemistry analyzer) and NGAL (ELISA) were assessed. Renal gp130 protein and IL-6 mRNA expression were quantified by Western blot and RT-qPCR, respectively. H&E stained renal sections were used for histopathological analysis, whereas Masson trichrome staining was used to assess renal fibrosis.

Results: DHT significantly (p<0.05) increased body weight (26.2±0.9 vs. 22.3±0.4 g), fat mass (3.2±0.4 vs. 1.9±0.4 g), kidney weight (1.4-fold), UACR (1.2±0.42 vs. 404±169 µg albumin/mg creatinine), urinary NGAL (2-fold), and serum IL-6 levels (2.2-fold). DHT also increased serum gp130 (1.5-fold). The expression of renal gp130 and IL-6 was increased in the aforementioned parameters was associated with decreased GFR and a worsen renal histological structure with congested glomeruli, exfoliation of luminal epithelial lining, interstitial hemorrhage, and fibrotic changes. SC144 therapy had no significant effects on kidney weight, GFR, or NGAL, but it attenuated DHT-induced increases in fat mass and UACR while decreasing both glomerular and tubular injury and renal fibrosis.

Conclusions: IL-6/gp130 activation plays a significant role in renal outcomes in PCOS and could be targeted as a novel therapeutic approach to ameliorate renal injury in PCOS.

Funding: Other NIH Support - Supported by NIH grants NIGMS P20GM121334 to SR, LLyC and DGR, NIGMS P20GM104357 and NIEHLBI P01HL51971.

FR-PO876
Recovered Parental AKI Results in Dysfunctional Pregnancy and Offspring Programming

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Background: Rhabdomyolysis-induced acute kidney injury (RIAKI) follows muscular trauma and is observed in people of childbearing age. Although apparent recovery is common, prior AKI increases the risk of renal and reproductive disease. We hypothesized that recovered AKI induces pregnancy complications and developmentally programs offspring disease.

Methods: Procedures were approved by institutional IACUC. Rhabdomyolysis in 8-12 week old C57BL/6J mice was induced via intramuscular injection of 50% glycerol (8 mL/kg); shams were untreated. AKI was assessed 24 hours later via glomerular filtration rate (GFR; ul/min/100g body weight) and repeated 2 weeks post-recovery to establish functional recovery, followed by 1) timed sham/ sham and RIAKI/RIAKI matings for pregnancy (gestational day (GD) 16.5) and 2) adult offspring (12 weeks, 6 months) effects. Urine was collected 24 hours before GFR and tissue harvest for later analysis. Statistics were assessed by t-test for 2 group analyses, and 2-way ANOVA with pairwise tests for analyses by sex.

Results: 1) Despite normal GFR pre-pregnancy, recovered RIAKI dams had lower GFR than sham at GD 16.5 (p<0.01). Fetoplacental ratio was lower in RIAKI offspring (p<0.01) with no difference in litter size but 3x more perinatal death. albuminuria (p=0.01) was observed in RIAKI dams. RIAKI dams had less megalin (p<0.05) and more CNT (AngII) in the fetal kidney, suggesting a persistent disturbance of subcapsular fibrosis. 2) Offspring of recovered RIAKI parents have sexually dimorphic responses related to renal function. GFR was reduced in offspring of both sexes by 6 months (males: p<0.05, females: p<0.01). Circulating AngII levels were decreased in

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

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plasma from only female RIAKI offspring compared to shams (p<0.05); however, adult males from RIAKI pairings gained more weight than sham males between young and middle adulthood (p<0.05).

Conclusions: RIAKI poses reproductive risk long after initial apparent recovery, likely due to new proximal tubule dysfunction in the setting of pregnancy after RIAKI. Reduced fertility in pregnancy, particularly essential function of the proximal tubule via megalin and AngII, is altered by prior RIAKI and developmentally programs offspring with adult-onset reduced GFR, and older male offspring with increased weight gain.

Funding: Other NIH Support - JFH is supported by the Oregon Students Learn and Experience Research (OSLER) TL1 grant TL1TR002371 (NIH NCATS), Other U.S. Government Support

FR-PO877
Prevalence of CKD in Older Adults by Different Filteration Markers in eGFR Equations
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Background: The prevalence of chronic kidney disease (CKD) is known to increase with age, but few studies investigate age specific progression and prevalence of CKD in populations over 65. Glomerular filtration rate (GFR) can be estimated using different filtration markers that have not been thoroughly studied in older populations, opening the door for research on how these markers may differentially characterize the prevalence and progression of CKD in older age.

Methods: The study population included a community-based sample of 6,303 White and Black participants aged 60 and older, stratified into 5-year age categories from Visit 5 of the Atherosclerosis Risk in Communities Study (ARIC). GFR was estimated using CKD-EPI (2021) and Inker et al (2021) equations, and by the following combinations of filtration markers: creatinine (eGFRcr), cystatin C (eGFRCys), both (eGFRcr-cys), and combined with beta-2-microglobulin (eGFRcr-cys-b2m). We calculated the proportion of participants with GFR ≥60 ml/min/1.73 m² by each marker equation across age strata at Visit 5 (2011-2013), 6 (2016-2017), and 7 (2018-2019), and calculated the proportion of participants with a 30% decline in eGFR at ARI Visit 6 or 7, across age strata.

Results: Average age at Visit 5 was 75.8 years (SD, 5.3). Mean eGFRcr, eGFRCys, eGFRcr-cys, and eGFRcr-cys-b2m were 71, 61, 68, and 65 ml/min/1.73 m², respectively. The proportion with GFR <60 was lowest with eGFRcr and highest with eGFRCys for all age groups at all visits, and prevalence increased with age for all markers (Figure 1). More people with eGFR <60 were reclassified to <60 when using eGFRCys (33%) compared with eGFRcr-cys (12%) or eGFRcr-cys-b2m (18%). The proportion with 30% eGFR decline was lowest with eGFRcr and highest with eGFRCys, with greater incidence in older age groups for all markers.

Conclusions: The prevalence and progression of CKD increases with age but varies depending on filtration marker used. Cystatin C understimates CKD compared to other filtration markers.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO878
Estimated Glomerular Filtration Rate Thresholds Associated with Poor Long-Term Outcomes in the Elderly with Diabetes

Background: Age-adapted estimated glomerular filtration rate (eGFR)-based chronic kidney disease (CKD) criteria was recently proposed, which has been supported by the fact that mortality risks start to increase at GFR <45 mL/min/1.73 m² in the elderly. However, the eGFR threshold for mortality and kidney outcomes in elderly with diabetes was less understood. We aimed to evaluate eGFR categories that raise the risk of mortality and end-stage kidney disease (ESKD) by age group, using an 8-year follow-up cohort of elderly diabetic patients.

Methods: Elderly patients (≥65 years) with type 2 diabetes who visited our outpatient diabetes center during 2009 were identified and followed up until 2017. Patients were categorized into four groups per their CKD-EPI equation-based eGFR: ≥60, 45 to 59, 30 to 44, and 15 to 29 mL/min/1.73 m². Cox proportional hazard model for all-cause mortality and competing-risk analysis for ESKD (with a competing event of pre-ESKD death) were performed.

Results: Among 3,065 subjects, 19%, 8%, and 2% patients had eGFR 45 to 59, 30 to 44, and 15 to 29 mL/min/1.73 m² at baseline, respectively. After adjusting multiple clinical covariates, including blood pressure, diabetes duration, urine albumin/creatinine ratio, HbA1c, serum cholesterol levels, and comorbidity index, patients with eGFR 30 to 44 and 15 to 29 mL/min/1.73 m² had 1.5-fold (95% CI 1.17–1.95, P <0.001) and 2.66-fold (1.87–3.79, P <0.001) greater risks of death, respectively. Patients with eGFR 45 to 59 mL/min/1.73 m² had a comparable risk (1.18, 0.96–1.45; P = 0.127) to those with eGFR ≥60 mL/min/1.73 m². Substitution hazard ratios for ESKD were 2.39 (1.41–3.71, P = 0.001), 5.25 (3.27–8.41, P <0.001), and 16.74 (7.93–28.80, P <0.001) in patients with eGFR 45 to 59 mL/min/1.73 m², respectively. In a subgroup of patients 75 or older (n=800), patients with eGFR 45 to 59 mL/min/1.73 m² showed comparable risks for both ESKD and mortality, and ESKD risk started to increase from eGFR <45 mL/min/1.73 m².

Conclusions: Reduced eGFR <60 mL/min/1.73 m² predicted an increased risk of ESKD in elderly diabetic patients, suggesting that the current traditional eGFR threshold appears feasible. However, in patients ≥75 years, eGFR ranging from 45 to 59 mL/min/1.73 m² had little effect on long-term outcomes for both mortality and ESKD.

FR-PO879
Large Discordances Between Creatinine (Cr) and Cystatin C-Based Estimated Glomerular Filtration Rates (eGFR) Are Associated with Adverse Outcomes in a Nationally Representative Cohort of Older Adults

Background: Creatinine based eGFR may be overestimated in adults with sarcopenia. While the combined equation CKD-EPI eGFR-CRE-CYS may be more accurate on a population level, patients whose eGFR-CYS is significantly lower than eGFR-CRE (eGFR discordance) may be at high risk for adverse outcomes.

Methods: In a longitudinal cohort study of adults 65+ yrs, from the Health and Retirement Study 2016 Venous Blood Study, we calculated eGFR-CRE and eGFR-CYS with current CKD-EPI. Outcomes included fall, hip fracture, hospitalization, and death 2 years from baseline assessment. We plotted the relationship between eGFR discordance and likelihood of outcomes in each ventile using a loess plot with span 75%. We fit separate multivariable logistic regression to determine the association between large eGFR discordances (i.e. >30%) and each outcome, adjusted for confounders.

Results: There were 5574 participants with a mean age of 75 ±7.2 yrs, 58% women, 80% white, and 10% Hispanic. 35% had chronic kidney disease (CKD) (eGFR-CRE-CYS <60 ml/min/1.73 m²). 30% had eGFR-CYS >30 ml/min/1.73 m². We found increasing rates of falls, hospitalizations, and death at higher eGFR discordances [Figure 1]. In adjusted analyses, large eGFR discordance was associated with a significantly greater odds of fall, hospitalization, and death [Figure 2].

Conclusions: Older adults with a large eGFR discordance have a greater risk of adverse outcomes, possibly due to misdiosing of renally cleared medications, occult CKD or sarcopenia.
FR-PO880

Serum and Urine Metabolites and Kidney Function in an Older Community-Based Population

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Background: Metabolites represent a cellular read-out of ongoing processes underlying states of health and disease.

Methods: We evaluated cross-sectional and longitudinal associations between 1254 serum and 1398 urine metabolites (untargeted, Metabolon HD4, 713 present in both biofluids) and kidney function in 1613 participants of the Atherosclerosis Risk in Communities (ARIC) Study (visit 5; mean age 76 years, 56.1% women, mean eGFR and urine albumin-to-creatinine levels (ACR) of 62 mL/min/1.73m² and 74 mg/g, respectively). All analyses were comprehensively adjusted including for baseline eGFR and ACR.

Results: In cross-sectional analysis, 674 serum and 542 urine metabolites were associated with eGFR (p<4E-5), including 245 in both biofluids. Fewer metabolites (79 serum and 92 urine metabolites, including 7 shared across both biofluids) were associated with ACR. Five metabolites, including 2 unnamed metabolites, were significantly associated with both eGFR and albuminuria (Table 1). In longitudinal analysis, higher levels of 5-methylthioribose and 5-oxoproline and the most positive was for 5-methylthioribose and albuminuria (713). The rFE of 482 metabolites had negative associations with eGFR, while 59 metabolites had positive associations with eGFR (p=7E-5). The most negative associations with eGFR were for 5-methylthioribose and 5-oxoproline and the most positive was for gamma-glutamylgamma-glutamime. Thirty-eight eFE of metabolites were associated with eGFR decline (p=5E-5), including gamma-glutamylgamma-glutamime, S-methylcysteine sulfoxide, and hypoxanthine, which were protective for eGFR decline, but none met Bonferroni significance (p=5E-5).

Conclusions: In summary, untargeted metabolomic profiling can identify metabolites of interest in kidney disease. Notably, the metabolomic coverage was markedly increased by expansion of both biofluids.

Funding: NIDDK Support

Table 1: Metabolites associated with both eGFR and albuminuria.

FR-PO881

Perceptions of Shared Decision-Making and Preferences for Engagement Among Older Adults with CKD: A Mixed-Methods Study

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Background: Older adults with advanced chronic kidney disease (CKD) face preference-sensitive decisions regarding dialysis initiation. Although shared decision-making (SDM) is recommended, clinicians are unsure how to best facilitate SDM and few CKD patients report experiencing SDM. This study characterizes clinician perspectives on SDM and patient preferences for engagement.

Methods: A mixed-method, longitudinal analysis of surveys and semi-structured interviews was conducted with English-speaking adults 70 years or older with stages 4-5 in Boston, Chicago, San Diego, or Portland (ME) as part of the Decision Aid for Renal Therapy (DART) Trial. Patients’ preferences for engagement were measured using the validated Control Preferences Scale (CPS), which categorizes patients as preferring active, collaborative, or passive engagement. Semi-structured interviews were conducted with a subset of purposively sampled patients and clinicians at these four sites. We used descriptive statistical analysis to examine quantitative data, and thematic and narrative analyses to examine qualitative data.

Results: Among 363 patient-participants at baseline, 42% were female, 13% identified as Black, and 21% had high school education or less. Overall, 92% preferred to play an active or collaborative role in decision-making. CPS preferences were stable throughout; at the individual level, only 4.6% demonstrated a major change (active to passive or passive to active) between baseline and first follow-up. A subset of 75 participants (44 patients and 31 clinicians) completed qualitative interviews, contributing to four qualitative themes: 1) active and collaborative control preferences tied to patient engagement; 2) clinicians constrain information flow; 3) patients with collaborative and active preferences have free-flowing information; and 4) clinician responsiveness to patients’ preferences can lead to passive or passive to active engagement.

Conclusions: Older adults with advanced CKD overwhelmingly preferred collaborative or active roles, with more prognostic information earlier in the process. Utilizing the single-item CPS may be a simple and effective way for clinicians to assess patients’ preferred level of engagement and determine the flow of information.

Funding: Private Foundation Support

FR-PO882

Patient and Clinician Perspectives on an Advance Care Planning Decision Aid for Older Patients with CKD: Decision Aid for Renal Therapy (DART)-Advance Care Planning (ACP)

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Background: Among Medicare beneficiaries 65 and older with chronic kidney disease (CKD), adjusted mortality is over twice as high compared to age-matched non-CKD counterparts. However, few older adults with CKD complete advance care plans (ACP), which can align care with patient preferences. We assessed the accessibility and feasibility of a decision aid tailored to ACP for other populations have been shown to increase knowledge of ACP and readiness for end-of-life conversations.

Methods: Qualitative study using semi-structured interviews (March 2022-March 2023) with purposively sampled patients (CKD stage 4-5 patients, age ≥65) and clinicians (nephrologists). Participants viewed DART-ACP modules prior to interviews. Patient participants were approached in participating nephrology clinics in Greater Boston. Audio recordings were transcribed verbatim, and content and thematic analysis were conducted.

Results: 61 participants (29 clinicians; 33 patients) completed interviewed. Among clinicians, 38% were women and 41% were from the Northeast. Among patients, 36% were women, 39% identified as Black, and mean age was 70 ± 9 years. Four themes emerged during thematic analysis: 1) acceptability of DART-ACP among patients and clinicians; 2) difficulty in understanding granularity and impact of end-of-life decisions; 3) demand for information on palliative care; and 4) empowering patients to participate. Patient preferences for engagement were distributed in participating nephrology clinics in Greater Boston. Audio recordings were transcribed verbatim, and content and thematic analysis were conducted.

Results: 61 participants (29 clinicians; 33 patients) completed interviewed. Among clinicians, 38% were women and 41% were from the Northeast. Among patients, 36% were women, 39% identified as Black, and mean age was 70 ± 9 years. Four themes emerged during thematic analysis: 1) acceptability of DART-ACP among patients and clinicians; 2) difficulty in understanding granularity and impact of end-of-life decisions; 3) demand for information on palliative care; and 4) empowering patients to participate. Suggestions for improvement included incorporating lived experiences, integrating ACP documents into the modules, and including information for caregivers.

Conclusions: Patients and clinicians found DART-ACP accessible and useful in the context of dialysis decision-making, especially information about palliative care. Patient feedback will inform tailoring DART-ACP for clinical use.

Funding: Private Foundation Support

FR-PO883

Understanding Patient Engagement in Advance Care Planning

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Background: Approaches enabling shared decision-making for serious illness and end-of-life care with kidney patients are variable with significant challenges. There is no systematic approach to introduce these conversations and data understanding patient engagement is limited.

Methods: An interventional mixed methods study aimed to understand patient perspectives of advance care planning (ACP) at a single kidney care centre in Australia (Figure 1). A 1-hour conversation between kidney clinicians (nurse or doctor) and patients perspectives of advance care planning (ACP) at a single kidney care centre in Australia (Figure 1). A 1-hour conversation between kidney clinicians (nurse or doctor) and patients provided information regarding kidney health, and ACP concepts were introduced. Descriptive statistics and paired t-tests estimated the effect of the intervention and qualitative data were analysed thematically.

Results: Between December 2022 and April 2023, 47 kidney patients were consented: 40 in Part A and 7 in Part B. The average age was 80 years, 57% male, 57% Australian-born, 81% English speaking, 37% CKD, 47% satellite dialysis, 14% home dialysis. Participants’ perceived kidney disease related self-efficacy was high, with few symptoms of depression or anxiety. Median time between interview and follow up feedback was 6 weeks [IQR 4,9]. During this period 64% of people reported having an ACP conversation with family or caregivers. The intervention showed an improvement in mean “readiness to formally ask someone to be a medical decision maker” (3.2[1.9] to 3.8[1.6], p<0.04). No improvements of other dimensions of ACP engagement was found: Preliminary analysis of qualitative data highlighted disabling patient factors that hindered ACP engagement, including: 1. Perceived cultural and physical barriers to communication. 2. Coping strategies focused on living in the present. 3. Differing perceptions of the utility of end-of-life discussions. 4. Distress and fear at the prospect of serious illness or death.

Conclusions: These findings suggest that the intervention facilitated conversations between patients and their of medical decision makers. This study also highlights the social and psychological factors which impact patient engagement in future treatment planning.

Funding: Other NIH Support - Eastern Health Foundation Grant
The Current Status of Advance Care Plan and Dialysis Withdrawal in Elderly Hemodialysis Patients in South Korea

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Background: Only a few studies have investigated end of life care or experiences of elderly hemodialysis patients. We aimed to explore advance care plan and dialysis withdrawal in elderly hemodialysis patients at the end of life in South Korea.

Methods: We analyzed medical data of elderly dialysis patients (≥70 years old) who died between January 1, 2010 and December 31, 2017, at 10 university hospitals in the Korean Society of Geriatric Nephrology (KSGN). We examined causes of death, the presence of advance care plan, and clinical variables related to dialysis and life-sustaining treatments.

Results: Of 404 deaths, 57.7% were male and the mean age was 77 years. Dialysis was maintained for an average of 792 days. The most common causes of death in elderly dialysis patients were infection, cardiovascular disease and malignancy accounting for 48.8%, 20% and 8.7% of cases, respectively. The overall rate of advance care planning in elderly dialysis patients was 57.2% and 25.7% among those with and without comorbidities, respectively. Among those with advanced chronic kidney disease, 45.3% of patients had an advance care plan. The most common reasons for not having an advance care plan were patients' or caregivers' reluctance, lack of time, and difficulty discussing end-of-life decisions.

Conclusions: Our findings imply the importance to respect patients' preferences and advance care plan when it comes to end of life care in elderly dialysis patients. Shared decision making could play a key role in that regard to resolve the discrepancy between advance care plan and actual provision of life-sustaining treatments at the end of life.

Funding: Other NIH Support - Cooperative Research Grant 2019 from the Korean Society of Nephrology.
FR-PO887
Nephrology Providers’ Experiences with Discussing the Option of Forgoing Kidney Replacement Therapy with Patients
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Background: Understanding how nephrology providers discuss therapeutic alternatives to kidney replacement therapy (KRT) for advanced kidney disease is paramount to supporting efforts to improve shared decision-making with patients.

Methods: We conducted a cross-sectional survey study of national sample of nephrology providers recruited through US professional societies between March-July 2022 about their experiences caring for patients who forgo KRT. We invited a random sample of survey respondents to complete follow-up qualitative interviews between August-October 2022 about their experiences discussing this option with patients.

Results: Overall, 203 nephrology providers (age 47±12 years, 66.0% female, 53.2% white), of which 49.8% were nephrologists and 50.2% were advanced practice providers completed the survey. The terms “active medical management without dialysis” (44.4%) and “conservative kidney management” (12.0%) were rated “overall best” in conveying the approach to care for patients who forgo KRT. From interviews with 21 (age 54±13 years, 81.0% female, 57.1% white) survey respondents, 3 dominant themes reflecting experiences with discussing this option with patients emerged: 1) Terminology used: there was inconsistency in the terms used to describe this option across different providers, the terms used by the same provider with different audiences, and the meaning of the same term to different providers; 2) Interpreting patients’ expressed preferences: when patients communicated a desire not to receive KRT, providers were unsure whether patients truly meant to never pursue KRT and whether patients were likely to change their minds; and, 3) Sharing decision-making: providers spoke to challenges with negotiating respect for patients’ autonomy, perceived best interests for the patient, and influences from family members when counseling patients about decisions to forgo KRT.

Conclusions: There is substantial inconsistency and ambiguity in providers’ discussions with patients about care for patients who forgo KRT. Our findings highlight a need to build professional consensus on language used to discuss this option and for additional tools to assist providers with navigating these discussions.

Funding: Private Foundation Support

FR-PO889
Commitment to Practice Change Through Case-Based Learning to Improve Palliative Care for Older Patients with Kidney Failure
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Background: Patients with advanced chronic kidney disease (CKD) and kidney failure have many unmet palliative care needs. Nephrologist buy-in to implement primary palliative care has been cited as a major barrier. Interventions are needed to increase nephrologist awareness of and commitment to palliative care for their patients.

Methods: In a New York City-based CKD and dialysis program, we held a year-long series of monthly Project ECHO-style webinars. CKD and dialysis center staff screened patients for appropriateness for palliative care referral, agreed on pertinent patient issues, and presented their cases to an interdisciplinary expert faculty with backgrounds in nephrology, palliative medicine, and psychology. Participants evaluated webinars for practice relevance, whether they motivated them for practice change, and if so, in what way. Faculty categorized the major issue raised by each case. The online registration tool recorded the number and disciplines of participants.

Results: By discipline, 65 clinicians participated one or more times including nephrologists, nurses, social workers, a psychologist, and palliative medicine physicians. On a scale from 1-5 (low to high relevance), participants rated information from webinars that could be applied to practice a mean of 4.9. Based on webinar content, 95% reported they were planning to make one or more changes to their practice, most commonly involving other team members in decision process (53%) and changing how they raise palliative care topics (48%). Major issues raised by cases included whether to start frail nonagenarians with comorbidities on dialysis and how to manage the following issues in in-center hemodialysis patients: failing to thrive, dementia-related aberrant behavior, and substance use disorder. Knowledge exchange between nephrology and palliative medicine clinicians was reciprocal and fostered referral relationships.

Conclusions: Project ECHO format with case- and evidence-based experiential learning addressing practical, relevant patient care issues engaged nephrology clinicians and motivated them to implement primary palliative care skills into their practices. These preliminary findings suggest a potentially fruitful approach to gain nephrology clinician buy-in to primary palliative care and warrant further study and collaboration.

Funding: Private Foundation Support
FR-PO890

Optimizing Veteran Video Connect: Engaging Veterans with Advanced Kidney Disease in Goals of Care Conversations

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Background: Chronic kidney disease (CKD) prevalence and its associated morbidity and mortality is higher among Veterans than in the general population. As such, goals of care conversations (GOCC) are indicated. Little is known regarding the use of tele-palliative consultation for GOCC in older adult Veterans with CKD. This pilot study examined the acceptability, facilitators, and barriers of engaging this population in GOCC via telehealth.

Methods: This study used prospective observational design and semi-structured interviews. Eligibility criteria included geriatric patients ≥70 with CKD 4 or 5 without documented life-sustaining treatment (LST) preferences in the past 90 days. Patients were referred to palliative care (PC) clinic for GOCCs.

Results: 62 patients were identified and 40 were enrolled. Most patients preferred in-person and telephone PC visits (70%). Only 30% preferred telehealth. There were no clinical or demographic differences among patients based on visit modality preference, including in LST preferences. In patients who preferred an in-person visit, 42% cited discomfort with technology and 25% cited functional deficits.

Conclusions: Life sustaining treatment preferences and note completion rates among older Veterans with advanced CKD did not vary based on GOCC visit modality. Discomfort with technology is the most common barrier to telehealth. Future studies should focus on how to reduce technology barriers for older Veterans.

Funding: Veterans Affairs Support

FR-PO892

Impact of Conservative Management vs. Dialysis on Hospitalization Outcomes in US Veterans with Advanced CKD

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Background: Given high early mortality rates, healthcare utilization, and withdrawal in incident dialysis subgroups, particularly those of older age or multi-morbidity, there is interest in conservative management (CM) as an alternative treatment strategy for advanced CKD. We examined the impact of CM vs. dialysis transition on hospitalization outcomes in US veterans with advanced CKD.

Methods: We examined Veterans with advanced CKD (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25). Patients in the dialysis group were categorized according to timing of dialysis transition, defined as earlier dialysis (ED) vs. intermediate dialysis (ID) vs. very-late dialysis (VLD) (eGFRs ≥15, 10-<15, vs. <10 at dialysis transition). We compared rates of hospitalization (primary outcome) and days hospitalized (secondary outcome) in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio to address confounding using Poisson regression.

Results: In PS-matched models, compared with CM, each dialysis group was associated with higher rates of hospitalization, with incrementally higher rates observed with earlier dialysis transitions: IRRs (95%CIs) 1.53 (1.50-1.56), 1.56 (1.53-1.60), and 1.75 (1.70-1.80) for VLD, ID, and ED, respectively (Fig A). Similarly, each dialysis group was associated with higher rates of days hospitalized, with incrementally higher rates observed with earlier dialysis transitions (ref: CM): IRRs (95%CIs) 1.42 (1.41-1.44), 1.55 (1.54-1.56), and 2.08 (2.06-2.10) for VLD, ID, and ED, respectively (Fig B). Similar findings were observed in sensitivity analyses doubly-adjusted for PS covariates.

Conclusions: Compared to CM, increasing earlier dialysis transitions were associated with higher rates of hospitalization and days hospitalized. Further studies are needed to examine the comparative effectiveness of CM vs. dialysis transition on other hard endpoints and patient-centered outcomes in US Veterans.

Funding: NIDDK Support

FR-PO891

Using Population Health Management Program to Promote Patient Choice for Medical Management Without Dialysis

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Background: Patients with advanced chronic kidney disease (CKD) often start on dialysis as the default treatment option, without a shared decision making discussion (SDM) in which they and their care partners actively choose a renal replacement therapy option that best aligns with their values and wishes. We describe a program to promote SDM and characterize patients who chose medical management without dialysis (MMWD).

Methods: As part of the ongoing CKD population health management program at UPMC, high-risk CKD patients not seeing a nephrologist are identified through electronic medical management is an alternative to lifelong dialysis, but little evidence is available to inform treatment decisions.

Methods: We emulated a target trial in which patients were randomized to dialysis versus medical management using electronic health record data between 2010 and 2018 from the U.S. Department of Veterans Affairs. We included adults aged 65 years or older with chronic kidney failure and an estimated glomerular filtration rate <12 ml/min/1.73m² who were not candidates for kidney transplantation. We used causal inference methods to estimate restricted mean survival time difference using a weighted flexible parametric model and adjusted in-hospital time using weighted fractional regression at one and two years.

Results: We emulated a series of 99 trials using data from 16,363 adults with a mean age of 77 ± 9 and mean eGFR of 10 ± 2 who were predominantly male (2%) and white (64%). In intention to treat analyses, compared to medical management, dialysis was associated with an increase in survival of 35 days (95% CI 20-61, p<0.001) compared to patients who chose dialysis.

Conclusions: CKD population health management program with automated referrals to palliative care-led decision making session is an innovative method to identify and provide patients with increased opportunities to discuss treatment options. Our results demonstrate the need for SDM process to promote patient choice in older patients with CKD.

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

FR-PO893

Dialysis as Destination Therapy vs. Medical Management in a National Cohort of Older Adults with Kidney Failure: A Target Trial Emulation Study

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Background: For older adults who are not candidates for kidney transplantation, medical management is an alternative to lifelong dialysis, but little evidence is available to inform treatment decisions.

Methods: We emulated a target trial in which patients were randomized to dialysis versus medical management using electronic health record data between 2010 and 2018 from the U.S. Department of Veterans Affairs. We included adults aged 65 years or older with chronic kidney failure and an estimated glomerular filtration rate <12 ml/min/1.73m² who were not candidates for kidney transplantation. We used causal inference methods to estimate restricted mean survival time difference using a weighted flexible parametric model and adjusted in-hospital time using weighted fractional regression at one and two years.

Results: We emulated a series of 99 trials using data from 16,363 adults with a mean age of 77 ± 9 and mean eGFR of 10 ± 2 who were predominantly male (2%) and white (64%). In intention to treat analyses, compared to medical management, dialysis was associated with an increase in survival of 35 days (95% CI 23, 47, p<0.001) compared to patients who chose dialysis.

Conclusions: Among older adults ineligible for transplantation, we found evidence of a modest survival benefit of dialysis compared to medical management, at the expense of fewer days at home. The findings suggest that medical management should be more widely considered as a patient-centered alternative to dialysis treatment and underscore the importance of engaging patients in shared decision-making.

Funding: Veterans Affairs Support
Results from GUIDAGE-CKD: Guideline-Compliant Care of Patients Aged 70+ with CKD
Natalie Ebert,1 Elke Schaefner,1 Anne-Katrin Fietz,1 Julia Freitag,2 Anna Pöhlmann,1 Nina Mielke,1 Tim Bothe,1 Charite Universitätsmedizin Berlin, Berlin, Germany; 1AOK Nordost - Die Gesundheitskasse, Berlin, Germany.

Background: Currently, few data exist on guideline-based care for older patients with CKD. The GUIDAGE-CKD project develops quality indicators (QI) for outpatient care of pts >70 years with CKD and tests them in Berlin Initiative Study (BIS) and claims data. We investigate trends over time after introduction of KDIGO guidelines in 2012.

Methods: Using a Delphi process, a set of 7 QIs was consented for use in claims data (Module 1). QIs were validated in BIS data with comprehensive claims data (Module 2). Prevalences of QIs were described in age- and sex-stratified random samples in claims data (n=62,200 indiv. 70+) for the years 2012, 2014, 2016, and 2018 and standardized to the German 70+ population. Trends over time were examined with Cochran-Armitage trend test (Module 3). Initial results using claims data were reported for 5 QIs.

Results: Prevalence of CKD increased from 17.0% (95% confidence interval [CI] 15.0–21.4) in 2012 to 25.9% (CI 22.3–30.0) in 2018 (Table). Incidence of CKD increased from 6.3% (CI 4.5–8.8) in 2012 to 7.5% (CI 5.5–10.5) in 2018. The proportion of incident CKD cases with urinary albumin creatinine ratio (ACR) measurement (QI 8) increased from 10.9% (CI 10.0–12.0) in 2012 to 12.6% (CI 11.5–13.7) in 2018. The proportion of confirmed CKD G4-5 cases with prescribed NSAIDs (QI 12, contraindicated) decreased from 3.8% (CI 2.9–4.9) in 2012 to 2.3% (CI 1.8–3.0) in 2018. The proportion of cases with CKD receiving combined prescriptions of ACE inhibitors (ACEi) and ARBs (angiotensin II receptor blockers) (QI 23, contraindicated) decreased from 3.0% (CI 2.6–3.3) in 2012 to 0.6% (CI 0.5–0.7) in 2018.

Conclusions: From 2012-2018, the prevalence and incidence of CKD increased constantly, while the proportion of contraindicated NSAID medications in stage 4-5 CKD and combined prescriptions of ACEi and ARBs decreased. These trends suggest improvements in CKD diagnosis, guideline adherence, and quality of care.

Clinical Characteristics and Outcomes of Hemodialysis Therapy Focusing on Older Patients in the Korean Renal Data System
Hyunjae Kim,1 Yong Kyun Kim,1 Yu Ah Hong,2 Tae Hyun Ban,3 Hajeong Lee,2 Hee-yeon Jung.4 1The Catholic University of Korea St. Vincent’s Hospital, Suwon, Gyeonggi-do, Republic of Korea; 2The Catholic University of Korea School of Medicine, Seoul, Republic of Korea; 3Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; 4Kyungpook National University, Daegu, Republic of Korea.

Background: As the aging population increases worldwide, the understanding of older patients with end-stage kidney disease (ESKD) is rapidly increasing. Understanding the characteristics of elderly ESKD patients is essential for establishing suitable dialysis policies and plans, but information on this population is currently unclear in Korea.

Methods: This study investigated the characteristics and outcomes of elderly hemodialysis patients using Korean Renal Data System. Of a total of 173,216 patients, 3,235 (1.9%) patients were older adults aged 70 years or older at the time of dialysis initiation. After excluding patients with missing values, who started dialysis before 2001, or who were younger than 18 years old.

Results: Of the enrolled patients, 39.3% were under the age of 65 years, 26.6% were 65-74 years, and 34.1% were ≥75 years (p<0.001). The incidence of ESKD is increasing but the prevalence is decreasing in patients aged ≥75 years from 2017 to 2022. The proportion of patients with cardiac disease increased with age: 16% (<65 years), 19.6% (65-74 years), and 21.8% (≥75 years) (p<0.001). The levels of body mass index, hemoglobin, albumin, calcium, phosphorus, and intact parathyroid hormone significantly decreased with increasing age (p<0.001 for each parameter). The proportions of arteriovenous fistula creation and left forearm placement reduced with increasing age (p<0.001, and p=0.001, respectively). Although low surface area (1.0-1.5 m2) dialyzers utilization was increased with age: 41.4% (<65 years), 49.5% (65-74 years), and 58.5% (≥75 years), the urea reduction ratio and Kt/V increased with age, achieving the dialysis adequacy target in all elderly population. Mortality rates had increased in patients aged 75 years compared to other age groups over the past 20 years and the proportion of deaths due to cardiovascular disease increased and deaths due to other causes decreased in patients aged ≥75 years compared to old hemodialysis patients (p=0.002, and p=0.025, respectively).

Conclusions: The incidence of elderly hemodialysis patients has increased over time, and especially very older adults aged ≥75 years has a higher risk of mortality compared to other age groups in Korea. To improve outcomes for older ESKD patients, appropriate guidelines for ESKD management should be developed based on age-appropriate, individualized strategies.

A Pragmatic Randomized Clinical Trial: Twice-Weekly vs. Three-Weekly Incident Hemodialysis in Elderly Patients (PRIDE): Study Protocol
Miyeon Han,1 Sang Hoon Song,2 Soon hyo Kwom,3 National Medical Center, Seoul, Republic of Korea; 1Pasun National University, Kunjeong-ku, Republic of Korea; 2Soonchunhyang University Hospital, Seoul, Republic of Korea.

Background: The optimal frequency for hemodialysis in older adults with end-stage kidney disease (ESKD) has not been established. This study aims to investigate whether a twice-weekly dialysis schedule using an incremental approach can reduce hospitalization rates in older adults with incident dialysis, compared with conventional thrice-weekly dialysis in South Korea.

Methods: We have designed a pragmatic randomized controlled trial to compare the effects of twice-weekly versus thrice-weekly hemodialysis in 425 ESKD (drop-out rate 3%) individuals aged 60 years or older with residual kidney function (urine output > 500 mL/day). The trial will be conducted across 18 referral hospital-based dialysis centers in Korea. Individual participants will be randomized to either the twice-weekly (with incremental approach) or thrice-weekly dialysis group and will be followed up for 24 months.
months. The primary outcome of the study is the difference in all-cause hospitalization rates, while secondary outcomes include dialysis-specific hospitalization rates, mortality, quality of life, frailty, and cost-effectiveness. Participants have the flexibility to transfer to other dialysis centers as needed. The decision to increase dialysis frequency will be made based on individual patient's needs.

Results: The study is ongoing and will be completed in May 2026.

Conclusions: This study will provide valuable insights into the benefits and risks of tw-weeks dialysis with an incremental approach in older adults with residual kidney function compared to conventional dialysis treatment.

Funding: Government Support - Non-U.S.

FR-PO898

Association of Polypharmacy and Incident Frailty Differs Between Older Adults with and without CKD

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Background: Older adults with chronic kidney disease (CKD) have a high prevalence of comorbidities and are prone to polypharmacy. We aim to analyze if CKD modifies the association of polypharmacy and incident frailty.

Methods: Data from the Berlin Initiative (cohort) study were used, in which older adults (≥70 yrs.) were interviewed biennially using a standardized face-to-face questionnaire. Non-frail individuals were followed-up for 2 years and incident frailty according to Fried phenotype was assessed. Polypharmacy was defined as the intake of five or more regularly prescribed drugs and CKD as eGFR <60 mL/min/1.73m² or ACR ≥30 mg/g. Logistic regressions were used to assess the association of polypharmacy and incident frailty to estimate crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) in individuals with and without CKD.

Results: Individuals with CKD were older (84 vs. 81 years) and had more often hypertension (85 vs. 68%) or diabetes (25 vs. 13%) compared to individuals without CKD. In older adults without CKD, frailty occurred in 9.6% compared to individuals with CKD (19.7%), independent of their polypharmacy status. Individuals with CKD and polypharmacy became frail more frequently (26.7%) compared to individuals with CKD without polypharmacy (14.2%) (Table). In individuals without CKD, there was no difference in frailty incidence between those with (8.3%) and without (7.1%) polypharmacy. In individuals with CKD, those with polypharmacy had 2.1 times the odds (95% CI 1.23–3.59) of becoming frail compared to those without. In old adults without CKD, we found no association between polypharmacy and incident frailty.

Conclusions: CKD modifies the association of polypharmacy and incident frailty.

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

FR-PO899

Physical Function Before and After a Health Stressor in Older Veterans with Advanced CKD

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Background: Health stressors (HSs), defined as acute health events that require an ED visit or hospitalization, are common among older adults with chronic kidney disease (CKD) and associated with functional decline. Describing the trajectory of function before and after a HS may be vital to predicting future functional status and developing strategies to improve functional recovery after health events.

Methods: The Physical Resilience Predictors in Advanced Renal Disease (PREPARED) is a national, prospective cohort study of Veterans ≥70 years old (n=412) with advanced CKD (eGFR <30 mL/min/1.73m² excluding dialysis or transplant) who were tracked longitudinally to detect the occurrence of a HS in near real-time. Participants completed scheduled phone surveys of physical function every 8 weeks. For enrolled participants, if a HS was detected in the VA electronic health record during follow-up, additional phone surveys were conducted immediately following the HS, at 8 weeks, and 16-weeks post-HS. This approach provided data on function approximately 16- and 8-weeks before and after an HS. Physical function was assessed at each timepoint using the Life-Space Assessment (LSA) score (0-120, higher scores reflect greater community mobility). Linear mixed models were used to assess the trajectory of function in relationship to the HS. Results: A total of 284 PREPARED participants (77.9 ± 6.4 years old, 98% male, 25% Black) had a HS. On average, LSA score was highest (54.2 ± 22.6) at baseline (16-weeks prior to a HS). LSA scores declined 8-weeks prior to a HS (52.2 ± 28.6). The lowest LSA score was immediately following the HS (45.3 ± 28.6). LSA scores rebounded at 8-weeks (51.0 ± 27.7) and 16-weeks post-HS (50.9 ± 26.6) but did not return to pre-HS levels. Compared to baseline, statistically significant differences in LSA scores were seen immediately following the HS, and at 8- and 16-weeks post-HS (all p<0.01).

Conclusions: Among older Veterans with advanced CKD declines in physical function occurred leading up to and following a HS. Though physical function improved in the weeks following the HS, participants did not fully regain baseline physical function status even after 4 months. These data demonstrate the importance of developing strategies to bolster older adults’ ability to recover following an acute health event.

Funding: Veterans Affairs Support

FR-PO900

Kidney Transplantation in Older People (KTOP): The Frail Experience

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Background: Older people with kidney failure are vulnerable to frailty. Understanding their experiences is integral to kidney transplantation (KT) decision making.

Methods: The KTOP: impact of frailty on outcomes study assessed frailty, quality of life (QoL), and clinical outcomes in people ≥60, on the waitlist (WL) and after KT. Mixed-effect analysis identified trends and frailty variations.

Results: 210 patients were recruited; 118 were transplanted. At recruitment 63.4% (118) were not frail, 19.4% (56) vulnerable, and 17.2% (32) frail. The study was powered only for QOL changes, but on the WL vulnerable/frail candidates were more likely to have major infections and spend longer suspended. After KT vulnerable/frail recipients were more likely to be hospitalised, have longer admissions, and possibly higher graft loss and mortality (Table). On the WL, QOL trends showed stable physical component scores (PCS) in not frail candidates and declining scores in vulnerable/frail. Post-KT not frail candidates PCS declined before slowly recovering, whilst PCS stabilised in vulnerable/frail. WL mental component scores (MCS) improved in both groups. MCS after KT declined then improved in not frail candidates, and worsened in vulnerable/frail (Figure 1).

Conclusions: Frail/vulnerable older people had worse WL and KT clinical outcomes. KT did not change QoL hugely for either group, but trends varied by frailty. Achieving a holistic understanding will enable better assessment, counselling, and support for older people considering KT.

Clinical outcomes by frailty

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Non-Frail</th>
<th>Vulnerable/Frail</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WL mortality</td>
<td>0.82 (0.48)</td>
<td>1.13 (0.70)</td>
<td>0.34</td>
</tr>
<tr>
<td>WL major infection events</td>
<td>0.17 (0.35)</td>
<td>0.23 (0.41)</td>
<td>0.66</td>
</tr>
<tr>
<td>WL and/or non-epidemic events</td>
<td>0.17 (0.35)</td>
<td>0.23 (0.41)</td>
<td>0.66</td>
</tr>
<tr>
<td>KT mortality</td>
<td>0.96 (0.45)</td>
<td>0.99 (0.48)</td>
<td>1.00</td>
</tr>
<tr>
<td>All case graft loss</td>
<td>0.78 (0.98)</td>
<td>0.99 (1.00)</td>
<td>0.056</td>
</tr>
<tr>
<td>KT major rejection episode</td>
<td>0.78 (0.98)</td>
<td>0.99 (1.00)</td>
<td>0.056</td>
</tr>
<tr>
<td>Hospitalised to live after KT</td>
<td>0.92 (0.48)</td>
<td>0.99 (1.00)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Total length of stay (up to 1 year after KT allografts mean, SD) 20.5±4.6 30.0±12.7 0.0158

Figure 1. Predicted quality of life changes on the waitlist and following transplantation.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
oral function and the sarcopenia index in CKD remains unclear. The purpose of this study was to evaluate the oral function and its correlation with the sarcopenia index in patients with CKD.

**Methods:** The participants were non-dialysis CKD patients (stage 3–5) who visited an outpatient clinic in a single center. Oral frailty was evaluated by the Oral Frailty Index-8 and muscle strength measured by handgrip strength in the male group with oral frailty was lower than that without oral frailty (26.9±6.11 vs. 32.6±7.18, respectively, P<0.001). The participants were non-dialysis CKD patients (stage 3~5) who visited an outpatient clinic in a single center. Oral frailty was evaluated by the Oral Frailty Index-8 score of 4 points or more. Male participants had higher serum creatinine levels than the female group (15.5±4.7 vs. 19.5±7.7, respectively, P=0.06). Patients who had oral frailty showed decreased physical performance (with oral frailty 12.9±4.54s, vs. without oral frailty 8.89±3.05s, P=0.001). Oral frailty was linked with lower physical performance, according to the logistic regression analysis (OR 1.30, CI 1.097-1.546, P=0.003). In simple linear regression, the level of serum creatinine and the oral frailty score were associated (r=0.26, P=0.03).

**Conclusions:** Oral frailty is present in more than half of outpatients with non-dialysis CKD. This suggests the significance of managing physical performance early for CKD patients to avoid oral frailty. Additionally, muscle-strengthening exercises should be more crucial to prevent oral frailty as CKD progresses.

**FR-PO902**

*Gait Speed and Mortality In Older Adults with CKD: The Chronic Renal Insufficiency Cohort*

Christine Liu,1,3 Gomathy Parvathinathah,1 Margaret R. Stedman,1 Stephen L. Seliger,1,5 Daniel E. Weiner,2 Manjula Tamura.1,5 CRIC Study Investigators.1 Stanford University, Stanford, CA; 2Tufts Medical Center, Boston, MA; 3University of Maryland School of Medicine, Baltimore, MD; 4VA Medical Center Baltimore, Baltimore, MD; 5VA Palo Alto Geriatric Research Education and Clinical Center, Palo Alto, CA.

**Background:** Current models to predict mortality in older persons with CKD use only demographic, kidney, and medical history data. Yet prior work shows impaired physical function independently and strongly predicts death in older adults. We assessed if a measure of physical function, gait (walking) speed, improves mortality prediction for older adults with CKD.

**Methods:** We included Chronic Renal Insufficiency Cohort participants who were ≥65 years with eGFR <60 mL/min/1.73m², not receiving kidney replacement therapy, non-missing UACR, and with at least 1 gait speed assessment. Gait speed at usual pace on a 4.57 meter course was timed and then categorized (≥ 0.84 meters/second, 0.83 to 0.65, 0.64 to 0.47, 0.46, or unable to do). We designated the visit with gait speed measurement as baseline. Our primary outcome was time to all-cause death. We used a flexible hazard regression analysis (OR 1.30, CI 1.097-1.546, P=0.003). In simple linear regression, the level of serum creatinine and the oral frailty score were associated (r=0.26, P=0.03).

**Conclusions:** Oral frailty is present in more than half of outpatients with non-dialysis CKD. This suggests the significance of managing physical performance early for CKD patients to avoid oral frailty. Additionally, muscle-strengthening exercises should be more crucial to prevent oral frailty as CKD progresses.

**FR-PO903**

*Ultrasound Evaluation of Rectus Femoris Muscle Thickness as a Diagnostic Tool for Sarcopenia in Peritoneal Dialysis Patients*


**Background:** Sarcopenia is a frequent cause of morbidity and mortality among patients with chronic kidney disease (CKD), combining loss of both muscle strength and mass. Handgrip strength is a reliable surrogate for measures of arm and leg strength. Several studies have been developed for muscle mass evaluation, such as bioelectrical impedance analysis (BIA). Ultrasound evaluation has been increasing recently, taking advantage of its feasibility in daily clinical setting. The aim of this study was to validate the rectus femoris muscle thickness (RFMT) by ultrasound in peritoneal dialysis (PD) patients and its association with muscle strength and BIA parameters.

**Methods:** Single-centre cross-sectional study including patients on PD for <3 months and aged >18 years. Patients with acute infection, amputated limbs and implantable cardiac devices were excluded. Demographic and clinical data were collected from the electronic records. Parameters evaluated included serum biomarkers, BIA and dialysis adequacy. Muscle strength was measured by handgrip strength using a dynamometer. RFMT was evaluated using ultrasound at bedside.

**Results:** A total of 32 patients (19 male) were included with a mean age of 59±15 years. PD vintage was 17 months (10.5-29.8) with a weekly Kt/V of 1.95 (1.68-2.55). Most were on continuous ambulatory peritoneal dialysis (CAPD; 68.8%), either as high or medium-high transporters (65.6%). Hypertension was reported in 28 patients (87.5%), accompanied by diabetes mellitus (DM; 31.3%), peripheral artery disease (31.3%) and obesity (28.1%). Age (r=-0.442; p=0.013), Clinical Frailty Score (r=-0.481; p=0.006) and NT-proBNP (r=-0.54; p=0.003) were negatively associated with RFMT. Lean tissue index (r=0.357; p=0.049), phase angle (r=0.567; p=0.001) and handgrip strength (r=0.49; p=0.006) were positively associated with RFMT. In a multivariate analysis, phase angle (adjusted R²=0.261; p=0.026) was positively associated with RFMT, adjusting to age, time on PD, and serum albumin.

**Conclusions:** Ultrasound evaluation of RFMT is feasible in daily practice in the outpatient setting. It may be useful as an additional tool to BIA for diagnosis of sarcopenia, particularly in elderly, frail and malnourished patients. Further prospective studies are warranted in order to validate this tool for PD patients.

**FR-PO904**

*Relationship Between Frailty, Sodium, and Blood Pressure in Elderly People*

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**Background:** The objective of the FRASNET project is to investigate the correlation between frailty, natriuresis, and blood pressure (BP) in the elderly population to identify subgroups useful for diagnostic and therapeutic algorithms.

**Methods:** The FRASNET geriatric population (1204 subjects) was an Italian observational cohort that includes frail (35%), pre-frail (37.3%) and robust (27.7%) subjects. They have been characterized for BP, renal function, sodium intake (Kawasaki formula), cognitive status, quality of life (QoL), anamnestic factors, health and socio-economic status. ANOVA and conditional inference tree analysis have been carried out.

**Results:** 745 participants out of 1203 (60%) were under anti-hypertensive treatment but 71.4% had a suboptimal control of BP. The significant elements are the male gender (p=0.002), waist circumference (p=0.037) and robust (27.7%) subjects. They have been characterized for BP, renal function, sodium intake (Kawasaki formula), cognitive status, quality of life (QoL), anamnestic factors, health and socio-economic status. ANOVA and conditional inference tree analysis have been carried out.

**Results:** 745 participants out of 1203 (60%) were under anti-hypertensive treatment but 71.4% had a suboptimal control of BP. The significant elements are the male gender (p=0.002), waist circumference (p=0.037) and robust (27.7%) subjects. They have been characterized for BP, renal function, sodium intake (Kawasaki formula), cognitive status, quality of life (QoL), anamnestic factors, health and socio-economic status. ANOVA and conditional inference tree analysis have been carried out.

**Conclusions:** The more severe the frailty, the lower the BP is supposed to be. The evidence of this inverse tendency is supported by physiological explanations and by therapeutic implications. Frail patients are usually more prone to injury; therefore, they are more likely to be prescribed more drugs and the most aggressive therapies to decrease risks. Ultimately, this correlation suggests that both conditions grant a relative decrease in risk with respect to the other one, at least when considering elder individuals.
FR-PO905

White Matter Alteration at Corpus Callosum and Stria Terminalis Contributes to the Cognitive Impairment in ESRD via Dysregulating Homeostasis of Calcium

Yi-Chou Hou, Cardinal Tien Hospital, New Taipei City, Taiwan.

Background: Cognitive impairment is common in patients with end stage kidney disease (ESRD). White matter alteration is important pathologic change in cognitive impairment, and fixed-based analysis quantifies the fiber loss. The study is to elucidate the white matter alteration in urmic cognitive impairment patients.

Methods: The study period was from August 2019 to December 2020. The participants were divided into three groups according to the MMSE score and the status with end stage renal disease or not: (1) control (n=16): MMSE10~24. All participants received magnetic resonance imaging and hematologic and biochemical parameters. Fixel-based analysis was performed to assess the fiber density.

Results: The fiber density, the fiber cross section and the summation of the fiber decrease was associated with cognitive impairment. Serum calcium positively correlated with the fiber density in corpus callosum and fornix terminalis.

Conclusions: The white matter density decreased in the ESRD patients, and the decrease was associated with cognitive impairment. Serum calcium positively correlated with the fiber density in corpus callosum and fornix terminals.

The association between impaired fibers and MoCA.
FR-PO908

Association Between Family Longevity and Kidney Function in Ashkenazi Jewish Older Adults

Laith Alzyood,1 Garry A. Graham,1,3 Sandra Aleksic,1,2,3 Tina Gao,1,2 Sofiya Milman,1,2 Wei Chen,1,2 LonGenity.1 Albert Einstein College of Medicine, Bronx, NY; 2Montefiore Health System, Bronx, NY; 3Columbia University, New York, NY.

Background: Familial longevity is associated with protection against age-related diseases; thus, studying familial longevity may provide insights into the mechanisms that protect against age-related decline in kidney function, which are not fully understood. LonGenity is a longitudinal cohort study of community dwelling Ashkenazi Jewish adults aged 65-94 years that aims to identify genetic determinants of familial longevity. Using this cohort, we hypothesized that offspring of parents with exceptional longevity (OPEL) had better kidney function than offspring of parents with usual survival (OPUS).

Methods: In this cross-sectional study, we used multiple linear regression to compare eGFR between OPEL (n=442, defined as having at least 1 parent living past the age of 95 years) and OPUS (n=455, defined as having neither parent who survived to 95 years). eGFR was calculated based on serum creatinine, age and sex using the CKD-EPI equation.

Results: Compared to OPUS, OPEL were younger (74 vs. 77 years), more likely to be female (59% vs. 51%), and less likely to have diabetes mellitus (7% vs. 11%), hypertensive (37% vs. 50%) and cardiovascular disease (11% vs. 19%). OPEL had higher mean eGFR than OPUS (73±16 vs. 70±18 mL/min/1.73m², p<0.001, Table 1). This association remained significant after adjusting for body mass index, socioeconomic status, diabetes and cardiovascular disease (p=0.03), but became non-significant after further adjusting for hypertension.

Conclusions: Using this unique cohort, we found familial propensity for longevity was associated with better kidney function independent of diabetes and cardiovascular disease, but this became nonsignificant after adjusting for hypertension. Whether hypertension mediates the relationship between familial longevity and kidney function needs further investigation.

Funding: NIDDK Support, Other NIH Support - NIA

Multiple linear regression of eGFR with familial longevity (OPUS vs. OPEL)

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient (95% confidence interval)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: Body mass index, socioeconomic status</td>
<td>-2.0 (1.6, 6.0)</td>
<td>0.31</td>
</tr>
<tr>
<td>Model 2: 2-plus diabetes mellitus, cardiovascular disease</td>
<td>3.3 (2.8, 3.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Model 3: 3-plus hypertension</td>
<td>8.0 (7.5, 8.5)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

FR-PO909

Familial Longevity Modifies the Association Between Hypertension and Kidney Function in Ashkenazi Jewish Older Adults

Wei Chen,1,2 Laith Alzyood,1,2 Sanish Sathyan,1,2 Sandra Aleksic,1,2,3 Tina Gao,1,2 Sofiya Milman,1,2 LonGenity.1 Albert Einstein College of Medicine, Bronx, NY; 2Montefiore Medical Center, New York, NY.

Background: Familial longevity is associated with protection against age-related diseases. Prior studies suggest that hypertension worsens age-related decline in kidney function. We hypothesized that familial longevity modified the association between hypertension and kidney function in older adults, and sought to identify its associated proteomic profile.

Methods: LonGenity is a cohort study of community dwelling Ashkenazi Jewish adults aged 65-94 years that aims to identify genetic determinants of familial longevity. Using this cohort, we examined multiple linear regression, stratified by OPEL (n=422) vs. OPUS (n=455), we examined the cross-sectional association between hypertension and eGFR. Plasma proteins (n=4,265) were identified after adjusting for age and sex using a p-value cut-off of 0.001, and then the association between hypertension and eGFR was examined by comparing offspring of parents with exceptional longevity (OPEL) with offspring of parents with usual survival (OPUS). Exceptional longevity was defined as living past the age of 95 years) and OPUS (n=455, defined as having neither parent who survived to 95 years). While further studies are needed to validate these findings, our study could have clinical implications on personalized medicine for the management of hypertension in older adults.

Funding: NIDDK Support, Other NIH Support - NIA

FR-PO910

Correlation Between Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratios and Progression of CKD in Elderly Patients

Juliana M. Cardoso,1 Ana Teresa P. Vieira,2 Julia Lauras,3 Luiza K. Araujo,2 Washington A. Freire Filho,4 Mariana L. Innecci,4 Rosa M. Moyes,2 Rosilene M. Elias,2 Universidade Federal de Sao Paulo, Sao Paulo, Brazil; 1Universidade de Sao Paulo, Sao Paulo, Brazil.

Background: The systemic inflammation associated with chronic kidney disease (CKD) increases acute-phase protein and inflammatory mediators, which has been associated with higher mortality. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratios (PLR) have been widely studied as inflammatory markers in malignancies, hypertension, heart diseases, and vascular diseases. NLR predicts CKD progression and PLR predicts mortality among hemodialysis patients. The role of NLR and PLR in predicting CKD progression, death or dialysis initiation in elderly is unknown.

Methods: We assessed the composite outcome of death/dialysis initiation and CKD progression in 139 patients with stages 4 or 5 CKD, aged 70 years or more, participants of an ongoing trial (Aginting Nephrophyathy Study - AGNES). NLR and PLR ratios were measured at the study entry. Fast progression was defined as > 5 mL/min/1.73m²/year loss of estimated glomerular filtration rate (eGFR).

Results: Average age was 83±7 years, eGFR 19.8±7.0mL/min/1.73m², 56% men, 50% with diabetes mellitus. NLR was 2.9±1.4 and PLR was 131.6. Over time, the decline in eGFR was 2.4 (1.1, 6.2) mL/min/yr. NLR but not PLR was higher in faster progressors (p=0.021 and 0.238, respectively). NLR (p=0.028) but not PLR (p=0.077) was higher in patients who died/distarted dialysis (N=55, 39.6%). Logistic regression/Cox regression revealed NLR as an independent risk factor for CKD progression and death/dialysis initiation, respectively, in fully adjusted models. ROC curve defined 3.77 as the best cut-off value of NLR to predict death/dialysis initiation (specificity 88.1%).

Conclusions: NLR seems to be a good marker for mortality/dialysis initiation and also CKD progression in older patients with advanced CKD, in a higher value than that described for the general population. NLR, a non-expensive tool, should be widely used in this population to identify patients at risk.
FR-PO912

Clinical Characteristics of Anti-Nephrin Autoantibody-Positive Minimal Change Disease in Adults: A Case Series in Elderly Japanese Patients

Background: Minimal change disease (MCD) is a leading cause of nephrotic syndrome in adults and is more common in the Japanese population. Recently, nephrin autoantibodies were reported in a North American Cohort of adults and children with MCD supporting an autoantibody mediated etiology. However, the clinical characteristics of nephrin autoantibody positive MCD in elderly Japanese patients have scarcely been studied.

Methods: In this single-center case series in Japan, we included 8 consecutive adult cases of biopsy-proven MCD presented to our center in 2021. We evaluated serum, obtained at presentation and following treatment, for circulating nephrin autoantibodies by indirect ELISA. The renal biopsies were evaluated for punctate IgG deposition and co-localization with nephrin by immunofluorescence confocal microscopy imaging.

Results: The median age was 75 years (range 56-84), 43% male, median creatinine and median urine protein/creatinine ratio at diagnosis were 0.92 mg/dL (range 0.47-4.5) and 10.9 g/g (range 7.7-14.0 g/gCr) respectively. Five out of eight cases (63%) had circulating anti-nephrin autoantibodies at presentation and this correlated completely with “punctate IgG” that colocalized with nephrin in the renal biopsies of all positive patients. All 8 patients achieved complete remission after therapy and those with serum circulating anti-nephrin autoantibodies at presentation and following treatment, had a shorter relapse-free time (median 16.5 months), compared to negative group (no relapse).

Conclusions: In our cohort of anti-nephrin antibody-positive adult Japanese MCD cases in elderly Japanese patients, we observed the correlation of anti-nephrin antibody with disease activity and shorter relapse-free time. Larger studies are needed to further characterize anti-nephrin antibody positive MCD cases in adults.

FR-PO913

Fludrocortisone-Responsive Hyponatremia in the Elderly

Introduction: Case studies report a rare manifestation of hyponatremia responsive to fludrocortisone, presenting as SIADH or salt-wasting syndrome (SWS), which fails to correct with both fluid restriction and Na replacement.

Case Description: A 79-year-old Japanese woman with T2DM and depression on duloxetine was found to have asymptomatic hyponatremia with Na level of 122 mEq/L. She reported eating 3 meals and drinking water 2 L/day. Vital signs were hemodynamically stable without presence of dehydration. Initial work-up showed serum osmolality at 256 mOsm/kg, urine Na at 94 mEq/L, urine osmolality at 292 mOsm/kg, serum creatinine at 0.4 mg/dL and BUN at 10 mg/dL, with normal serum glucose, AM cortisol and TSH. CT brain without contrast was unremarkable. Duloxetine was initially held. The patient received 2 L of IV normal saline, followed by NaCl tabs 6 g/day. Fluid intake was restricted to <800 mL/day. The serum Na remained low between 122-126 mEq/L for the next 48 hrs. After initiating fludrocortisone acetate 0.1 mg daily, the serum Na increased to 133 mEq/L within 60 hours, without falling after resuming duloxetine. Her urine output was 1-2 L/day. Her pre- and post-admission weights were 35 and 32.9 kg. Her hematocrit was stable at 34%.

Discussion: Reports in the literature list 10 non-neurosurgical patients with hyponatremia responsive to fludrocortisone, 5 with cerebral salt-wasting, 3 with SIADH, and 2 did not have a clear diagnosis. All of them were Japanese elderly patients. To our knowledge, this case had a prior history of traumatic brain injury. The clinical response of SIADH or SW to fludrocortisone is rarely discussed as a treatment of hyponatremia in medical patients. This is another case of fludrocortisone-responsive hyponatremia. Common characteristics include Japanese race, female, elderly, hypo osmolality, hypertonic urine and high urine Na. Volume status can be either hypo or euolemic. In 1987, Ishikawa et al. proposed the concept of mineralocorticoid-responsiveness hyponatremia of the elderly (MRHE). MRHE is thought to be caused by a decline in the response to the RAAS and in the kidneys’ ability to retain sodium.

FR-PO914

Kappa Light Chain Myeloma Presenting as Acute Renal Failure

Introduction: Multiple Myeloma is a plasma cell dyscrasia commonly affecting the elderly. Acute renal failure carries a particularly poor prognosis. Here we present a 95-year-old woman who came with fatigue, polyuria and new onset renal failure. Work up showed multiple myeloma with kidney biopsy showing diffuse tubular necrosis and bone marrow biopsy showing kappa light chain myeloma. She was started on chemotherapy within 13 days of admission. Despite prompt initiation of chemotherapy, kidney function did not improve, and she deteriorated in a month’s time.

Case Description: The patient was a 95-year-old woman with a history of HTN/ HLD and a remote history of PI on warfarin. She was fully functional and independent at baseline; she was compliant with medication and labs 6 months prior were normal. She was referred to the ED for bradycardia, had been having polyuria and fatigue one week prior. In the ED, vitals were normal, physical exam showed chronic bilateral hearing loss, labs were notable for a Hgb of 6.5, MCV of 104, a BUN of 150 and a Cr of 12 with a potassium of >7.5, her corrected calcium was 9.5; a stool occult test was positive, and her INR was 7.9. She was admitted to the ICU for CVVHD, concern for acute GI bleed with severe pre-renal AKI, however her hemoglobin normalized and was unable to wean off HD. Workup for RPGN, vasculitis and multiple myeloma was done which showed significantly elevated kappa/lambda ratio, kidney biopsy showed diffuse acute tubular necrosis without glomerulonephritis and bone marrow biopsy and serum studies showed kappa light chain myeloma. Chemotherapy was started 13 days after diagnosis; however, her kidney function did not improve, and she deteriorated within a month from episodes of fluid overload while on dialysis and vascular access site infections.

Discussion: Renal impairment in multiple myeloma has a life expectancy of less than a year, and is an independent negative prognostic factor when noted in the first 6 months of diagnosis. The biggest indicator of overall prognosis is renal response to treatment including dialysis and chemotherapy. Our patient’s case showed a rare case of kappa light chain myeloma presenting with acute renal failure from ATN which unfortunately did not improve with treatment. More research into modalities such as high output dialysis or plasmapheresis in this population would be useful to reduce light chain burden and resulting ATN.

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

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FR-P0915

Association of Serum Magnesium Concentration with Renal Prognosis in Patients with CKD

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Background: Magnesium plays a crucial role in various physiological processes, and disruptions in its balance have been linked to adverse health effects. By investigating the impact of magnesium levels on renal outcomes, this study aims to contribute to our understanding of managing magnesium levels in CKD patients. The findings may provide valuable insights for clinical practice and future intervention studies in this population.

Methods: This study utilized the J-CKD-DB-Ex database, comprising CKD patients enrolled between 2014 and 2020. Only patients with at least two measurements of magnesium and eGFR were included. The index date was established as the time of the initial magnesium measurement, and individuals with an eGFR greater than 15 and less than 60 mL/min/1.73 m² at the index date were selected. The study categorized participants into three groups based on their magnesium levels: low, normal, and high magnesium. Patients who had a single clinic visit or a history of hospitalization were excluded from the analysis. The primary outcome was defined as the progression to ESKD, determined by an eGFR below 15 mL/min/1.73m² or a decline of 30% or more in eGFR from baseline. Regional Universitaire de Nancy, Nancy, France; 8Hopital Ambroise-Pare Billancourt, France; 4Centre de Recherche en Epidemiologie et Sante des Populations, Villejuif, France; 5Hopscipes Civils de Lyon, Lyon, France; 1Universite Claude Bernard Lyon 1, Villeurbanne, France; 2Centre Hospitalier Regional Universitaire de Nancy, Nancy, France; 3Hospital Ambroise-Pare Service de Nephrologie Dialyse, Boulogne-Billancourt, France.

Results: A total of 210,806 ND-CKD patients from 19 hospitals were screened, of whom 157,987 (74.94%) had serum phosphate testing during the first hospitalization. The overall prevalence of HP was 14.83% in these patients (CKD G1 8.26%, G2 6.17%, G3a 7.32%, G3b 12.43%, G4 26.74%, G5 65.85%). The utilization rates of phosphorus-lowering medications (including calcium acetate, calcium carbonate, lanthanum carbonate, and sevelamer carbonate) in ND-CKD G3-5 were 9.62% (G3a), 11.29% (G3b), 14.84% (G4), and 23.92% (G5), respectively. Among 64,662 patients with a median follow-up of 3.3 years on death, patients with HP (n=8856) had a 1.3% increased risk of all-cause mortality (HR 1.13, 95% CI 1.06-1.22) and a 2.8% increased risk of cardiovascular mortality (HR 1.28, 95% CI 1.04-1.56), compared with those with normal serum phosphate concentration at baseline with confounders adjusted for age, sex, region, CKD stage, comorbidity. Among the patients with HP the risk of all-cause mortality and cardiovascular mortality were reduced by 12% and 16%, respectively, in patients with phosphorus-lowering medications compared to those without phosphorus-lowering medications. Among 47,581 patients with a median follow-up of 1.8 years on kidney function, patients with HP (n=3622) had a 9% increased risk of kidney disease progression than those with normal serum phosphate concentration at baseline (HR 1.08, 95% CI 1.05-1.17).

Conclusions: HP is common in ND-CKD in China and is an independent risk factor for mortality and kidney disease progression. The use of phosphorus-lowering medications was associated with the decreased risk of all-cause mortality and cardiovascular mortality in patients with CKD G3-5.

Funding: Commercial Support - Sanofi

FR-P0918

Intensification of Serum Phosphate Lowering Is Related to the Risk of RRT in Non-Dialysis Dependent (NDD)-CKD Patients with Hyperphosphatemia Sheng Nie,1 Qi Gao,1 Shiyu Zhou,1 Lichen Hao,3 Yan Zhang,3 Muhan Yuan,3 Southern Medical University Nanshan Hospital, Guangzhou, China; 2Sanofi, Bridgewater, NJ; 3Sanofi, Beijing, China.

Background: Few studies have explored the association between intensity of serum phosphate lowering and risk of renal replacement therapy (RRT) in patients with non-dialysis dependent chronic kidney disease (NDD-CKD).

Methods: Data was extracted from the Optum Humedica EHR database. The study period started from July 1, 2007, to June 30, 2021. We enrolled NDD-CKD adult patients with two consecutive results of elevated serum phosphorus (defined as non-same day but ≤180 days apart, >4.5 mg/dL on both occasions). The study exposure was defined as the

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FR-PO920

Serum Uric Acid Trajectories and CKD Progression in the African American Study of Kidney Disease in Hypertension (AASK)

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Background: Serum uric acid levels increase with progressive kidney disease, due to retention of uric acid resulting from a reduced glomerular filtration rate (eGFR). Chronic elevations in circulating and tissue levels of uric acid may contribute to progression of chronic kidney disease, although this remains controversial.

Methods: We used data from the African American Study of Kidney Disease in Hypertension (AASK) to examine the hypothesis that subjects whose serum urate levels declined during the study period would manifest less composite end-stage kidney disease (ESKD) event. The composite ESKD outcome was defined as 50% decline from baseline eGFR, eGFR ≥15 mL/min/1.73 m2, self-reported initiation of chronic dialysis, or kidney transplantation. To estimate the trajectory, the group-based trajectory modeling of the uric acid level change was done. We classified into 5 groups: high-stable group, the high-increasing group, the extreme high-stable group, normo-increasing group, and high-decreasing group. Cox proportional hazards model was used to estimate whether the different group membership would predict the composite ESKD outcomes.

Results: We found that compared with subjects in the normal-increasing uric acid group (i.e., those who had the lowest overall serum uric acid levels), three groups had higher incidence of the composite ESKD event: the high-stable uric acid group, HR = 2.28, p = 0.012, the high-increasing uric acid group, HR = 1.95, p = 0.042, and the extremely high-stable uric acid group, HR = 3.21, p < 0.001. Further, the extremely high-stable group had a higher composite ESKD incidence, compared with the high-decreasing group, HR = 1.98, p = 0.046.

Conclusions: Uric acid trajectories are associated with ESKD incidence. In particular, subjects whose uric acid levels decreased over time had a better composite ESKD event than other groups.

Funding: Government Support - Non-U.S.

FR-PO919

Metabolic Acidosis and CKD Progression

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Background: An inverse relationship between venous bicarbonate and CKD progression has been reported in several observational studies, but only sparse longitudinal observations testing this relationship exist. Bicarbonate supplementation trials have been conflictual, with limited power and a high risk of bias. Longitudinal studies may provide circumstantial new evidence for implicating metabolic acidosis in the risk of adverse kidney outcomes.

Methods: We performed a longitudinal study in 528 patients with at least 3 longitudinal measurements of bicarbonate over 32 months (IQR: 30-36). The association between bicarbonate trajectories over time and the incidence of renal events (>30% eGFR reduction, dialysis or transplantation) were investigated by a two stages analysis: 1) in the first stage, we identified distinctive group-based bicarbonate trajectories analysis (GBTM); 2) in the second stage we assessed the association between bicarbonate trajectories groups and the risk of renal events by Cox model.

Results: Overall, 126 patients had renal events. Four trajectories of bicarbonate were identified and labelled as low trajectory [bicarbonate: 19.07 ± 2.5 mEq/L], moderate [21.2 ± 2.3 mEq/L], moderate-high [25.1 ± 2.2 mEq/L] and high [27.9 ± 2.8 mEq/L]. In crude and adjusted analyses (age, gender, systolic BP, haemoglobin, albumin, phosphate, PTH, 24h phosphorus concentration at 360 days, 11,599 (41.2%), 10,135 (36.0%), 3,165 (11.2%), 2,293 (8.1%) and 975 (3.5%) were categorized into the high decrease group (decrease of ≥25%), decrease group (decrease of 5% to 25%), stable group (decrease of <5% to increase of <5%), increase group (increase of 5% to <25%), and high increase group (increase ≥25%), respectively. The high decrease group and decrease group were associated with lower risk of RRT compared with the stable (high decrease: adjusted hazard ratio (aHR)=0.51, 95% confidence interval (CI): 0.47-0.56; decrease: aHR=0.75, 95% CI: 0.69-0.81). Meanwhile, the high increase group and increase group were associated with higher risk of RRT compared with the stable (high increase: aHR=1.34, 95% CI: 1.19-1.51; increase: aHR=1.24, 95% CI: 1.13-1.36).

Conclusions: The level of serum phosphate change was associated with the risk of RRT in patients with NDD-CKD and hyperphosphatemia. Our findings suggest that intensive lowering of serum phosphate might help to delay the time to RRT in patients with NDD-CKD.

Funding: Commercial Support - Sanofi
Difference in cumulative \[ \text{Infection Complications} \] incidence with/without treatment

Figure. Difference in incident complications in CKD pts between treated (intervention) and untreated (baseline) uncontrolled gout scenarios.

**FR-PO922**

Factors of Poor Prognosis Associated with CKD by Stage in Ambulatory Patients: A Cross-Sectional Study
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Background: Mexico has a high prevalence of chronic kidney disease (CKD) but limited information about the early stages of CKD and their clusters of poor prognosis factors (PPF) such as hyperuricemia, electrolyte abnormalities or comorbidities.

Objective: To assess the prevalence of PPF by CKD stages in ambulatory patients.

Methods: A cross-sectional study with 1772 adult patients with CKD that attended the Nephrology Outpatient Clinic. PPF data is reported as adjusted OR (95% confidence interval).

Results: Mean age was 56.2 ± 15.8 years. Kidney Replacement Therapy (KRT) was reported in 12% of the patients. Type 2 diabetes mellitus (T2DM), age >50 years and male gender were the PPF associated with all CKD stages. The PPF in CKD 2 and 3a hyperuricemia OR 3.4 (2.02,6.4) and 4.4 (2.5,7.6), and hypertension OR 1.8 (1.01,3.4) and 2.3 (1.2,4.3) respectively. In CKD 3b were hyperuricemia OR 5.1 (3.1,8.6), hypertension OR 2.7 (1.5,4.9) and hyperkalemia OR 3.4 (1.5,7.6). For CKD 4, 5 without KRT and 5 with PPF were hyperuricemia OR 7.02 (4.1,11.8), 13.5 (7.4,24.6), 3.9 (2.2–6.9), hypertension OR 3.4 (1.9,6.3), 3.4 (2.7,1.1), and hyperkalemia OR 2.9 (1.3,6.3), 7.9 (3.6,17.3), 8.7 (3.9,19.3), respectively. Anemia was important for CKD 5 without KRT and 5 with OR of 5.7 (3.09,10.6) and 8 (4.2,15), respectively.

Conclusions: This is the largest study of Mexican patients with CKD; most of them without KRT. Patients had multiple modifiable PPF. Early and comprehensive management of PPF could prevent or delay progression to KRT. Treatment of associated PPF should be a priority, as it could make a significant difference both for CKD progression and its subsequent cardiovascular risk.

**FR-PO924**

Polygenic Risk Affects the Penetrance of Monogenic Kidney Disease
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Background: Chronic kidney disease (CKD) is a genetically complex disease determined by an interplay of monogenic, polygenic, and environmental risks. Most forms of monogenic kidney diseases have incomplete penetrance and variable expressivity. It is presently unknown if some of the variability in penetrability can be attributed to polygenic factors.

Methods: Using the UK Biobank (N=469,835) and the All of Us (N=98,622) datasets, we examined the two most common forms of monogenic kidney disorders, autosomal dominant polycystic kidney disease (ADPKD) caused by deleterious variants in the PKD1 or PKD2, and COLA4-associated nephropathy (COLA4AN) caused by deleterious variants in COL4A3, COL4A4, or COL4A5. We used the eMERGE-III electronic CKD phenotype to define cases (estimated glomerular filtration rate (eGFR) <60 or kidney failure) and controls (eGFR >90). The effects of the genome-wide polygenic score for PKD were tested in monogenic variant carriers and non-carriers using logistic regression controlling covariates.

Results: As expected, the carriers of known pathogenic and rare predicted loss-of-function variants in PKD1 or PKD2 had a high risk of CKD (OR meta=-1.71, 95% CI: 1.11–2.64, P=1.8E-37). The GPS was comparably predictive of CKD in both ADPKD variant carriers (OR meta=-2.28 per SD, 95%CI: 1.55–3.37, P<2.6E-05) and non-carriers (OR meta=-1.72 per SD, 95%CI: 1.69–1.76, P<3E-030) independent of age, sex, diabetes, and genetic ancestry. Compared to the middle tertile of the GPS distribution for non-carriers, ADPKD variant carriers in the top tertile had a 54-fold increased risk of CKD. In contrast, ADPKD variant carriers in the bottom tertile had only a 3-fold increased risk of CKD. Similarly, the GPS was predictive of CKD in both COL4AN-variant carriers (OR meta=-1.78, 95% CI: 1.22–2.58, P=2.3E-03) and non-carriers (OR meta=-1.70, 95% CI: 1.68–1.73, P=E-300). The carriers in the top tertile of the GPS had a 2.5-fold higher risk of CKD, while the risk for carriers in the bottom tertile was similar to the middle tertile of non-carriers.

Conclusions: Variable penetrance of kidney disease in ADPKD and COLA4AN is partially explained by differences in polygenic risk profiles. Accounting for polygenic factors has the potential to improve risk stratification in monogenic kidney disease and may have implications for genetic counseling.

Funding: NIDDK Support, Other NIH Support - NHGRI

**FR-PO925**

Association Between Dyslipidemia and the Risk of Incident CKD
Affected by Genetic Susceptibility: Polygenic Risk Score Analysis
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Background: In most forms of monogenic kidney disorders, incompletely penetrant inheritance is often observed. It is presently inconclusive, and it requires further clarification. Therefore, we aimed to investigate the effects of genetic factors on the association between dyslipidemia and the risk of chronic kidney disease (CKD) using polygenic risk score (PRS). The impact of PRS and PRS on incident CKD were assessed using Cox proportional hazard model. To investigate the interaction between lipid and genetic factor on incident CKD, the PRS was constructed using GWAS summary statistics of CKD-gen overall European ancestry (n=480,697). The impacts of lipids and PRS on incident CKD were assessed using Cox proportional hazard analysis exclusively for subjects with available follow-up data.

Methods: We employed genome-wide association study summary statistics, excluding the United Kingdom Biobank (UKB) datasets among published CKD-gen Consortium papers—to calculate the PRSs for CKD in white background subjects. To validate PRS performance, we divided the UKB into two datasets and test the data. We used logistic regression analysis to evaluate the association between dyslipidemia and CKD, and assessed Cox proportional hazard analysis exclusively for subjects with available follow-up data.

Results: In total, 438,253 clinical data points and 4,307,940 single nucleotide polymorphisms from 459,155 samples were included. We observed a significant positive association between PRS and CKD and the presence and development of CKD. Hyperuricemia significantly increased CKD risk (adjusted odds ratio 1.54, 95% confidence interval 1.49–1.58). The impact of hyperuricemia on CKD was maintained irrespective of PRS range but was more pronounced in subjects with low PRS (1st tertile range). Survival analysis indicates that the presence of hyperuricemia significantly increased the risk of CKD development.

Conclusions: The PRS for CKD thoroughly reflects the risk of CKD development. Hyperuricemia is a significant indicator of CKD risk, even after incorporating the genetic risk score for CKD. Irrespective of genetic risk, patients with a prospective risk of developing CKD require uric acid monitoring and management.

Funding: NIDDK Support, Other NIH Support - NHGRI
we introduced multiplicative interaction terms between them to multivariable analysis model and performed subgroup analysis stratified by PRS tertiles.

**Results:** A total of 4,424 participants developed CKD. In multivariate analysis, the PRS was significantly predictive of the risk of incident CKD (continuous variable; HR, 1.075; 95% CI, 1.045-1.109). I-SD lower levels of total cholesterol (HR, 0.898; 95% CI, 0.867-0.931), LDL-C (HR 0.899, 95% CI, 0.831-0.971), HDL-C (HR, 0.877; 95% CI, 0.841-0.914), and higher triglyceride (HR, 1.078; 95% CI, 1.048-1.109) were significantly associated with the risk of incident CKD. The interactions between triglyceride and intermediate (HR, 1.122; 95% CI, 1.026-1.228) and high PRS (HR, 0.932; 95% CI 0.872-0.995) were significant, and the interactions were inversely associated with the risk of incident CKD. Similar relationship between triglyceride and PRS were observed in subgroup analysis stratified by PRS tertiles.

**Conclusions:** The PRS for incident CKD presented significant predictive power for incident CKD. Higher triglyceride, lower total cholesterol, lower LDL-C, and lower HDL-C increased the risk of incident CKD. There were interactions between triglyceride and genetic factor, and the individuals in the low-PRS group had a higher risk of triglyceride-related incident CKD.

**FR-PO926**

Presence of a Novel Exon 27 Skipping Event in COL4A4 Associated with Hematuria and Albuminuria

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**Background:** Limited ancestral diversity in genome-wide association studies (GWASs) on kidney function confines their generalizability to regions with a high incidence of end-stage kidney disease (ESKD).

**Methods:** We conducted a meta-analysis of GWASs (n=244952) of estimated glomerular filtration rate (eGFR) and a replication dataset (n=27058) from Taiwan and Japan. Additionally, polygenic risk scores (PRSs) for chronic kidney disease (CKD) substantially differentiated the CKD risk in independent cohorts from Taiwan (n=30433) and the United Kingdom (n=260245).

**Results:** Our analysis identified 238 independent signals in 97 loci that were associated with eGFR. Functional analyses revealed that variants associated with F2 expression and ABCG2 missense mutation link inflammation, coagulation, and urate metabolism to a high risk of decreased kidney function. The median time to 10% CKD incidence in PRS10% risk groups (above, in-between, and below two standard deviations of mean) was 64, 66, and 71 years after birth, respectively (Fig. 2). The 7-year difference between high- and low-genetic risk groups can be observed from the age of 50.

**Conclusions:** Our findings suggest that PRS10% has the potential to be used for early kidney disease prevention, particularly in countries with a high incidence of ESKD.

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

Figure 1. Study design flowchart

Figure 2. Cumulative incidence of CKD based on PRS stratification

**FR-PO927**

Abstract Withdrawn

**FR-PO928**

Common Genetically Predicted Skipping of COL4A4 Exon 27 Is Associated with Hematuria and Albuminuria

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**Background:** Hematuria is an established sign of glomerular disease and can be associated with kidney failure, but there has been limited scientific study of this trait.

**Methods:** Here, we combined genetic data from the UK Biobank with predicted gene expression and splicing from GTEx kidney cortex samples (n = 65) in a transcriptome-wide association study (TWAS) to identify additional biological mechanisms influencing hematuria.

**Results:** Our TWAS using kidney cortex identified significant associations for 5 genes in terms of expression and 3 significant splicing events. Notably, we identified an association between hematuria and the skipping of COL4A4 exon 27, which is genetically predicted by intronic rs11899084 (minor allele frequency 13%). The association was also found with urinary albumin excretion. We found independent evidence supporting the existence of this skipping event in glomeruli-derived mRNA transcriptomics data (n = 245) from the NEPTUNE dataset. The functional significance of loss of exon 27 was demonstrated using the split NanoLuc-based type IV collagen α3α4α5(IV) heterotrimer assay, in which heterotrimer formation was quantified by luminescence.

**Conclusions:** Altogether, our results highlight the value of investigating the role of non-coding sequence, an underexplored region, by integrating multiple data types to shed light on kidney traits and their underlying disease mechanisms.

**Funding:** NIDDK Support

Figure 1. Genomic overview of the exon 27 skipping event of COL4A4.

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

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FR-PO929
Circulating Proteins Associated with Mortality in Patients with CKD Nityasree Naito,1,2 Eisei Naito,1,3,4 Soichiro Kinosaki,1,5 Shunsuke Inaba,1,2 Motohiro Kaneko,1,6 Takaaki Ichikawa,1,7 Miki Higashiyama,1,8 Tomohiro Tsukahara,1,9 Jiro Watanabe,1,10 Takashi Ando,1,11 Shinya Uchida,1,12 Masamichi Yamashita,1,13 and Tomoyuki Shiozawa,1,14 1Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 2Department of Geriatric Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 3Department of Biomedical Engineering, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 4Department of Social Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 5Department of Internal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 6Department of Internal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 7Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 8Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 9Department of Geriatric Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 10Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 11Department of Geriatric Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 12Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 13Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 14Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan.

Background: The global economic burden of chronic kidney disease (CKD) and end-stage-kidney disease (ESKD) is still increasing. However, non-invasive techniques to predict CKD progression have yet to be established. This study aimed to determine circulating small extracellular vesicle (cEV)-encapsulated miRNAs predictive of kidney outcome in patients with CKD.

Methods: We enrolled 36 Japanese adults with non-dialysis-dependent CKD patients from the previously published cohort studies. We performed miRNA transcriptomic analyses using cEVs extracted from the serum of the participants. The patients were followed up until death, transfer, or ESKD requiring dialysis. The correlation between miRNA expressions and baseline eGFR was examined with the linear regression model. A stratified Cox regression model was used to assess the risk of a kidney composite outcome including ESKD or 30% eGFR reduction. We also performed the logistic regression analysis to examine the risk of rapid eGFR decline, which was defined as eGFR reduction ≤5 mL/min/1.73 m²/year or dialysis initiation within a follow-up of six months. All analyses were adjusted for potential confounders including age, sex, diabetes mellitus, and cardiovascular disease.

Results: The median age of the participants was 71 years (interquartile range, 61-79), 25% were female, and the median baseline eGFR was 51 (21-53) mL/min/1.73 m². After a median follow-up period of 636 days, the kidney composite outcome and rapid eGFR decline occurred in 16 and 16 patients, respectively. Among 2578 miRNAs identified, all three criteria including the negative association between miRNA expression levels and baseline eGFR (P < 0.1), increased odds ratios for a risk of the kidney composite outcome (HR ≥ 1.5; P < 0.05), and increased odds ratios (ORs) for a risk of rapid eGFR decline (OR ≥ 1.5; P < 0.1) were met for three miRNAs. The KEGG molecular pathways associated with miRNA target molecules found ubiquitin-mediated proteolysis, Hippo signaling pathway, protein processing in endoplasmic reticulum, and MAPK signaling pathway.

Conclusions: This study uncovered miRNA signature encapsulated in cEVs that is strongly associated with a risk of CKD progression in adults.

Funding: Private Foundation Support

FR-PO931
The Transcriptomic Landscape of microRNAs Encapsulated in Circulating Extracellular Vesicles and CKD Progression in Japanese Adults Hiroshi Ando,1,2,3 Tomohiro Tsukahara,1,9 Jiro Watanabe,1,10 Takashi Ando,1,11 Shinya Uchida,1,12 Masamichi Yamashita,1,13 and Tomoyuki Shiozawa,1,14 1Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 2Department of Geriatric Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 3Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 4Department of Social Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 5Department of Internal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 6Department of Internal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 7Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 8Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 9Department of Geriatric Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 10Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 11Department of Internal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 12Department of Internal Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 13Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan; 14Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Japan.

Background: Circulating microRNAs (miRNAs) are small non-coding RNAs that play critical roles in regulating gene expression. In patients with chronic kidney disease (CKD), the expression levels of miRNAs in circulating extracellular vesicles (cEVs) have been proposed as potential biomarkers for kidney disease progression. However, the specific miRNA signatures that are differentially expressed in cEVs from patients with CKD compared to healthy controls have not been fully characterized.

Methods: We performed an in silico analysis of miRNA expression data from a previously published cohort study of 2,851 participants. We focused on data from patients with CKD (n = 1,547) and healthy controls (n = 1,298). We used the Gene Expression Omnibus (GEO) database to identify miRNAs that were differentially expressed between the two groups. We then validated the findings using an independent cohort of 565 participants with CKD and 542 healthy controls from the Japanese General Health Checkup Study (JGHC). We next performed a functional enrichment analysis of the differentially expressed miRNAs to identify pathways and biological processes that were significantly altered in CKD patients.

Results: In total, 2578 miRNAs were identified in the GEO cohort, of which 1287 were differentially expressed between CKD patients and healthy controls. In the JGHC cohort, 1646 miRNAs were detected, with 816 showing significant differences in expression. The functional enrichment analysis revealed several pathways that were significantly enriched in the miRNA expression profiles of patients with CKD, including focal adhesion, epithelial-mesenchymal transition, and extracellular matrix-receptor interactions.

Conclusions: The transcriptomic landscape of miRNAs in cEVs from patients with CKD can provide insights into the molecular mechanisms underlying CKD progression. These findings suggest that miRNAs may serve as potential biomarkers for monitoring kidney disease progression and identifying novel therapeutic targets.

Funding: NIDDK Support

FR-PO932
Evaluation of Novel Candidate Filtration Markers from a Global Metabolomics Discovery for Glomerular Filtration Rate Estimation Benjamin Haaland,1,2 Michael Shilpak,3 Veronica T. Costa e Silva,4 Roberto S. Kahl,5 Ayse L. Mindikoglu,6 Susan L. Furth,7 Jesse C. Seegmiller,8 Andrew S. Levey,9 Lesley A. Inker,10 CKD-EPI, University of Utah Health, Salt Lake City, UT; 2Tuscaloosa Medical Center, Boston, MA; 3Johns Hopkins University Department of Epidemiology, Baltimore, MD; 5San Francisco VA Health Care System, San Francisco, CA; 6Serviço de Nefrologia, Instituto do Câncer do Estado do Sá Paulo, São Paulo, Brazil; 7University of Michigan School of Medicine, Baltimore, MD; 8Baylor College of Medicine, Houston, TX; 9University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 10The Children’s Hospital of Philadelphia, Philadelphia, PA; 11University of Minnesota Twin Cities, Minneapolis, MN.

Background: Estimating glomerular filtration rate (eGFR) is critical for the care of patients with chronic kidney disease (CKD). However, the current methods of GFR estimation (eGFR) have limitations, such as significant underestimation of mGFR in CKD patients. Therefore, there is a need for new markers that can accurately predict kidney function.

Methods: We analyzed metabolites from seven diverse studies of 2,851 participants on the Metabolon H4 platform that had Pearson correlations with log mGFR. We used a stepwise approach to develop models to estimate mGFR including with and without inclusion of creatinine and demographics. We then selected candidate filtration markers from those metabolites found >20% in models that did not demonstrate substantial overfitting in cross-validation and with small (<0.1 in absolute value) coefficients for demographic variables. We validated the models in an independent dataset and compared the performance of the final model with other established GFR estimation methods.

Results: In total, 456 metabolites were present in all studies, and 36 had correlations >0.5 with mGFR. We developed 2,225 models including these metabolites; all had lower root mean square errors (RMSE) and smaller coefficients for demographic variables compared to estimated creatinine. Cross-validated RMSEs (0.1870-0.213) were similar to original RSMEs for models with 10 metabolites (Figure). Our criteria identified 17 metabolites, including 12 new candidate filtration markers.

Conclusions: We identified candidate filtration markers with a combination of minimal association with mGFR and minimal association with demographic variables compared to estimated creatinine. Cross-validated RMSEs for the final model were lower than the original RSMEs for models with 10 metabolites (Figure). This novel approach offers a promising new method for estimating GFR that is more accurate and less reliant on demographic variables than current eGFR.

Funding: NIDDK Support
**FR-PO933**

Association Between Serum Kynurenine Levels and Cardiovascular Outcomes and Overall Mortality in CKD

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**Background:** Kynurenine is a protein-bound uremic toxin. Its circulating levels are increased in chronic kidney disease (CKD). Experimental studies showed that it exerted deleterious cardiovascular effects. We sought to explore the association between serum kynurenine levels and adverse fatal or nonfatal cardiovascular events and all-cause mortality before kidney replacement therapy (KRT) in patients with CKD.

**Methods:** The CKD-REIN study is a prospective cohort of CKD patients before KRT (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²) followed-up over five years. Baseline frozen samples of total and free fractions of kynurenine and tryptophan were measured using a validated liquid chromatography tandem mass spectrometry technique. Cause-specific Cox models were used to estimate hazard ratios (HRs) for each outcome.

**Results:** Of the 2,406 included patients (median age: 68 years; median eGFR: 24.7 ml/min/1.73 m²), 52% had a history of cardiovascular disease. A 1.5-fold increase in serum free kynurenine levels was associated with a 12%-increased hazard of cardiovascular events (466 events, HR[95% CI]: 1.12 [1.02, 1.23]), independently of eGFR, serum free kynurenine levels was associated with a 12%-increased hazard of cardiovascular events and all-cause mortality before kidney replacement therapy (KRT) in patients with CKD.

**Conclusions:** In a multi-ethnic, community-based cohort of US adults, higher levels of gut microbiota-generated TMAO-related metabolites were associated with elevated albuminuria and its progression.

**Funding:** Private Foundation Support

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**FR-PO935**

On the Accuracy of the Kidney Failure Risk Equation

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**Background:** The accuracy of Kidney Failure Risk Equation (KFRE) is based on the Receiver Operating Characteristic (ROC) curve. Area Under the ROC Curve (AUC), and Harrell’s C-statistic. We examined the predictive power of the 4-variable KFRE described in [1] and considered the limitations of ROC curves and C-statistics.

**Methods:** We used data from the UK’s NURTuRE CKD cohort with outcomes for 2426 CKD patients. 149 patients had reached ESKD at follow up. Model performance was assessed by: * Harrell’s C-statistic * AUC * Average precision * Average negative predictive value.

**Results:** The C-statistic was 0.89 and AUC for 2-year discrimination 0.91, both corroborating [1]. The C-statistic on the subset of patients with known time to ESKD was 0.64. Average negative predictive value was 0.99. Average precision was 0.32. Excluding patients above age 40, average precision was 0.42.

**Conclusions:** The C-statistic is computed by counting patient pairs that the model orders correctly for time to ESKD. Most pairs include a patient who reached ESKD before follow-up and one who did not. Therefore, the C-statistic overestimates the KFREs ability to order patients for time to ESKD. For the subset of patients whose time to ESKD was known, the C-statistic was only 0.64. In other words, the KFRE cannot be used reliably to sort NURTuRE patients by time to ESKD. The AUC is the probability that a randomly chosen positive patient would be assigned a larger risk score than a randomly chosen negative patient. Since most such pairs can be easily sorted for time to ESKD, this metric turns out well. In contrast, precision measures the probability that a patient will reach ESKD given that (s)he is predicted to by the KFRE. A precision of 0.32 in this case means that only 32% of patients predicted to reach ESKD within 2 years will do so. Interestingly we see an increase in precision in younger patients, which we believe is due to a higher correlation between eGFR and time to kidney failure in younger age brackets. In summary: With a negative predictive value of 0.99, the KFRE can rule out near term kidney failure with high probability but cannot confirm it. Therefore, while its application for referrals is appropriate, the KFRE should not be used as a basis for costly or risky medical intervention.

**Funding:** Commercial Support - AstraZeneca
**FR-PO936**  
**Kidney Failure Risk Equation Prediction in a Real-World Population with CKD**  
Leonid Shpaner,1 Panayiotis Petousis,1 Obidiugwu Duru,1 Ken B. Daratha,2 Keith C. Norris,3 Katherine R. Tuttle,2 Susanne B. Nicholas,1 Alex Bui,1 Center for Kidney Disease Research, Education, and Hope (CURE-CKD),1 University of California Los Angeles David Geffen School of Medicine, Los Angeles, CA, 2 Providence Medical Research Center, Spokane, WA.

**Background:** Risk prediction helps to identify patients with chronic kidney disease (CKD) who may benefit from awareness, detection, and intervention to preserve kidney function. The purpose of this study was to externally validate the Kidney Failure Risk Equation (KFRE) using the 4-variable (4-KFRE) and 6-variable (6-KFRE) equations to predict end stage renal disease (ESRD; eGFR <15 mL/min/1.73 m²) over 2- and 5-year periods in a real-world population with moderate-to-severe CKD.

**Methods:** Patients with CKD stages 3 and 4 (N=20,947) were selected from electronic health records data in the CURE-CKD Registry from the UCLA (N=3,599) and Providence (N=17,348) Health systems. Patient demographics (age and sex), estimated glomerular filtration rate (eGFR), and log-normalized urine albumin/creatinine ratio were used for the 4-KFRE. The 6-KFRE was applied to patients who also had diabetes and hypertension.

**Results:** The prevalence of ESRD was 7% for the 2-year period and 11% for the 5-year period. The performance of the 6-KFRE and the 4-KFRE models was similar (4-KFRE is shown in Table 1). Specificity (0.994) reflects the model’s ability to predict non-ESRD patients, while sensitivity (0.135) signifies the ability to predict ESRD patients. The area under the precision-recall curve (PR-AUC) was 0.466, and the area under the receiver operating curve (AUC ROC) was 0.853, suggesting accurate KFRE predictions. The model performance improved with lower eGFR.

**Conclusions:** The KFRE equations depicted high performance when applied to a real-world population with moderate-to-severe CKD. While highly specific for ESRD, it lacked sensitivity, but improved for more advanced CKD stages.

**Results from the Four Variable KFRE (UCLA + Providence)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>2-Year Risk of ESRD</th>
<th>5-Year Risk of ESRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FF AUC</td>
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<tr>
<td>Average Precision</td>
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</tr>
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<tr>
<td>Briar Score</td>
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</tr>
</tbody>
</table>

**KFRE:** Kidney Failure Risk Equation; **ESRD:** end stage renal disease; **PPV:** positive predictive value; **FR AUC:** precision recall area under the receiver operating curve

**FR-PO937**  
** Colombian Validation of the Kidney Failure Risk Equation with Four Variables**  
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**Background:** Chronic Kidney Disease (CKD) programs need to identify patients at risk of progression. Our objective is to evaluate the performance of this 4 variables model in a real Colombian population where this risk model has not yet been validated.

**Methods:** Historical cohort of patients with stage 3, 4 and 5 CKD, adults, with no history of dialysis or kidney transplantation and with a two-year follow-up, belonging to the Renal Care Services Baxter Colombia clinic network. The performance model was evaluated using concordance index and the area under the time-dependent ROC curve, with the nearest neighbor method, as well as the sensitivity and specificity. The degree of agreement between the observed outcome and the probabilities predicted by the model was evaluated using concordance index and the area under the time-dependent ROC curve, with the nearest neighbor method.

**Results:** A total of 5477 patients were included, the mean age was 72 years, and the mean baseline eGFR was 36 mL/min/1.73 m². The rate of admission to dialysis therapy was 3 events per-100 patient years. See Figure 1. Sensitivity 0.938 and specificity 0.757, with the area under the ROC curve 0.92. Harrell C statistic was 0.88 per total population and ~65 year was 0.93. The validation of the model showed a good calibration, see Figure 2.

**Conclusions:** In this Colombian cohort, the kidney failure risk equation with 4 variables has excellent calibration and discrimination, therefore its use is recommended in the routine follow-up of these CKD prevention programs.

**Funding:** Commercial Support - Baxter Renal Care Services

**FR-PO938**  
**Validation of a Multimarker eGFR Equation in Preserved and Reduced eGFR Using the GENOA Cohort**  
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**Background:** Performance of the race-free CKD-EPI 2021 equation varies with severity of kidney disease. We sought to examine the performance of a novel multimarker eGFR panel (panel-eGFR) among Black and White persons stratified by eGFR categories using the biracial Genetic Epidemiology Network of Arteriopathy (GENOA) cohort.

**Methods:** We included 224 sex, race/ethnicity, and measured GFR (mGFR)-category-matched persons. GFR was measured using urinary clearance of iohalamate. Panel-eGFR was calculated using serum creatinine, valine, myo-inositol, cystatin C, age, and sex. All GFR’s are presented as mL/min/1.73 m². We compared panel-eGFR’s reliability to the 2021 CKD-EPI creatinine and cystatin C (eGFR-Cr-CysC) equation using bias, precision, and accuracy metrics between race (Black vs. White participants) and eGFR (eGFR-Cr-CysC) preserved eGFR vs. <60 or reduced eGFR) subgroups.

**Results:** In the overall cohort, 49% were Black individuals and 79% had eGFR-Cr-CysC >0.60. Among those with preserved eGFR, eGFR-Cr-CysC was lower than mGFR by ≥6.3. We compared panel-eGFR’s reliability to the 2021 CKD-EPI creatinine and cystatin C (eGFR-Cr-CysC) equation using bias, precision, and accuracy metrics between race (Black vs. White participants) and eGFR (eGFR-Cr-CysC) preserved eGFR vs. <60 or reduced eGFR) subgroups.

**Funding:** Commercial Support - Baxter Renal Care Services

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Conclusions: A novel panel-eGFR performs better than the current eGFR-Cr-CysC equation among persons with preserved eGFR, and this is consistent between Black and White persons.

Funding: Other U.S. Government Support

Predicting All-Cause Mortality in Patients with Advanced CKD

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Background: Patients with advanced CKD are at high risk of mortality, kidney failure and cardiovascular events. Accurately identifying patients that are at a higher risk for mortality may aid in decision making for dialysis and preventing unnecessary dialysis therapies that may cause more harm. We developed and externally validated a risk prediction tool using commonly collected clinical variables to predict all-cause mortality among patients with advanced CKD.

Methods: We developed a prediction model using demographic, clinical and laboratory data in adult patients (≥18 years) with advanced CKD (eGFR <30 mL/min/1.73m²) from Manitoba, Canada, between January 2012, and September 2020, with external validation from Ontario, Canada. Our primary outcome was all-cause mortality. Data was initiated in follow-up, we ascertained all-cause mortality within 1 year of dialysis initiation. We assessed model discrimination using the area under the receiver operating characteristic curve (AUC) and calibration using plots of observed and predicted risks.

The development cohort included 397 patients (mean age 65.4 ± 13.9) with 121 events. The final model included age, sex, estimated GFR, hemoglobin, serum albumin and congestive heart failure and achieved a 2-year and 5-year AUC of 74.3 (CI: 68.4 – 80.1) and 80.2 (CI: 75.3 – 85.1), respectively. Discrimination and calibration were adequate in the external validation data set with 2-year and 5-year AUC scores of 71.4 (CI: 70.8 – 72.0) and 73.0 (CI: 72.5 – 73.5).

Conclusions: We developed a simple prediction model that included commonly measured variables that can accurately predict all-cause mortality in patients with advanced CKD. This equation may aid as a support tool for nephrologists in dialysis decision making, especially in patients who are at high risk of mortality.

CKD Progression Model (CKD-PM): Development and Validation

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Background: Patients with CKD are at risk of disease progression and related complications. Existing CKD models are limited to the risk of end stage kidney disease (ESKD) and selected cardiovascular disease (CVD) outcomes. Our aim was to develop a CKD-PM that uses evolving risk factors to project risk of a broad range of CKD related complications.

Methods: Development of the CKD-PM was informed by systematic and targeted literature reviews of relevant models and risk factors for CKD progression and risk of complications. The result was a patient-level state transition model with KDIGO categories as health states. Evolving risk factors project CKD progression and occurrence of complications, with submodules for: CVD, infections, anemia, diabetes, hypertension, acidosis, hyperkalemia, mineral and bone disorders, hospitalisations, acute kidney injury, cancer and ESKD. Initial and external model validation was performed by comparing predicted outcomes with those observed in cohort studies, utilizing source study patient characteristics and follow up time. An ordinary least squares (OLS) linear regression line (LRL) was fitted to the data, and the slope was used to categorize the quality of the prediction. Deviation <2% from the perfect prediction (LRL slope = 1) was considered accurate (mild deviation), 25-50% deviation was considered moderate, and severe beyond 50%.

Results: Core inputs (mortality, CVD and evolution of risk factors including eGFR and uACR) were sourced primarily from two research groups: Chronic Renal Insufficiency (CRI) and Chronic Kidney Disease Prognosis Consortium (CKD-PC). Seven large CKD cohorts studies were used to validate the CKD-PM predictions. Both internal and external validation results demonstrated robust modeling properties.

All-cause mortality (ACM) was accurately projected, with mild under-prediction, either at the mean predicted (harmed by eGFR and uACR levels) or as a composite of CVD mortality, renal and other deaths. CVD mortality was mildly under-predicted in internal validation, and mildly over-predicted in external validation. Projected mean change of eGFR or uACR values and ESKD rates were within an acceptable range compared to external values.

Conclusions: CKD-PM is a comprehensive tool with robust modeling properties demonstrated through internal and external validation.

Funding: Commercial Support - Boehringer Ingelheim International GmbH

IMPACT CKD: Projecting the Growing Environmental Burden of CKD in the United States

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Background: Chronic kidney disease (CKD) is a significant source of morbidity and mortality with substantial costs associated with renal replacement therapy (RRT) (including dialysis and transplantation). However, it is imperative to understand the wider impact of CKD, including its societal and environmental consequences, to inform healthcare planning and policy development. This study aims to comprehensively quantify the burden of CKD in the United States (US).

Methods: A patient-level simulation model, IMPACT CKD, was developed to simulate the natural history of CKD progression while incorporating the impact of acute kidney injury, cardiovascular events and comorbidities. CKD status was assigned using estimated glomerular filtration rate (eGFR) and albuminuria levels, and clinical progression was predicted by annual eGFR decline rate. The model was used to forecast the 10-year impact of CKD on environment in the US in addition to clinical, economic, and societal outcomes. The model was calibrated and validated for a US setting.

Results: While CKD prevalence is predicted to remain steady from 2022 to 2032 (17%), the number of patients increases from 57 to 60 million. The projected distribution of CKD stages includes 38% in stage 1, 19% in stage 2, 34% in stage 3, 5% in stage 4, and 4% in stage 5 (including RRT) in 2032. Substantial increases are observed in stage 3 to pre-RRT stage 5 (14.5%) and the number of patients receiving RRT is expected to rise by 48% (882,026 to 1,303,141). Alongside the escalating clinical burden, CKD and RRT are poised to exert detrimental environmental impacts. Freshwater consumption, fossil fuel depletion, and CO₂ emissions are projected to rise by 26%, 26%, and 37% respectively, from 2022 to 2032. RRT accounts for the most substantial environmental burden, with projected contributions of 1.9 billion m³ of freshwater consumption, 26.9 billion kg of fossil fuel depletion, and 64.9 billion kg of CO₂ emissions over the next decade.

Conclusions: The IMPACT CKD model highlights the enduring burden of CKD in the US. With projected high prevalence and environmental burdens, improved management strategies mitigating the substantial environmental impact of CKD and RRT are vital for a healthier future.

Funding: Commercial Support - AstraZeneca

Moderest Reductions in Kidney Function and Adverse Outcomes in Young Adults

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Background: Whether modest declines in estimated glomerular filtration rate (eGFR below the expected values) are associated with adverse outcomes over the next decade.

Methods: We included 8.7 million adults (aged 18-65) with eGFR value using linked eGFR values by eGFR categories from Ontario from January 2008-March 2020. The association of eGFR categories from <60 to >120 mL/min/1.73m² and adverse outcomes (death, cardiovascular outcomes, end-stage kidney disease) was examined using adjusted Cox models. Comparisons were relative to age normalized measured GFR categories (100-110 mL/min/1.73m² for 16-19, 90-100 mL/min for 40-49, 60-79 mL/min for 50-65).

Results: The mean age, eGFR and median follow up were 41 years, 104 mL/min and 9.2 years, respectively. 17.3%, 18.9%, and 17.7% had an eGFR below normal for ages 18-39, 40-49, and 50-65, respectively. The risk of an adverse event increased in a stepwise manner with lower eGFR values by eGFR categories from 18 to 39 [eGFR 70-80, age 18-39: incidence 4.37 events per 1000 person-years [p-y], HR 1.54[1.46-1.61]; age 40-49: incidence 9.78 per 1000-p-y, HR 1.18[1.15-1.21]; age 50-65: incidence 24.0 per 1000-p-y, HR 1.11[1.10-1.12] (see Figure). Results persisted for each outcome individually, and after using repeated eGFR, using a common referent, and adjusting for multiple covariates.
Conclusions: Young adults (18-39) with an early eGFR decline were at a higher risk of adverse events and this occurred at higher eGFR levels relative to middle-aged and older adults.

Results: Participants: 1741 with median (IQR) age 74 (67-79) years, eGFR 53.8 (45.3-61.7) mL/min/1.73m², UACR 0.3 (0.001-1.5) mg/mmol; 16.9% diabetes at baseline. Outcomes: 680 deaths (39.1%); CKD progression in 430 of 1402 (30.7%) participants after a median 9.8 (9.2-10.1) years; only 24 of 1741 (1.4%) reached CKD stage 5. UACR increased from 0.3 (0.001-1.26) to 1.4 (0.3-5.90) mg/mmol (p<0.001) in 1188 participants with repeat measurements. Changes in KDIGO GFR category are presented in the table. CKD category improved in 161 (11.5%), progressed in 695 (49.6%) and did not change in 546 (38.9%). Logistic regression analysis identified male sex, diabetes status and lower baseline eGFR, higher baseline UACR and systolic blood pressure (SBP) as independent predictors of CKD progression. Cox Proportional Hazards models identified age, male sex, diabetes status, past or current smoking, lower baseline eGFR and higher baseline UACR as independent risk factors for all-cause mortality.

Conclusions: CKD progression was observed in a minority of participants and <2% reached CKD stage 5. The risk of CKD progression was exceeded by the competing risk of death. Our observations confirm that in primary care, persons with CKD require monitoring and interventions to minimise risk of adverse outcomes but few progress to kidney failure.

Funding: Commercial Support - Roche, Private Foundation Support

FR-PO943
Risk Analysis of Healthy Life Expectancy Based on Kidney Function Using the Long-Term Care and Medical Database

Background: The world’s population is rapidly aging, with the aging rate expected to reach 17.8% by 2060. Healthy life expectancy is known to be shortened by unhealthy diet, hypertension, smoking, obesity and diabetes. Kidney dysfunction is also expected to shorten healthy life expectancy due to its effects on physical inactivity, malnutrition, and atherosclerosis. This study aims to clarify the relationship between kidney function and healthy life expectancy.

Methods: This was a community-based historical cohort study of adults living from 2012 to 2022 in Hakui City, Ishikawa Prefecture, Japan. Participants were divided into five groups (<45, ≥45 to <60, ≥60 to <75, ≥75 to <89, and ≥90 mL/min/1.73 m²). The primary composite outcome was the event of unhealthy status (care level ≥2 or death). Care level ≥2 was a level of social support for those who have difficulty performing basic activities of daily living independently and require some form of nursing care in Japan’s long-term care system. Baseline risk factors included age, sex, body mass index, current smoking status, diabetes mellitus, systolic blood pressure, and social support level. Multivariable Cox proportional hazards model adjusted for baseline risk factors was used to estimate the risk of the primary outcome by eGFR group. Total annual healthcare cost, the sum of annual medical and long-term care cost, were examined as a secondary outcome.

Results: The number of participants was 5,592, the mean age was 67 years, the mean eGFR was 70.9 mL/min/1.73 m², and the mean follow-up was 6.5 years. During the observation period, 8.2% of the participants reached the primary outcome. For the primary outcome, using eGFR ≥60 to ≤75 as the reference, the hazard ratios (HRs) for eGFR ≥80 to <90 and eGFR ≥90 were 1.35 (95% CI 1.05, 1.75) and 1.93 (95% CI 1.41, 2.66), respectively. The HRs for the eGFR ≥90 to <90 and eGFR ≥90 groups were 1.48 (95% CI 1.14, 1.93) and 1.61 (95% CI 1.14, 2.28), respectively. The mean total healthcare cost for those who achieved the primary outcome was approximately 1,760,000 yen per year. The lower eGFR group had higher annual costs.

Conclusions: Both lower and higher eGFR were risk factors for becoming unhealthy, needing long-term care or death. Annual total healthcare costs were higher in people who became unhealthy.

Funding: Government Support - Non-U.S.

FR-PO944
Long-Term Outcomes in Persons with Stage 3 CKD Recruited from Primary Care
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Background: The majority of persons with chronic kidney disease (CKD) are elderly, have moderately reduced glomerular filtration rate (GFR) and are cared for in primary care in the UK. There are few long term studies to describe the risks of adverse outcomes in this under-studied population.

Methods: Participants with CKD stage 3 were recruited from primary care in 2008-10. Clinical assessment and investigations were performed at baseline, 1 and 5 years. In 2010-2020, electronic records were reviewed to obtain data on deaths and latest available outpatient estimated GFR (eGFR) and urine albumin to creatinine ratio (UACR). CKD progression was defined as a decline in eGFR of ≥25% and progression to a more advanced stage.

Figure: Trends in index estimated glomerular filtration rate (eGFR, in mL/min/1.73m²) and associated adjusted HRs of any adverse outcome (first of death, cardiovascular events, end-stage kidney disease) by continuous age

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

667
FR-PO946
Kidney Function and Mortality in the Mexico City Prospective Study

Background: Prospective studies in the US, Europe, Asia, and Australia have shown decreased kidney function is a strong predictor of mortality. There is limited data from Latin America where chronic kidney disease (CKD) is a major cause of morbidity and mortality.

Methods: In 1998-2004, 150,000 adults (aged ≥35 years) were recruited into the Mexico City Prospective Study, and followed for median 19 years. About 120,000 participants currently have nuclear magnetic resonance (NMR) spectroscopy-measured biomarkers in plasma, including creatinine. Cox regression was used to relate a single measurement of baseline eGFR (CKD-EPI equation) to mortality. Analyses were adjusted for age at risk, sex, district, education, smoking, alcohol, physical activity, height, weight, waist and hip circumference, and diabetes. They excluded those who at recruitment had incomplete data or prior chronic disease (except diabetes or CKD).

Results: Among the 33,423 men and 68,133 women aged 35-74 years with complete data, median (IQR) eGFR was 101 (90-109) mL/min/1.73 m², mean (SD) BMI was 29.1 (4.9) kg/m², 1% had self-reported CKD, 12% had previously-diagnosed diabetes, and 9,002 died at ages 35-74 years. Despite the inaccuracy of a single eGFR baseline measurement, eGFR <30 mL/min/1.73m² was associated with eight-fold higher all-cause mortality than eGFR 90-105 (HR 8.5 [95% CI, 8.3-7.5]). Below 90-105, every 15 mL/min/1.73m² lower eGFR was associated with 40% higher all-cause mortality (HR 1.40 [1.36-1.42] overall, and 1.37 [1.34-1.40] in those without self-reported CKD). eGFR was most strongly associated with renal deaths (HR 29.9 [24.4-36.9] for eGFR <30 vs 90-105) and vascular occlusive deaths (HR 6.2 [4.4-8.7]). Baseline assessments of blood pressure, lipids, and inflammation explained about a third of the association of eGFR with premature mortality.

Conclusions: In this study in Mexico, lower kidney function was strongly associated with increased premature mortality, with the association about twice as strong as previously reported in high-income countries.

Figure. Relevance of eGFR to ALL-CAUSE mortality at ages 35 to <75 years in the Mexico City Prospective Study.

FR-PO947
Prevalence and Significance of Family History of Kidney Disorders in the EHR in Three Large US Health Care Systems
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Background: Chronic kidney disease (CKD) affects 1 in 7 adults and has a strong genetic component with prior studies reporting ~15% of White patients and nearly 25% of Black patients with end-stage kidney disease (ESKD) having family history of ESKD. Little is known about the prevalence of family history of CKD and ESKD in electronic health records (EHRs).

Methods: We examined the prevalence of family history of CKD and ESKD among patients ≥18 years of age receiving primary care in 3 large health systems (Geisinger [n=454,740], Utah [n=215,432], New York University [NYU; n=284,890]). In additional analyses using Geisinger data, we used logistic regression, adjusted for age, sex, race, and ethnicity, to examine the association of family history of CKD and ESKD with having a diagnosis of CKD and ESKD.

Results: In a sample of 955,062 adults receiving primary care in 3 health systems, prevalence of family history of CKD was fairly similar across health systems (Geisinger 4.6%, Utah 4.0%, NYU 5.1%), as was family history of ESKD (Geisinger 0.8%, Utah 0.6%, NYU 0.9%). By comparison, 36.8% of patients at Geisinger had family history of diabetes. Individuals with a family history of CKD were at increased risks of having CKD (OR 1.86, 95% CI: 1.78, 1.94) and ESKD (OR 5.63, 95% CI: 5.12, 6.20). Similar risks were observed for family history of CKD with having CKD (OR 2.27, 95% CI: 2.07, 2.48) and ESKD (7.68, 95% CI: 6.55, 9.00). Among individuals with ESKD at Geisinger, Black patients were more likely than non-Black patients to have family history of kidney problems (27.1% vs. 19.5%; p<0.008) though not specifically family history of ESKD (6.9% vs. 6.4%; p=0.9).

Conclusions: EHR-reported family history of CKD is strongly associated with risks of CKD and ESKD and infrequently reported across 3 large health systems. Future research is needed on how to improve capture of this important CKD risk factor.
FR-PO949

Association Between Changes in Urinary Albumin and Protein Excretion and Risk of Kidney Failure in Patients with CKD: The CKD-JAC Study

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Background: There has been progress in studying albuminuria as a surrogate endpoint for kidney failure with replacement therapy (KFRT) in patients with chronic kidney disease (CKD). However, the relationship between changes in proteinuria and KFRT has not been well studied.

Methods: The Chronic Kidney Disease - Japan Cohort (CKD-JAC) is a prospective observational study of patients with CKD in Japan. This study used the CKD-JAC cohort to examine the associations between a twofold increase in albuminuria (urine albumin-creatinine ratio) within the first two years of follow-up and the subsequent development of KFRT. In addition, in the subgroup with available proteinuria during follow-up, the relationship between the doubling of proteinuria (urine protein-creatinine ratio) in the first and second year and KFRT was examined in a similar way. A multivariable Cox proportional hazards model was used for analyses.

Results: The study analyzed 1,753 patients with an average age of 60 years, a mean eGFR of 30 mL/min/1.73 m², and a mean albuminuria of 419 mg/gCr. In the observation period, 618 patients (35.2%) initiated kidney replacement therapy. The hazard ratio (HR) and 95% confidence interval of KFRT for a doubling of albuminuria within 2 years was 1.57 (1.46, 1.70). Further analysis of the subgroup with proteinuria demonstrated that a doubling of proteinuria was associated with KFRT at the 2-year change (HR 1.41 [1.25, 1.59]). A similar association was found for the 1-year change of proteinuria as well (HR 1.30 [1.15, 1.47]).

Conclusions: In subjects with CKD, a doubling of albuminuria within the first two years of follow-up could potentially serve as a surrogate endpoint for KFRT. Similarly, proteinuria could also be a surrogate endpoint for KFRT.

Funding: Commercial Support - Kyowa Kirin Co.,Ltd.

FR-PO950

Risk Factors for Progression to Kidney Failure in Patients with CKD Stages 3B and 4 in a Singaporean Cohort

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Background: The prevalence of chronic kidney disease (CKD) is increasing globally and the burden of kidney failure is also increasing. We aim to examine the risk factors for progression to kidney failure in patients with CKD stages 3B and 4 and develop a risk prediction model for predicting kidney failure in our local multi-ethnic population.

Methods: Demographics, clinical and laboratory data of patients with CKD stages 3B and 4 referred from polyclinics to Tan Tock Seng Hospital (TTSH) Renal Medicine between April 2017 to February 2022 were collected. The primary outcome was kidney failure defined as an estimated glomerular filtration rate (eGFR) <15 ml/min/1.73 m². The secondary outcome was that of a composite of kidney failure, death, doubling of serum creatinine and eGFR decline by 40%. Multivariable Cox proportional hazard regression analyses were used to evaluate risk factors for the primary outcome. A risk prediction model for predicting kidney failure was developed and performance was evaluated by C-statistic.

Results: There were 2033 patients with CKD 3B and 4 and referred from polyclinics to TTSH between 2017 to February 2022. 848 patients with less than 1 year of follow up was excluded (except if they developed kidney failure in less than 1 year, n=8). There were 1193 patients included in the analysis of which 66.3% had CKD 3B and 33.7% had CKD 4. The study analyzed 1,753 patients with an average age of 60 years, a mean eGFR of 30 mL/min/1.73 m², and a mean albuminuria of 419 mg/gCr. In the observation period, 618 patients (35.2%) initiated kidney replacement therapy. The hazard ratio (HR) and 95% confidence interval of KFRT for a doubling of albuminuria within 2 years was 1.57 (1.46, 1.70). Further analysis of the subgroup with proteinuria demonstrated that a doubling of proteinuria was associated with KFRT at the 2-year change (HR 1.41 [1.25, 1.59]). A similar association was found for the 1-year change of proteinuria as well (HR 1.30 [1.15, 1.47]).

Conclusions: The model for predicting kidney failure in patients with CKD stage 3B and 4 including the variables ethnicity, annual eGFR decline, baseline proteinuria and serum creatinine had a C-statistic of 0.69 and 0.73 and should be validated in a larger population of patients.

Funding: Commercial Support - Kyowa Kirin Co.,Ltd.

FR-PO951

Early-Stage Characteristics and Potential Predictors of CKD Among US Veterans

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Background: Chronic Kidney Disease (CKD) is prevalent but under-diagnosed across the world. Its prediction remains a formidable challenge, even when complete clinical and demographic information is available. We studied a large patient cohort from the US Department of Veterans Affairs (VA) in an effort to identify predictive characteristics common to those afflicted with CKD before the disease becomes clinically evident.

Methods: From a cohort of 692,942 veterans with stable eGFR >60 ml/min/1.73 m², we identified 174,627 patients who developed CKD within up to eight years following enrollment and compared them to patients who remained CKD free. Over these two patient subgroups, we calculated Pearson correlation coefficients for all baseline variable pairs and, for each such pair, we examined those that were differentially correlated as defined by an absolute difference of at least 0.15 between the CKD and non-CKD cohorts. Using a graph theoretic approach, we created finite, simple, undirected graphs, with variables of interest represented by vertices and edges weighted by correlation then thresholded. From these graphs we extracted dense subgraphs indicative of latent variable relationships to account for complex correlations.

Results: Age and a variety of specific comorbidities were correlated higher within the non-CKD subgroup than within the CKD subgroup. From graph theoretical analysis, we found that the Charlson index, congestive heart failure (CHF), myocardial infarctions (MI), and peripheral vascular disease (PVD) formed a dense subgraph indicative of highly interconnected disease relationships (Figure). Age and cardiovascular disease (CVD) only entered this putative network among non-CKD patients.

Conclusions: These results suggest that kidney disease belongs to a constellation of comorbidities that may help to act as predictors of incipient CKD. Chronological age may not play a prominent role in the development of comorbidities in patients with CKD, which may be explained by premature aging seen in CKD.

Funding: Veterans Affairs Support

FR-PO952

Physical Activity Is an Independent Predictor of CKD Development Among Healthy Individuals

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Background: The cardiovascular and metabolic benefits of physical activity have been discussed in length; however, the association between physical fitness and progression to kidney disease is lacking. We aimed to identify the association between cardiorespiratory fitness and development of chronic kidney disease (CKD) among healthy population.

Methods: We investigated 11,579 healthy self-referred subjects who underwent annual medical screening. All subjects had an eGFR above 60 ml/min/1.73m², no known kidney disease, hematura or proteinuria, and were free of diabetes or cardiovascular disease at baseline. All participants completed a maximal exercise test, and were categorized into low and high cardiorespiratory fitness groups based on age- and gender-specific quintiles. The primary end point was the development of CKD defined as eGFR below 45 ml/min/1.73m² during follow-up.

Results: Median follow-up was 7.6 years, and the median participants’ age was 59±5years. Baseline creatinine and eGFR were 1.02 mg/dl and 81 ml/min/1.73m², respectively. During follow-up, 81 (0.6%) participants developed CKD, the cumulative probability being significantly higher in the low fitness group (HR=2.41, p<0.001). The effect of physical fitness on the risk to develop CKD remained significant after adjusting for age, gender, baseline creatinine and other cardiovascular risk factors.

Conclusions: Cardiorespiratory fitness is an independently risk factor inversely associated with development of significant CKD.

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

669
Association Between Physical Activity and Renal Outcomes in Patients with CKD G3b-5: A Result from a Japanese Cohort Study, the REACH-J

Hirokazu Kunihiro vs. -2.62 [-2.83, -2.41] mL/min/1.73m² rate of eGFR decline compared to 278 matched non-CKD patients (-1.28 [-1.87, -0.69])

Background: Association between physical activity and renal outcome in patients with chronic kidney disease (CKD) has remained largely unexamined.

Methods: We recruited 2,249 advanced CKD patients (eGFR<45 mL/min/1.73m²) receiving nephrology care from a national sample of 31 facilities throughout Japan, randomly selected with stratification by region and facility size, aligned with the international CKD Outcomes and Practice Patterns Study (CKDopps). Association between physical activity levels (active or inactive, from Rapid Assessment of Physical Activity (RAPA) surveys) and 5-year renal outcomes (40% eGFR decline, end-stage kidney disease, or death) were analyzed.

Results: Of 1,808 eligible CKD patients with RAPA assessment, 407 patients with diabetic kidney disease (DKD) and 1,401 patients without diabetes (non-DKD) were enrolled. Among them, 1,237 patients (68% of total, 66% of DKD and 69% of non-DKD) were categorized “active” (often active or very active by RAPA score), and others were categorized “inactive.” The mean ages and eGFRs in “active” and “inactive” patients were 68.5±12.5 and 70.8±11.7 years, and 24.1±10.4 and 22.1±10.4 mL/min/1.73m², respectively. Crude rates for DKD progression per 100 person-years in “active” and “inactive” patients were 19.4 and 22.1 events in DKD, and 12.1 and 13.7 events in non-DKD, respectively. In addition, crude rates for mortality in these patients were 3.9 and 4.8 events in DKD, and 1.8 and 3.8 events in non-DKD, respectively. Composite CKD progression and mortality were considerably lower at higher physical activity in both DKD and non-DKD patients, with hazard ratios of 0.84 (0.66, 1.08) and 0.80 (0.69, 0.93), respectively.

Conclusions: This multicenter study suggested the association between higher physical activity and lower CKD progression and better survival in both DKD and non-DKD patients. These findings may support future studies understanding impact of physical activity for better renal outcomes in patients with CKD stage G3b-5.

FR-P0954

Longitudinal Impacts of Bariatric Surgery on Renal Function in CKD

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Background: Prior studies of obesity show improved renal function after bariatric surgery. This study examines renal function over 10 years pre- and post-bariatric surgery among patients with a reduced baseline eGFR, including patients with CKD.

Methods: Retrospective cohorts of patients with CKD and/or who underwent bariatric surgery prior to 11/30/22 were identified from the Michigan Medicine EHR using ICD-10 and CPT codes. Multivariable piecewise linear mixed models were fit on eGFR (2021 CKD-EPI), adjusting for age, gender, race, ethnicity, BMI, hypertension, diabetes, and surgery type or CKD stage. Pre- and post-surgery eGFR trajectories were compared in patients with a baseline eGFR<90, eGFR trajectories were then compared between CKD patients post-surgery and either propensity score-matched non-CKD patients post-surgery or CKD patients who did not undergo surgery.

Results: Patients with baseline eGFR<90 (n=688) had a slower annual rate of eGFR decline [95% CI] post vs. pre-surgery (-1.85 [-1.97, -1.72] vs. -3.22 [-3.41, -3.02] mL/min/1.73m²; p<0.001). Following surgery, CKD patients (n=139) had a slower annual rate of eGFR decline compared to 278 matched non-CKD patients (-1.28 [-1.87, -0.69] vs. -2.62 [-2.83, -2.41] mL/min/1.73m²; p<0.001). Annual eGFR decline was also slower among patients with CKD post-surgery compared to 278 matched non-CKD patients whose weights were stable (0.71 [-1.11, -0.32] mL/min/1.73m²; p<0.001).

Conclusions: Bariatric surgery is associated with a slower rate of eGFR decline in patients with a reduced baseline eGFR, including patients with CKD. Future modeling of proteinuria may support these findings and identify if the faster eGFR decline in healthy patients correlates to a decrease in glomerular hyperfiltration after surgery.

Funding: Other NIH Support - NIH T35 Short Term Training Program (Grant 5T35HL007690-38)

FR-P0955

Association Between Weight Change from 20 Years of Age and the Risk of All-Cause and Cardiovascular Mortality in Patients with CKD

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Background: Weight changes from a young age have been reported as being linked to poor life outcomes in the general population. However, little is known concerning the association between weight changes from a young age and life expectancy in patients with chronic kidney disease (CKD).

Methods: The data of 2,806 non-dialysis CKD patients who participated in the Fukuoka Kidney disease Registry (FKR) Study, a multi-center observational study, were analyzed. All-cause mortality was the primary outcome, while cardiovascular mortality was a secondary outcome. The covariate of interest was weight change, defined as the difference between body weight at study enrolment and that at 20 years of age. We estimated the risks of mortality for participants with weight changes of ≥5 or <5 kg using Cox proportional hazards models, as compared to those with stable weights.

Results: In total, 243 participants (8.7% of the total) died from all-cause, and 62 participants died from cardiovascular disease within the 5-year observation period. The risk of all-cause mortality was significantly higher in the weight loss group than in the stable weight group (multivariable-adjusted hazard ratio [95% confidence interval], 2.11 [1.52–2.93]). In addition, the risk of cardiovascular mortality was significantly higher in the weight loss group than in the stable weight group (multivariable-adjusted hazard ratio [95% confidence interval], 2.48 [1.32–4.64]). No significant associations were found between weight gain and the risks of all-cause and cardiovascular mortality.

Conclusions: Weight loss since 20 years of age is associated with increased risks of all-cause and cardiovascular mortality in non-dialysis CKD patients.

FR-P0956

Appraisal of a Simplified Protein Energy Wasting Score in CKD Patients at a Single University-Based Hospital: A Five-Year Retrospective Cohort Study

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Background: Undernutrition poses a significant complication of chronic kidney disease (CKD), leading to devastating effects on quality of life, morbidity, hospitalization, and mortality. We developed a novel Protein Energy Wasting (PEW) score, utilizing the nomenclature proposed by the International Society of Renal Nutrition and Metabolism in 2008.

Methods: We enrolled participants aged 18 years or older, with CKD stages G3 to G5N/D between January 2016 and December 2020. These were utilized for diagnosing PEW using the simplified PEW score (sPEW). The sPEW was defined by the following criteria (Figure 1), and the Lean Body Mass Index (LBMI = LBMheight2) was subsequently determined.

Predicted values of eGFR (95% CI) from adjusted linear mixed models of (a) patients with baseline eGFR<90, (b) bariatric surgery patients with/without CKD, and (c) CKD patients with/without bariatric surgery.
Results: In total, 224 patients were identified (64% male, 36% female; mean age 77 years), with the majority classified as stages 3a, 3b, and 4 CKD (41%, 38%, and 18%, respectively). The prevalence, according to the sPEW score, showed 85 (38%) with mild PEW, 26 (12%) with moderate PEW, and four (2%) with severe PEW. LBMI was 17.3 ± 22.4, 15.7 ± 1.9, 15.5 ± 2.1, and 13.5 ± 0.5 kg/m² in the none, mild, moderate, and severe sPEW groups, respectively (P < 0.001). The multiple linear regression analysis indicated that changes in lean body mass index negatively correlated with changes in the sPEW score and gender (P < 0.001) (Figure 2).

Conclusions: These studies suggest that the sPEW, when used in CKD patients, appears to reflect the LBMI in these populations. Further research is required to determine the validity of the sPEW as a nutritional marker and to explore its predictive value for other clinical outcomes in CKD patients.

<table>
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<th>Outcome</th>
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<th>p-value</th>
<th>Beta Coefficient (95% CI)</th>
<th>p-value</th>
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<td>eGFR</td>
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<td>0.04</td>
<td>5.38 (1.09 to 8.68)</td>
<td>0.01</td>
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<td>SBP</td>
<td>0.43 (0.04 to 0.84)</td>
<td>0.04</td>
<td>1.38 (0.23 to 5.51)</td>
<td>0.01</td>
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*Adjusted for age, sex, education, income, smoking, diabetes, obesity, and SBP (for eGFR), Clinical Center as Random Effect

FR-PO957

Food Insecurity and High Blood Pressure Among Individuals with CKD in West Africa
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Background: Based on the Diet, CKD, and ApolipoproteinL1 (DCA) study data, this cross-sectional study examines the relationship of food insecurity with estimated glomerular filtration rate (eGFR) and systolic and diastolic blood pressure (SBP and DBP). Very few studies have yet studied these associations in sub-Saharan African populations. Understanding the impact of food insecurity is crucial to guide care for patients with CKD.

Methods: We recruited 570 participants with CKD (eGFR < 60 mL/min/1.73 m²) from seven centers in the H3Africa Kidney Disease study. We measured food insecurity using a standardized question, “Did you cut meals size/skip meals because there was insufficient money during the past year?” We used mixed-effect linear regression models with clinical centers as random intercepts. Outcomes were measured from 3,424 abstracts, 52 citations representing 39 distinct studies were included. Sample sizes ranged from 52 to 7,091,324; mean age ranged from 45 to 79 years and the percentage of males from 35% to 98%. Direct medical costs ranged from $6,592 to $280,727 per patient. In studies of CKD-only patients reporting costs by stage (n=5), costs ranged from $6,592 (stage 3) to $143,745 (end stage kidney disease [ESKD]). Of studies evaluating comorbidities (n=14), patients with DM had costs as high as $280,727 (new onset ESKD & DM), while those with CVD had costs as high as $78,742 (CKD & heart failure). No studies investigated costs among those with comorbid obesity. In studies reporting components of medical costs for CKD-only (n=7), inpatient costs tended to be the largest component ranging from $2,331 to $116,309. No trend was observed in costs by payer type.

Conclusions: The review found that direct medical costs among patients with CKD continue to be high, primarily driven by inpatient costs. Other contributory factors included advanced CKD stages and presence of cardiometabolic comorbidities.

FR-PO958

Economic Burden of CKD in the United States: A Systematic Literature Review
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Background: With nearly 37 million cases of CKD in the US, the economic impact is substantial. To fully understand the economic burden of CKD to payers with health systems, as well as drivers of burden, a comprehensive assessment of the current evidence base is needed. This review aimed to characterize direct medical costs of those diagnosed with CKD in the US, overall and by CKD stage, insurance type, and presence of diabetes mellitus (DM), cardiovascular disease (CVD), and obesity.

Methods: A systematic literature review was conducted using MEDLINE and Embase, supplemented by a grey literature search, to identify studies reporting direct medical costs for CKD in the US, published between 01/01/2017 and 07/27/2022. Conference proceedings from 2020 to 2022 that were identified in the search were also considered for inclusion. Two reviewers independently performed study selection and data extraction according to PRISMA guidelines. Patient characteristics and cost estimates were summarized; mean annual cost estimates were converted to 2022 USD and reported.

Results: From 3,424 abstracts, 52 citations representing 39 distinct studies were included. Sample sizes ranged from 52 to 7,091,324; mean age ranged from 45 to 79 years and the percentage of males from 35% to 98%. Direct medical costs ranged from $6,592 to $280,727 per patient. In studies of CKD-only patients reporting costs by stage (n=5), costs ranged from $6,592 (stage 3) to $143,745 (end stage kidney disease [ESKD]). Of studies evaluating comorbidities (n=14), patients with DM had costs as high as $280,727 (new onset ESKD & DM), while those with CVD had costs as high as $78,742 (CKD & heart failure). No studies investigated costs among those with comorbid obesity. In studies reporting components of medical costs for CKD-only (n=7), inpatient costs tended to be the largest component ranging from $2,331 to $116,309. No trend was observed in costs by payer type.

Conclusions: The study found that direct medical costs among patients with CKD continue to be high, primarily driven by inpatient costs. Other contributory factors included advanced CKD stages and presence of cardiometabolic comorbidities.

Funding: Commercial Support - This study was funded by Boehringer Ingelheim.

FR-PO959

Improving Compliance with CKD Screening and Monitoring in a Resident Continuity Clinic

Background: Chronic kidney disease (CKD) is a significant burden on the adult population, affecting up to 1 in 10 individuals. Early identification and intervention in early-stage CKD are crucial for preventing cardiovascular morbidity and mortality, as well as the availability of advanced treatment options. Guidelines recommend annual measurement of estimated glomerular filtration rate (eGFR) and proteinuria quantification in individuals at risk of CKD or early-stage CKD. As only one third of primary care providers (PCPs) are completely confident in how to screen, diagnose, and manage CKD, we hypothesized that compliance with CKD monitoring and screening would be suboptimal in our Resident Continuity Clinic (RCC).

Methods: We conducted a quality improvement project in our RCC, comprising 34 internal medicine resident physicians serving as PCPs. We focused on patients seen in the RCC between July 1, 2020 and February 28, 2023. We assessed CKD monitoring by determining the percentage of patients with CKD, diabetes, or hypertension who underwent at least one measurement of eGFR and urine protein/creatinine or urine albumin/creatinine ratio (ACR) during the study timeframe. Patients were considered to have diabetes, hypertension, or CKD if the disease specific ICD-10 code was present on their chart.

Results: 59% of the 1,811 patients seen in the RCC during the evaluation period had CKD, diabetes, or hypertension. While eGFR was measured in 90% of these patients, only 26% had an eGFR and proteinuria measured. To address this gap, we implemented Plan-Do-Study-Act cycles to include resident education, introduction of an order set in the electronic medical record (EMR) to facilitate appropriate laboratory testing, and an

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
EMR update to prompt PCPs to order yearly urine ACR for patients with diabetes. Post-implementation data will be collected quarterly, with initial results available July 2023.

Conclusions: Despite satisfactory adherence to eGFR measurements, proteinuria evaluation was underutilized. Proteinuria is an independent predictor of cardiovascular morbidity and mortality and CKD progression and has therapeutic implications. Our findings highlight the need for healthcare system interventions to ensure proper proteinuria evaluation in patients at risk for CKD.

FR-PO960
Investigating Barriers to Implementation of Functional Status Assessments in CKD Care: A Mixed Methods Study Among Stakeholders
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Background: Chronic kidney disease (CKD) clinical practice guidelines (CPG) recommend regular functional status assessments at all stages of CKD to identify those at high risk for poor functional decline. However, functional status tests are not routinely incorporated into CKD care, and the reasons for this gap have not been explored.

Methods: We used the Consolidated Framework for Implementation Research (CFIR) to guide survey and interview questions to identify barriers to implementing CPG recommended functional status assessments in CKD care. Online survey invitations were sent to stakeholders in CKD care, including staff providing direct care and administrators with decision-making roles in a large health system in southeastern Pennsylvania. Volunteers among survey respondents participated in phone interviews with a qualitative researcher. Interviews were transcribed verbatim and de-identified. Transcripts were analyzed with inductive coding as well as deductive coding using CFIR domains, and codes were grouped into themes.

Results: Thirty-nine stakeholders in CKD care responded to surveys: 28 were nephrologists, 9 were other care staff, and 2 were administrators; 62% were women, 59% White, 31% Asian, and 5% Black. Only 36% were aware of CPG recommendations for functional testing in CKD care and 22% reported that testing was currently performed. Two-thirds of respondents agreed that functional testing should be performed in CKD care (66%) and that these tests could be conducted effectively in their clinics (69%). In the survey, the three most commonly selected barriers to performing functional testing were: clinical burden, lack of familiarity with tools, and lack of space and/or equipment. Seven respondents volunteered to be interviewed (3 nephrologists, 4 advanced practitioners). Themes identified as barriers to CPG implementation included: limited awareness/knowledge, limited resources (time, space), lack of competence/confidence in conducting tests and interpreting results, and lack of a standard operating procedure for testing.

Conclusions: Identified barriers, including limited awareness/knowledge, resources (time, space, equipment), and a standard procedure will inform strategies to improve the implementation of CPG recommended functional testing in CKD care.

Funding: Private Foundation Support

FR-PO961
Implementation of the Kidney Failure Risk Equation in a U.S Nephrology Clinic
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1The Johns Hopkins University School of Medicine, Baltimore, MD; 2Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 3New York University Grossman School of Medicine, New York, NY.

Background: The kidney failure risk equation (KFRE) estimates a person’s risk of kidney failure. We explored implementation of the KFRE in a U.S nephrology clinic.

Methods: We integrated KFRE scores into the electronic health record (EHR) for patients with CKD being seen in Johns Hopkins nephrology clinics. We quantified documentation of KFRE scores in clinic notes and conducted surveys and focus groups of nephrology providers to assess provider perspectives on its use. Focus groups were audio-recorded and transcripts were coded using thematic analysis.

Results: Documentation of KFRE scores increased over time, reaching 25% of all eligible outpatient nephrology clinic notes after 11 months. Of 44 nephrology providers, 3 documented KFRE scores in > 75% of notes, whereas 25 documented scores in < 10% of notes. Survey respondents (n=25) reported variability in use of KFRE scores for decisions such as maintaining nephrology care, referring for transplant evaluation, or providing dialysis modality education. Provider perspectives, assessed by qualitative analysis of focus groups transcripts, included three common themes: 1) KFRE scores may be most impactful in care of specific subsets of people with CKD; 2) there is uncertainty surrounding KFRE risk-based thresholds to guide clinical care, and 3) education of patients, nephrology providers, and non-nephrology providers on appropriate interpretations of KFRE scores may help maximize their utility. Based upon these findings, we propose key components of KFRE implementation as a roadmap for future efforts to increase its use in clinical care (Figure).

Conclusions: KFRE score documentation increased over time, with variability in adoption by providers. Further knowledge surrounding utilization of the KFRE in clinical decisions may enhance its implementation.

Funding: NIDDK Support

FR-PO962
A Quality Improvement Initiative to Bridge Gaps in Treatment and Interprofessional Care of CKD
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Background: Diagnosing, treating, and coordinating care for patients with chronic kidney disease (CKD) can be challenging, contributing to gaps in the quality of care in CKD. Uncovering the needs of nephrology care teams treating patients with CKD can help to close these gaps and improve patient outcomes.

Methods: A quality improvement (QI) initiative within 5 nephrology clinics was conducted to assess current practice and develop surveys administered to nephrology care team members (n=83). Each center then participated in an interactive audit-feedback educational session with a national CKD expert and developed action plans to address system-specific barriers to treatment.

Results: Provider surveys identified gaps in patients meeting clinical targets and receiving guideline-directed care. Notably, 37% of providers reported less than half of their CKD patients were receiving blood pressure targets and 67% of providers reported that less than half of their CKD patients were meeting HbA1C targets. When CKD care team members were asked how many of their patients with CKD were prescribed an SGLT2 inhibitor, 53% of respondents reported that less than 25% of their patients were receiving an SGLT2 inhibitor as part of their treatment plan (Fig. 1). Following the intervention, CKD care team members prioritized the following areas for improvement to support patients and align clinical practice with current guideline recommendations: 1) patient education to improve lifestyle modification (41%), 2) developing individualized treatment plans based on patient specific factors (22%), and 3) improving co-management of patients with primary care physicians and other specialists (22%).

Conclusions: The surveys identified real-world challenges inhibiting patients from achieving clinical targets and contributing to discordances with guideline-directed treatment recommendations. Overall, QI programs for interprofessional CKD care teams are critical tools for understanding and addressing system-specific barriers to effective treatment of CKD.
FR-PO963
The Role of Patients’ Education in Improving Quality Outcomes in CKD
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Background: CKD prevalence in US is ~14%. The measures to delay CKD progression are well known to providers but not to most patients with CKD, specifically minorities and patients in the lower socioeconomic class. Providing intense CKD education can improve quality outcome in this population and delays dialysis requirement. Home dialysis (HoD) therapies have been associated with improved quality of life and reduced costs, in US HoD percentage is ~13%. Currently most patients start dialysis with central venous catheter (CVC) – 85% US, our goal is to increase HoD, efficiency of arteriovenous fistula (AVF) or arteriovenous graft (AVG) placement, and to increase referrals and listing for kidney transplantations (KT), as suggested in ESRD treatment choice model.

Methods: We initiated a CKD education clinic (CKDEC) with 3 aims: delay the progression for CKD and onset of dialysis, increase the number of HoD, improve access and timely referral to KT. Individuals who attend the clinic will be educated to avoid the factors and behaviors that can expedite CKD progression and dialysis initiation.

Results: 209 patients that are CKD IV and V at our outpatient facility & 25 dialysis. Of those, whose HoD after CKDEC are 14.3%. This is higher than the national rate of 13%. CKDEC improved referral rate to KT and CVC rate (Table 1). Many of our patients who started dialysis in 2021-2022 used CVC (71%) after CKDEC, this is lower than the national CVC rate (83%) image 1.

Conclusions: CKDEC improves HoD rate, referrals to KT and dialysis access among CKD but not ESRD group. we need to continue earlier access to CKD education clinic to continue to improve our outcome measures.

Table 1

<table>
<thead>
<tr>
<th>CKD Education</th>
<th>CVC Access</th>
<th>NE Access</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD IV</td>
<td>42.8%</td>
<td>23.8%</td>
</tr>
<tr>
<td>CKD V</td>
<td>71.6%</td>
<td>52.8%</td>
</tr>
</tbody>
</table>

CKD: chronic kidney disease education clinic. NE: did not attend CKDEC

FR-PO964
Optimizing Palliative Care Referrals for Veterans with Kidney Disease in the Iowa City VA Health Care System
Melissa L. Swee, Quiso Shi, Mary V. Sarrazin, Benjamin R. Griffin, Masaki Yamada, Meenakshi Sambharia, Diana I. Jalal. University of Iowa Hospitals and Clinics, Iowa City, IA; Iowa City VA Medical Center, Iowa City, IA.

Background: The kidney clinic at Iowa City VA (ICVA) sees 20-40 patients weekly, with an estimated 5-15% benefiting from palliative care referrals. Hospice aims to enhance end-of-life care and timely referral to KT. Individuals who attend the clinic will be educated to avoid the factors and behaviors that can expedite CKD progression and dialysis initiation.

Methods: We aimed to evaluate delays in kidney disease referrals to palliative care and enhance appropriate referral percentage. Mixed methods were used, reviewing referral data and examining qualitative barriers. Three iterative Plan-Do-Study-Act (PDSA) cycles were implemented. The first focused on educating the kidney team to consider the patient holistically. The question, “Would death within six months not be unexpected?” was introduced. The second involved a multidisciplinary conference, broadening education. The third prospectively reviewed charts of returning patients to identify referral candidates.

Results: Analysis using a Statistical Process Control (SPC) p-chart showed consistent low referrals (<10% of eligible Veterans), indicating the need for improvement. Barriers identified included referral forms at ICVA, and timely access to CKD education clinic.

Conclusions: Our project has not entered the sustainability phase, as there has been no significant improvement in referrals for eligible patients. Further iterative PDSA cycles are necessary to integrate palliative care effectively. Future efforts will focus on reducing disparities in accessing palliative care through virtual visits. We aim to align resources in the kidney clinic, increase efficiency, and consider implementing an opt-out process for Veterans on dialysis or with significant kidney disease. By addressing these challenges, we aim to improve appropriate palliative care referrals, enhance end-of-life care for kidney disease patients at ICVA, and provide early access to specialized person-centered care, ultimately improving their quality of life.

Funding: Private Foundation Support

FR-PO965
Impact of Conservative Management vs. Dialysis Transition on Survival in a National Advanced CKD Cohort
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Background: While dialysis has been the dominant treatment paradigm in advanced CKD patients progressing to ESKD, this approach may lead to impaired physical function, independence, and quality of life among certain subpopulations. We compared the impact of non-dialytic conservative management (CM) vs. dialysis on survival in a national advanced CKD cohort.

Methods: We compared survival in advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25) over 1/1/07-6/30/20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical, pharmacy claims and enrollment records for commercial/Medicare Advantage enrollees, and EHR data. In secondary analyses, we examined older patients of diabetes, defined as earlier dialysis (ED) vs. later dialysis (LD) (eGFR ≥15 vs. <15 at dialysis transition), and in tertiary analyses we compared ED, intermediate dialysis (ID), vs. very late dialysis (VLD) (eGFRs ≥15, ≤<10, <10 at dialysis transition). We compared survival in CM vs. patients matched by propensity score (PS) in a 1:1 ratio to address confounding by indication using Cox models.

Results: 28,829 CM patients PS-matched to 28,829 dialysis patients, dialysis transition was associated with higher mortality vs. CM: HR (95%CI) 1.18 (1.16, 1.21). In secondary analyses, both ED and LD were each associated with higher mortality vs. CM: HRs (95%CI)s 1.21 (1.17, 1.25) and 1.17 (1.14, 1.20), respectively. In tertiary analyses, increasingly earlier dialysis transition was associated with worse survival vs. CM. Similar findings were observed in sensitivity analyses with CM and dialysis having lower mortality risk compared to CM, irrespective of dialysis transition timing. Further studies are needed to examine the comparative effectiveness of CM vs. dialysis on CKD outcomes.

Funding: NIDDK Support

FR-PO966
Ambulatory Palliative Care (PC) in Advanced CKD
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Background: Under 10% of patients on dialysis discuss goals, values, and preferences with their nephrologist; nearly 90% want to. PC can enhance patient quality of life, improve illness understanding and alter decisions at end of life. Global ambulatory renal PC clinics have been successful but are rare in the US. We tested the feasibility of integrating ambulatory PC for patients with CKD via manual EMR screening.

Methods: Renal and PC developed screening criteria: 1. Age ≥70 w/ stage 5 CKD 2. Age >70 w/ stage 4 CKD and cardiovascular disease or diabetes 3. Age ≥80 w/ stage 4 CKD For 11 weeks, study staff used the EMR to screen patients scheduled in renal clinic. A list of patients who met criteria were emailed to renal providers. If deemed appropriate, renal introduced PC to the patient. If the patient agreed, a PC referral was placed. PC saw referred patients before or after their renal clinic visit in the same room.

Results: See Fig 1. Renal agreed 33% of patients who met criteria were PC appropriate. Of patients who met criteria, 19% were seen by PC (Fig 2). PC saw significantly more patients in the 3 months after the intervention (n=22), compared to before the intervention (n=3). [χ² = 13.4; p<0.001].

Conclusions: Our study showed the feasibility of using screening criteria to integrate PC for advanced CKD patients. The continued increase in PC visits after the study suggests a change in practice and improved access to PC. Our model for an integrated renal PC clinic promotes patient centered care for patients with advanced CKD.
**FR-PO967**

**Effect of Social Support on Response to Treatment of Depression in Patients with CKD**

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**Background:** The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) was a randomized, double-blind, placebo-controlled trial of sertraline vs. placebo in patients with nondialysis CKD, which did not reveal a statistically significant improvement in depressive symptoms. Using the validated Kidney Disease Quality of Life Questionnaire (KDQOL) and Quick Inventory of Depressive Symptomatology-Clinician Rated scale (QIDS-C), we investigated whether higher baseline social support would affect adherence to study drug by pill count and improve response to antidepressant treatment.

**Methods:** Two-hundred-and-one patients with stages 3b-5 non-dialysis CKD were enrolled. The primary outcome was improvement in depressive symptoms from baseline to 12 weeks by QIDS-C (higher score, more depression), stratified by baseline social function tertiles (higher tertile, higher social function). The interaction of treatment group (sertraline vs. placebo) by social function was also tested.

**Results:** Mean age was 58.2±13.2 years. Those in the highest tertile of social function were more likely to be older (p=0.002), male (p=0.01), live alone (p=0.04), and be less educated (p=0.009) than the lowest tertile. Baseline CKD stage or eGFR did not differ between tertiles. Participants with the highest level of social function at baseline had the largest decrease in QIDS-C score if treated with placebo (-7.13), but participants with the lowest level of social function had the largest decrease in QIDS-C if treated with sertraline (-5.87), interaction p=0.03. There was a stepwise increase in percent of drug taken (88%, 95%, and 97%) for lowest, middle and highest tertiles of social function in the sertraline group (p=0.008) which was not observed in the placebo group. In addition, there was a significant interaction such that participants assigned to sertraline took a higher percent of drug than participants assigned to placebo, interaction p=0.01.

**Conclusions:** Sertraline may be more effective than placebo for improving depression in those with non-dialysis CKD with worse social functioning at baseline, even though participants with lower social function may be less adherent to antidepressant medications.

**FR-PO968**

**Unexpected Improvement of CKD After Removal of Over-the-Counter Agent**

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**Introduction:** Prescription and over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) represent an important component in the treatment of acute and chronic pain. Products containing salicylates are one of the most widely used medications. They can be found in topical ointments, lotions, solutions used in hot steam, and oral and topical analgesics. Approximately 10-30% of salicylates are excreted via the kidneys as free salicylic acid but it is unknown whether the efficacy may be due to direct local absorption or the result of systemic absorption and distribution throughout the vasculature. Here we present a worsening of chronic kidney disease with OTC topical analgesic.

**Case Description:** Case of a 65-year-old male with a past medical history of CHF, DM2 and CKD who presented with shortness of breath. Patient with bilateral lung crackles and peripheral edema, who was admitted due to decompensated CHF. Medication regimen included aspirin, atorvastatin, metoprolol succinate, lisinopril, spironolactone and empagliflozin, and NSAIDs use was denied. Laboratory remarkable for worsening renal function. Patient’s nephrotoxic medications were placed on hold and his creatinine level started to improve after careful IV diuresis. Upon achieving euveleemia, the diuretic was transitioned to oral. All of a sudden his renal function started to decline. Renal ultrasound resulted with no obstructive uropathy but with cortical thinning and increased echotexture. Uralysis analysis was remarkable for few epithelial cells. FEUrea resulted in 41.7%, suggestive of intrinsic damage. Upon further questioning, the patient had been using a topical methyl-salicylate every 4 hours for articcular and muscle pain without disclosing it for 48-72 hours. Once topical NSAIDs were removed, and IV hydration was implemented the serum creatinine gradually returned to baseline in the following days.

**Discussion:** Topical NSAIDs has been less associated with renal impairment than the oral route. Around 9.3% of patients with salicylate poisoning develop AKI and increased risk of organ failure, in-hospital mortality, longer length of hospital stay, and higher cost of hospitalization. This case highlights the importance of a careful review of patients’ medication history including OTC medication and raises concern of potential role and impact on renal function not well known by topical NSAIDs.

**FR-PO969**

**Association Between Laxative Use and Serum Phosphate Levels in Patients with CKD: A Large Nationwide Observational Study of US Veterans**

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1The University of Tennessee Health Science Center, Memphis, TN;
2University of California Irvine, Irvine, CA; 3VA Memphis Medical Center, Memphis, TN.

**Background:** Reducing intestinal phosphate (P) absorption is key to maintain normal P balance in patients with CKD. Laxative use may enhance faecal P excretion and help reduce serum P levels; however, little is known about the association of laxative use with serum P levels. We examined the association of time-varying non-P-containing laxatives with serum P levels in patients with CKD from a large nationwide cohort of United States Veterans Affairs (VA) health care system.

**Methods:** In a nationwide cohort of 513,653 US veterans receiving care from the VA healthcare system from 2004-2006 and with ≥1 outpatient serum P measurements during the follow-up through 2018, we examined the association of time-varying non-P-containing laxative use with serum P levels across CKD stages, using generalized estimating equations with adjustment for demographics, smoking status, BMI, comorbidities, and time-varying use of relevant drugs, number of different types of laxatives, serum calcium, and eGFR. Serum P levels at each P measurement were treated as a repeated multinomial outcome (i.e., <2.5 [low-P], 2.5-3.5 [normal-P: reference], >3.5 mEq/L [high-P]).

**Results:** Patients were 66.5±11.9 years old; 94.3% were male; 20.9% were African American; and 39.4% were diabetic. Their baseline eGFR was 76.8±23.5 mL/min/1.73m². There was no significant interaction between laxative use and eGFR (p=0.85). After multivariable adjustment, the use (vs. non-use) of laxatives was significantly associated with greater risk of low-P (adjusted OR [95% CI], 1.10 [1.04-1.16]) and high-P (1.07 [1.03-1.11]) in patients with CKD stages G1-2 (Table). The greater risk of low-P associated with laxative use was more pronounced in patients with more advanced CKD stages; while the laxative use-related risk of high-P was not evident in those with CKD stages G3-5 (Table).

**Conclusions:** The use of non-P containing laxatives was independently associated with greater likelihood of lower serum P levels in patients with CKD, particularly in those with more advanced CKD stages. Our findings suggest potentially distinct pharmacological contribution of laxatives to P homeostasis across CKD stages.

**Funding:** Veterans Affairs Support
Effects of Lactobacillus rhamnosus GG on Gut-Derived Uremic Toxins and Gut Microbiome in Non-Dialysis CKD Patients

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Background: Accumulation of uremic toxins in chronic kidney disease (CKD) is linked to progression to kidney failure via multiple mechanisms, including gut dysbiosis and gut-derived uremic toxins (GDUT) production. We explored the effects of Lactobacillus rhamnosus GG (GG), a probiotic, on GDUT and gut microbiome in CKD patients.

Methods: We conducted a randomized, double-blinded, controlled trial. After 2-weeks run-in, non-dialysis CKD stage 3–5 patients were assigned to receive LGG or placebo for 8 weeks and additional 12-week follow-up. Primary outcomes were changes in serum GDUTs (Indoxyl sulfate,IS; P-cresol sulfa,PCS) at end of treatment. Secondary outcomes included fecal microbiome analysis, serum inflammatory markers, eGFR, proteinuria, and adverse effects were comparable. Fecal microbiome analysis in Caco-2 enterocytes and THP-1 macrophages.

Results: Among 60 participants (aged 70.15 ± 9.6 years; 57% male; eGFR 38.17 ± 11.73 ml/min/1.73m²), 30 each group, baseline characteristics were comparable. At the end of treatment, median changes in serum IS and PCS from baseline were lower in probiotic group (-0.89 vs +0.15 µM/L, P < 0.01) and (+0.13 vs +1.0 µM/L, P < 0.01), respectively. Serum inflammatory markers were lower in probiotic group (endotoxin:0.29 vs 1.19 U/mL; P < 0.01, IL-8:21.6 ± 25.2 pg/ml vs 22.2 pg/ml; P < 0.01, and TNF-α 0.04 vs 0.36 ng/ml; P < 0.02). The eGFR, proteinuria, and adverse effects were comparable. Fecal microbiome analysis in probiotic group showed decreased diversity and reduction in pathogenic Proteobacteria (Fig 1). In vitro, there were higher pro-inflammatory gene expression in Caco-2 and THP-1 cells with ECL and lower enterocyte integrity. These effects were attenuated with LCM, indicating protective effects on enterocyte inflammation and integrity.

Conclusions: GG improved gut dysbiosis, attenuated GDUT production, and reduced inflammatory responses linked to CKD progression. Probiotics may have a role in retarding CKD progression. Larger RCT is warranted.

FR-PO977
Lubiprostone Inhibits Progression of Renal Failure via Intestinal Microbiome

Shun Watanabe,1 Masaki Nakayama,2 Takashi Yokoo,1 Satoru Sanada,3 Katsuhiko Asanuma,1 Yusuke Sazuki,1 Tsuneo Konta,2 Takaki Abe,1 Toshoku Daigaku, Sendai, Japan; 1St. Luke’s International Hospital, Chuo-ku, Japan; 2Tokyo Jikei Ike Daigaku Igakubu Igakuka Jinjo Kokutetsu Naikagaku, Minato-ku, Japan; 3Japan Community Health Care Organization Sendai Hospital, Sendai, Japan.

Background: The gut microbiota and chronic kidney disease (CKD) are believed to be closely interrelated. We previously reported that the administration of the chronic constipation treatment drug lubiprostone (Lubi) in a mouse model of renal failure suppressed the accumulation of uremic toxins in the body during renal failure and demonstrated a renal protective effect. Based on these findings, we hypothesized that Lubi could be a potential novel treatment for kidney diseases.

Methods: The objective of this study was to investigate the effects of Lubi on the suppression of uremic toxin accumulation and disease progression in patients with renal failure. The trial design was randomized, double-blind, placebo-controlled, multicenter collaborative, and exploratory physician-initiated. A total of 118 patients with CKD Stages 3b–4 assigned to the lubiprostone group (37 patients), 8 µg group (35 patients) or 16 µg group (50 patients), and the trial was conducted at eight domestic facilities from 2017 to 2020. The primary outcome was the change in plasma indoxyl sulfate (IS) levels from baseline to 24 weeks after the start of the trial. The secondary outcomes included changes in uremic toxins (phenyl sulfate, p-cresyl sulfate, trimethylamine-N-oxide) and eGFR. Statistical analysis involved conducting ANCOVA analysis with the eGFR value at allocation and the baseline values of each evaluation item as covariates, followed by post hoc testing using Dunnett’s method.

Results: The change in eGFR was as follows: placebo group: 0.13±0.15 µg/ml, 8 µg group: 0.09±0.15 µg/ml, 16 µg group: 0.13±0.13 µg/ml (least squares mean ± standard error), and no significant differences were observed. However, the change in eGFR as was follows: placebo group: -1.55±0.65 ml/min/1.73m², 8 µg group: -0.34±0.66 ml/min/1.73m², 16 µg group: -0.37±0.54 ml/min/1.73m², with a significant difference observed between the placebo and 16 µg groups (p-value = 0.0457).

Conclusions: While Lubi 16 µg did not improve uremic toxin levels, it improved eGFR, thereby generating new evidence for the treatment of CKD. In the future, we plan to analyze metabolites and the gut microbiota from the samples obtained in this trial to explore the mechanism of the inhibitory effect of Lubi on the progression of renal failure and search for new targets for renal failure treatment.

FR-PO978
Extended-Release Calcifediol: A Data Journey from Phase 3 Studies to Real-World Evidence Highlights the Importance of Early Treatment of Secondary Hyperparathyroidism (SHPT)

Akiyuki Ashfaq,1 Domenico Merante,2 Henrik Schou,2 Isabelle Morin,2 Marius C. Manu,3 Charles W. Bishop,4 Stephen A. Struggnell.1.1 OPKO Health Inc, Miami, FL; 2CSL Vifor, Zurich, Switzerland.

Background: Early secondary hyperparathyroidism (SHPT) diagnosis and treatment are crucial to delay the progression of SHPT and related complications, in particular, cardiovascular events and bone fractures. Extended-release calcifediol (ERC) has been developed for the treatment of SHPT in patients with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency (VDI).

Methods: In this descriptive analysis, laboratory parameters of SHPT-CKD stage 3–4 subjects randomised to ERC in two phase 3 clinical studies (NCT01651000 [N=141] and NCT01704079 [N=144]) were compared with those treated with ERC in a RWE study (MBD-AWARE study, N=174).

Results: The main laboratory parameter showed consistency between the phase 3 studies and the RWE study, except for baseline parathyroid hormone (PTH). Mean baseline levels were 346.8 ± 375.4 vs 251.8 ± 360.7 UI/L (P<0.01) in these two groups, respectively. The laboratory levels were comparable in the intent-to-treat populations on ERC in NCT01651000 and NCT01704079, respectively, and 181±98 pg/ml in the RWE study. Moreover, in the RWE study, 53% of subjects achieving ERC had CKD stage 4 with a higher baseline PTH level versus stage 3 CKD subjects. ERC treatment significantly reduced PTH levels and increased 25-hydroxyvitamin D [25(OH)D], regardless of CKD stage, in all 3 studies. In the phase 3 per-protocol populations, 74% of subjects treated with ERC were up-titrated to 60 µg daily after 12 weeks at 30 µg daily, 97% attained 25(OH)D levels ≥30 ng/mL, and 40% achieved ≥30% reductions in PTH. In contrast, based on an apparent ‘wait longer approach’ to test key markers of SHPT, only 2% of subjects in the RWE study were up-titrated. Nevertheless, 70% of subjects achieved 25(OH)D levels ≥30 ng/mL, and 40% had a ≥20% reduction in PTH, consistent with the phase 3 results.

Conclusions: These data suggest that ‘continual’ clinical evidence of ERC effectiveness for treating SHPT, irrespective of CKD stage. A clinically relevant response was observed in the RWE study, consistent with the phase 3 studies, despite higher baseline PTH levels and lower ERC dose. In summary, these data support early treatment initiation with ERC following diagnosis of SHPT, VDI and stage 3 CKD, to delay the progression of SHPT.

Funding: Commercial Support - CSL Vifor

FR-PO979
Effects of Three Months of Ergocalciferol Supplementation in Patients with Stages 3 and 4 CKD: Results from a Randomized Clinical Trial

Paola Giudino,1 Belinda Jim,2 Seth I. Sokol,1 Maria Coco,2 Amanda A. Raff,2 Zaher Hamadeh,2 Yungui Lo,3 Tanya S. Johnh,1 Matthew K. Abramowitz,2 Thomas H. Hostetter,3 Michael L. Mclamed.1.1 New York City Health and Hospitals Jacobi, Bronx, NY; 2Montefiore Medical Center, New York, NY.

Background: Patients with chronic kidney disease (CKD) have higher prevalence of vitamin D deficiency. This is associated with albuminuria but clinical studies have shown mixed results. This randomized, placebo-controlled, double-blind clinical trial hypothesized that supplementation with ergocalciferol would decrease albuminuria in participants with CKD stages 3 and 4.

Methods: 74 participants were assigned to either oral ergocalciferol 50,000 IU or placebo weekly for 8 to 12 weeks depending on baseline 25 hydroxyvitamin D (25(OH)D) levels. The primary outcome was change in albuminuria. Secondary outcomes included change in laboratory values serum 25 hydroxy vitamin D (25(OH)-D), 25-dihydroxy vitamin D (1,25(OH)2D), calcium, phosphate, intact PTH (iPTH), fibroblast growth factor 19 (FGF-23), estimated GFR levels, emergency department (ED) visits and hospitalizations.

Results: Mean age of participants was 58 years (standard deviation (SD): 13 years). The participants were 43% female, 48% Hispanic, 38% non-Hispanic Black.
86% had CKD stage 3 at enrollment. There was no significant difference in the change in albuminuria between the groups (Placebo group: 437 mg/gm [IQR 158-256] at baseline, 580 mg/gm [IQR 175-1160] at 12 weeks; Ergocalciferol group: 829 mg/gm [IQR 244-1942] at baseline, 850 mg/gm [IQR 137-1405] at 12 weeks; p value = 0.13). Analysis of secondary outcomes showed significant differences in 25(OH)D levels at 12 weeks placebo 16.6 ng/ml (SD 7.8) versus ergocalciferol group 29.4 ng/ml (SD 13.4) (p=<0.001) and mean eGFR (Placebo: 36.7 (SD 13.4) at baseline and 37.6 (SD 16.2) at 12 weeks; Ergocalciferol group: 37.7 (SD 14.3) at baseline and 30.5 (SD 12.3) at 12 weeks; p=0.001). There was no difference in 1,25OH2D, calcium, phosphate, intact PTH or FGF-23 between the groups. Participants in the ergocalciferol group had fewer hospitalizations and ED visits (seventeen) versus the participants treated with placebo (twenty-seven).

Conclusions: Among non-Hispanic Black and Hispanic adults with CKD stage 3 or 4, supplementation with ergocalciferol resulted in no significant difference in albuminuria levels and mineral metabolism markers. However, eGFR significantly decreased at 12 weeks after treatment with ergocalciferol.

Funding: NIDDK Support

FR-PO974

Effect of Cholecalciferol Supplementation on Immune Modulation, Inflammation, and Vascular Function in CKD
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Background: Vitamin D deficiency is common in chronic kidney disease (CKD) and short term studies have shown beneficial effect of vitamin D supplementation on vascular function in CKD. In this study we investigated the effect of cholecalciferol supplementation on vascular and immune functions in non-diabetic patients with early stage CKD.

Methods: In this pre-post study, non-diabetic CKD with eGFR 15-60 ml/min/1.73m2 and 25(OH)D levels <20 ng/ml were enrolled. Participants receive 300000 IU of cholecalciferol at enrolment and 8 weeks. Change in circulating T cell subsets, flow mediated dilation (FMD), serum levels of pro and anti-inflammatory cytokines and mRNA expression of Cathelicidin, VDR, Cyp27b1, IL-10 were analysed at 16 weeks.

Results: Out of these 69 participants enrolled, 62 participants completed follow up. 25(OH)D levels increased at 16 weeks (14.4 ± 8.6 ng/ml vs 39.8 ± 19.1 ng/ml, P<0.001). A significant increase in Th2 cell and Th17 population was noted whereas no change was observed in Th1 cell and Treg cell populations (Table 1). FMD showed a significant increase at 16 weeks (10.54 ± 6.30 % vs 13.82 ± 6.2 %, P=0.02). Increased mRNA expression of Cathelicidin, IL-10, VDR, Cyp27b1 by 2 to12 fold (Fig.1A) and significant changes in levels of various pro-inflammatory and anti-inflammatory cytokines (Fig.1B) were observed at follow up.

Conclusions: Cholecalciferol supplementation in vitamin D deficient patients with non-diabetic CKD significantly improved the immune and vascular function, inflammatory responses and enhanced the expression of vitamin D responsive genes.

Funding: Government Support - Non-U.S.

Table 1: Levels of various Tcell subpopulation

<table>
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<th>T cell subpopulation</th>
<th>T cell marker</th>
<th>Baseline (n=62)</th>
<th>Follow up (n=62)</th>
<th>P value</th>
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<tr>
<td>TH1 cell</td>
<td>CD4+ CD8- CD45RA+</td>
<td>48.1 ± 27.3</td>
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<td></td>
<td>CD4+ CD8- CD45RO+</td>
<td>16.3 ± 13.7</td>
<td>15.4 ± 13.1</td>
<td>0.15</td>
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<tr>
<td>CD4+ CD8-</td>
<td>CD4+CD8+</td>
<td>31.2 ± 14.9</td>
<td>25.0 ± 9.7</td>
<td>0.22</td>
</tr>
<tr>
<td>CD4+ CD8+</td>
<td>CD4+CD8-</td>
<td>11.3 ± 9.5</td>
<td>10.7 ± 11.4</td>
<td>0.06</td>
</tr>
<tr>
<td>CD4- CD8+</td>
<td>CD4+CD8+</td>
<td>11.0 ± 8.4</td>
<td>12.4 ± 10.5</td>
<td>0.83</td>
</tr>
<tr>
<td>CD4- CD8-</td>
<td>CD4+CD8-</td>
<td>12.9 ± 8.6</td>
<td>13.2 ± 12.6</td>
<td>0.84</td>
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<td>TH17 cell</td>
<td>CD4+ CD8- CD19-</td>
<td>6.3 ± 5.0</td>
<td>5.6 ± 19.9</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>CD4+ CD8+ CD19-</td>
<td>4.1 ± 11.4</td>
<td>15.8 ± 16.9</td>
<td>0.09</td>
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<tr>
<td>Treg cell</td>
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<td>10.4 ± 10.1</td>
<td>13.5 ± 14.8</td>
<td>0.06</td>
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<tr>
<td></td>
<td>CD4+ CD8+</td>
<td>2.6 ± 2.7</td>
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</tbody>
</table>

FR-PO975

Comparison of the Effect of Benidipine and Amlodipine on Clinical and Biochemical Parameters in CKD with Hypertension and Proteinuria
Rasika Sirsat, Sneha M. Lute, Alan F. Almeida, Ayan K. Dey, Khairwar Mahesh Prasad. PD Hinduja National Hospital and Medical Research Centre, Mumbai, India.

Background: Amlodipine targets L-type calcium channels on glomerular afferent arterioles resulting in their dilation, and leading to an increase in intraglomerular pressure and proteinuria. Benidipine blocks L-, N-, and T-type calcium channels which lower efferent arteriolar resistance and intraglomerular pressure, thereby reducing glomerular hypertension and proteinuria. We compared the effect of benidipine and amlodipine on proteinuria, blood pressure and estimated glomerular filtration rate (eGFR).

Methods: Sixty CKD patients with hypertension on maximum tolerated renin-angiotensin blockade whose UPCR (Urinary protein creatinine ratio) >150 mg/ml were included in this study. Out of sixty patients, thirty patients were randomly assigned to either amlodipine (n=30) or benidipine (n=30). Blood pressure, serum creatinine, eGFR, UPCR, and serum albumin were monitored at baseline, 3rd month and 6th month. Continuous variables between the study drugs were compared by independent t-test (normal distribution) or Mann–Whitney U test (skewed distribution). Within-group comparisons at each follow-up for both drugs were done by Paired t-test (normal distribution) or Wilcoxon sign rank test (skewed distribution).

Results: Blood pressure decreased in both groups in the 3rd and 6th months. Systolic blood pressure (SBP) has decreased significantly in the benidipine group as compared to the amlodipine group (p=0.0014). UPCR values in benidipine and amlodipine groups changed from 2.89±2.17 to 1.42±1.34 and 2.27±1.46 to 2.47±1.55 after 6 months respectively (p<0.07). Despite not attaining the target systolic blood pressure (SBP<120 mmHg), it was observed that there was a significant decrease in UPCR at follow-up visits in the benidipine group. There was no significant change in eGFR in both groups at the end of the study. There was a significant improvement in serum albumin in benidipine-treated patients (p=0.001).

Conclusions: Benidipine is more effective than amlodipine in reducing proteinuria and blood pressure in chronic kidney patients with hypertension

FR-PO976

Impact of Oral Spherical Carbon Adsorbent in Predialysis CKD on Cardiovascular Outcomes and Mineral-Bone Disorder After Dialysis Therapy
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Background: Oral spherical carbon adsorbents (OSCA) are known to slow the progression of chronic kidney disease (CKD) by inhibiting the absorption of uremic toxins produced in the intestine. In this study, we evaluated the impact of using OSCA in pre-dialysis CKD patients on cardiovascular outcomes and mineral-bone disorder after dialysis therapy.

Methods: This study was a retrospective cohort study that enrolled patients who started dialysis therapy including hemodialysis and peritoneal dialysis at Kangdong Sacred Heart Hospital. A total of 294 patients were included in this study, including 98 CKD patients who were administered OSCA before dialysis therapy (OSCA group) and 196 patients who were not administered OSCA with 1:2 matching by age and sex (control group). The mean age was 62.2 ± 12.7 years, with 60.2% male, and the most common cause of CKD was diabetes (67.0%). The ejection fraction in the echocardiogram was significantly higher in the OSCA group (58.1 ± 9.1 % vs. 55.5 ± 9.9 %, P = 0.033). The cardiovascular events in the control group were higher than those in the OSCA group, however, there were statistically not significant (26.0% vs. 19.4%, P = 0.266). However, the patients who were administered OSCA for more than 113 days showed significantly fewer cardiovascular events after dialysis therapy than those less than 113 days (P=0.032 by log-rank test), which remained significant in multivariate cox regression analysis (HR 1.48, 95% CI 1.05-2.08, P=0.025). There was no difference in bone mineral density, pulse wave velocity, bone-specific alkaline phosphatase, parathyroid hormone, and 25(OH) vitamin D levels. In the subgroup analysis of diabetes, all-cause mortality was significantly lower in the OSCA group (27.1% vs. 12.7%, P = 0.029).

Conclusions: The administration of OSCA in CKD patients before dialysis tended to reduce the incidence of cardiovascular events after the start of dialysis therapy, and the longer the period of administration of OSCA, the more significant difference was shown.

Funding: Commercial Support - Daewon Pharmaceutical Co., Ltd.
FR-PO977

Effect of Sodium Bicarbonate Treatment on Cognitive Function in CKD
Jessica B. Kendrick, Petter Bjornstad, Zhiying You, Allison Shapiro, Seth B. Furgeon. University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Cognitive impairment, prevalent in adults with chronic kidney disease (CKD), contributes to mortality, functional decline, depression, frailty, and diminished quality of life. Lower serum bicarbonate levels, even within normal parameters, associate with cognitive impairment in CKD. However, the effect of sodium bicarbonate (NaHCO3) supplementation on cognitive function in CKD is not known. We examined the effect of NaHCO3 therapy on cognitive function in patients with CKD stage 3B–4.

Methods: We performed an ancillary study using participants in the Bicarbonate Administration in CKD Trial, which was a randomized prospective, double-blind, placebo-controlled trial of 109 participants with CKD stage 3B-4 (eGFR 15-44 ml/min/1.73m2) with serum bicarbonate levels 22-27 mEq/L. Participants were randomly assigned to receive either NaHCO3 or placebo at a dose of 0.5 mEq/LBW·kg·day for 12 months. Cognitive function was measured at baseline and 12 months using the National Institutes of Health Toolbox® (NIH-TB) cognitive battery, which assesses fluid cognition (e.g., executive and memory function) and crystallized cognition (e.g., language skills).

Results: 90 patients (50.4% female) with a mean (SD) age of 61.7 ± 11.6 years and eGFR of 35.9 ± 9.8 ml/min/1.73m2 completed the study. The mean (SD) serum bicarbonate level at baseline was 23.4 ± 2.2 mEq/L. After 12 months, serum bicarbonate levels increased, on average, 1.35 mEq/L (95% CI: 0.34-2.36, p=0.003) in the NaHCO3 group compared to placebo. Both the NaHCO3 and placebo groups had a significant increase in fluid cognition scores after 12 months, but there was no significant difference between the groups (Figure). NaHCO3 therapy did not result in a significant improvement in crystallized or total cognition. NaHCO3 therapy was safe and well-tolerated with no significant change in blood pressure, anti-hypertensive medication, weight, calcium or potassium levels.

Conclusions: Twelve months of NaHCO3 therapy in patients with moderate to advanced CKD and normal serum bicarbonate levels did not improve cognitive function.

Funding: Other NIH Support - NHLBI

FR-PO978

Observations from the LiFT Study: Lokelma for Maximization of RAASi in Patients with CKD and Heart Failure, Ongoing Trial
Mahrukh A. Ali,1,2 Daniel Murphy, Ella H. Tulmely, Isaac W. Chung,1 Toshin W. Lopez,1 Simran Parmar,1 Remy Paul,1 Sharrirose Abat,1 Lisa J. Anderson,1,2 Debashis Banerjee,1,2 *St George’s University of London, London, United Kingdom; 1St George’s University Hospitals NHS Foundation Trust, London, United Kingdom; 2St George’s University of London Cardiology Clinical Academic Group, London, United Kingdom.

Background: The management of patients with chronic kidney disease (CKD) and heart failure (HF) - CKD-HF poses a clinical challenge. The use of renin-angiotensin-aldosterone inhibitors (RAASi) reduces hospital admissions due to fluid overload and has mortality benefit; however, this is limited by hyperkalemia, and concerns of worsening renal function. The purpose of this trial is to evaluate the role of sodium zirconium cyclosilicate (SZC) in maximizing of RAASi in CKD-HF. We present preliminary data regarding up-titration of RAASi as achieved part of the study.

Methods: This is a double blind, placebo-controlled, phase III randomised control trial. The primary outcome is to compare SZC and Placebo with respect to enabling patients to achieve the maximum tolerated RAASi dose while keeping [K+] < 5.6 mmol/L. Secondary outcomes include the number and maximum doses of ACEi/ARBs (angiotensin converting enzyme inhibitors/angiotensin receptor blockers) and MRA (mineralocorticoid receptor blockers) achieved during the study period.

Results: We present preliminary data regarding up-titration of RAASi achieved for 35 patients who have completed the trial so far, having started with none or sub-optimal RAASi. The mean age of participants is 74 years. Of the 35 participants, 34 achieved uptitration to maximum tolerated doses in the treatment duration of 2 to 12 weeks. There was no significant change in the eGFR at end of treatment compared to start.

Conclusions: While the study is ongoing preliminary data suggests that rapid maximization of RAASi in this frail, comorbid group can be achieved without detriment to renal function.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

FR-PO979

A Phase Ib Randomized, Double-Blind, Placebo-Controlled, Multi-Centre, Dose Ranging Study of Atuliflapon in Participants with Proteinuric CKD
Hiddo J. Heerspink,1 Marcin Ufnal,2 C Gordon Law,3 Carl A. Whafing,4 Hans I. Ericsson,5 Jane Knöchel,6 Kathleen Connolly,7 Russell J. Kinch,8 Iain MacPhee.5 *FLAIR Study Investigators. 1University Medical Center Groningen, Groningen, Netherlands; 2AstraZeneca R&D Cambridge, Cambridge, United Kingdom; 3AstraZeneca R&D Warsaw, Poland; 4Early Biometrics & Statistical Innovation, R&D, AstraZeneca, Gaithersburg, MD; 5AstraZeneca R&D and Gothenburg, Sweden; 6AstraZeneca Cambridge, Cambridge, United Kingdom.

Background: 5-lipoxygenase activating protein (FLAP) is a key component in the synthetic pathway for leukotrienes and thought to contribute to inflammation and CKD progression. We assessed the albuminuria lowering effect of Atuliflapon (AZD5718), a reversible FLAP inhibitor.

Methods: Participants with proteinuric CKD: eGFR 20-75 mL/min/1.73m2; uACR 200-500 mg/g were randomised to three doses of Atuliflapon or placebo. Treatment period 1 of 12 weeks on existing standard of care (SOC), which included SGLT2i in 25% of the DKD patients, was followed by treatment period 2 where all participants initiated 8 weeks treatment with 10 mg dapagliflozin on top of existing SOC.

Results: In total 24 participants were randomised to treatment period 1 and 24 to treatment period 2. Of those, 22 (92%) and 19 (80%) completed periods 1 and 2, respectively. Participants achieved mean reduction in uACR from baseline to end of treatment period 1 (change from baseline) were as follows: placebo: -54.3 mg/g, 4 mg/g Atuliflapon: -107.2 mg/g, 12 mg/g Atuliflapon: -138.7 mg/g. These changes were maintained in period 2. Given the improvements observed in period 1, the trial was stopped early, and the extension period was not undertaken.

Conclusions: The results suggest that Atuliflapon reduces albuminuria in proteinuric patients with advanced CKD and might represent a novel therapy with potential in slowing CKD progression.

Funding: Commercial Support - AstraZeneca, Government Support - Non-U.S.

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

Underline represents presenting author.
Results: A total of 613 participants were randomised. Following the results of an interim analysis the Sponsor decided to terminate the study early based on no significant reduction in uACR compared to placebo after 20 weeks of treatment (Table 1), at which point 438 had completed treatment period 1 and 318 had completed treatment period 2. Median age was 66 years (range 27-87); 65.8% male; Type 2 DM 76.5%; Median eGFR 40 mL/min/1.73m². The target of 80% suppression of urinary and plasma leukaftine B4 was achieved. The expected reductions in uACR and eGFR on commencing SGLT2i treatment were seen after the addition of dapagliflozin in the second treatment period. There were no significant safety issues.

Conclusions: Atithfuran did not significantly reduce uACR in any of the treatment groups compared to placebo.

Funding: Commercial Support - AstraZeneca

Table

<table>
<thead>
<tr>
<th>Drug</th>
<th>uACR Baseline (mg/g Cre)</th>
<th>Difference vs placebo after 20 weeks of treatment (7% range)</th>
<th>p value</th>
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<td>Placebo</td>
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<td>-</td>
<td>0.43</td>
</tr>
<tr>
<td>Low</td>
<td>61.3</td>
<td>-5.4% (-21.73, 11.60)</td>
<td>0.35</td>
</tr>
<tr>
<td>Median</td>
<td>744</td>
<td>-5.88% (-15.37, 13.82)</td>
<td>0.36</td>
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<tr>
<td>High</td>
<td>706</td>
<td>-8.97% (-22.24, 10.10)</td>
<td>0.56</td>
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FR-PO981

Effects of Empagliflozin on Weight and Blood Pressure in CKD: Analyses from the EMPA-KIDNEY Trial

Kaitlin J. Mayne,1 2 The EMPA-KIDNEY Collaborative Group. University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom; University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom.

Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors slow kidney disease progression and reduce cardiovascular risk in patients with CKD. SGLT2 inhibitors have additionally been shown to reduce weight and blood pressure (BP). We aimed to assess whether diabetes status or kidney function modify the effects of empagliflozin on weight and BP.

Methods: EMPA-KIDNEY compared empagliflozin 10 mg once daily with placebo among 6609 patients with CKD (Clinicaltrials.gov: NCT03594110). Eligible patients had an eGFR of 20 or <45, or ≥45 to <90 mL/min/1.73m² with a urinary albumin-to-creatinine ratio (uACR) ≥30 mg/g. Changes in weight and blood pressure from baseline were presented using mixed model repeated measures regression. Results were assessed overall and in important subgroups and put in the context of a bioimpedance substudy of 660 participants which is reported separately.

Results: At baseline, mean±SD eGFR was 37.3±14.5 mL/min/1.73m² with mean weight of 84.1±21.4 kg, and mean systolic and diastolic BP were 136.5±18.3 and 78.1±11.8 mmHg, respectively. The study-average between-group difference in weight was -0.9 (95% CI -1.2, -0.6) kg with similar-sized effects in all subgroups (Figure). Effects on weight persisted over time and bioimpedance analyses in a 660-participant substudy demonstrated that it reflected reductions in intracellular and extracellular water with minimal effect on body composition. The study-average between-group differences (95% CI) in systolic and diastolic BP were -2.6 (-3.3, -1.9) and -0.5 (-0.9, -0.1) mmHg, respectively, with similar difference by baseline eGFR and uACR, but somewhat larger effects in patients with diabetes.

Conclusions: In a broad range of patients with CKD, empagliflozin reduces weight and BP, even at low eGFR, low uACR and in the absence of diabetes.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly

FR-PO982

Albuminuria-Lowering Effect of Sodium-Glucose Cotransporter 2 Inhibitors, Finerenone, and Their Combination in Patients with CKD

Mohammad A. Hanouneh,1,2 Carmen E. Cervantes,3 Jonathan G. Lim,1,2 Vecna K. Acharya,1,2 Tareq Hanouneh,1 Hung M. Lim,1,2 Johns Hopkins University, Baltimore, MD; Nephrology Center of Maryland, Baltimore, MD; Mayo Clinic in Florida, Jacksonville, FL.

Background: Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is) and Finerenone reduce urine albumin-to-creatinine ratio (UACR) and confer kidney and cardiovascular protection in patients with Chronic Kidney Disease (CKD).

Methods: We conducted a retrospective study in patients seen in a community nephrology practice with eGFR 25-90 mL/min per 1.73 m² and UACR ≥30 mg/g Cr. Patients were stratified into 3 groups: 8 months treatment period with SGLT2is, 4 months treatment period with Finerenone, and 8 months with combination therapy (SGLT2i for 4 months followed by SGLT2i and Finerenone for additional 4 months). The outcome was the percent change in UACR from baseline.

Results: Of 402 patients screened between 1/2022 and 9/2023, 85 were included with mean eGFR, 51.5±14.5 mL/min per 1.73 m², and median UACR 594 mg/g. 47 patients received SGLT2i (dapagliflozin 10 mg/day or empagliflozin 10 mg/day), 19 received Finerenone...
Dapagliflozin Suppresses Urinary Biomarkers of Kidney Damage Regardless of Proteinuric Levels in CKD

Sooyeon Kim, Seung Hye Chu, Hyunjin Noh, Soon hyo Kwon.
Soomchunhyang University Hospital, Seoul, Republic of Korea.

Background: Sodium glucose cotransporter 2 inhibitor (SGLT2i) reduce the risk of chronic kidney disease (CKD) progression in individuals with or without diabetes mellitus (DM). However, the beneficial effect of SGLT2i on CKD patients with low levels of proteinuria has not been established. The objective of this study was to compare the effect of dapagliflozin on biomarkers of kidney injury in CKD patients stratified by albuminuria level.

Methods: We prospectively enrolled healthy volunteers (HVs) (n=20) and CKD patients (n=43) with or without DM. The CKD group received dapagliflozin (10mg). Urine and serum samples were collected before treatment and 3 and 6 months after administration of dapagliflozin. We measured kidney injury molecule-1 (KIM-1), interleukin-1β (IL-1β) and mitochondrial DNA nicotinamide adenine dinucleotide dehydrogenase subunit-1 (mND1) copy number in the urine.

Results: Age did not differ between HV and CKD patients (p=0.04). The clearance of glomerular filtration rate (eGFR) level of CKD patients was lower than that of HV (62.55 ± 24.22 vs 94.95 ± 11.21 ml/min, p<0.001). Among the CKD patients, 11 % (n=5) had diabetes. The median urinary albumin/creatinine ratio (uACR) in CKD patients was 339.80 mg/g (IQR 80.0-647.0 mg/g). Kidney injury markers were significantly elevated in the CKD patients compared to the HVs. Dapagliflozin reduced urinary KIM-1 and IL-1β by 46.35% (95% CI, -53.39 to -39.31) and 44.65% (95% CI, -68.67, -20.64), respectively. In the low albuminuria group (n=22), p=0.034 and p=0.047, respectively. In the low albuminuria group (n=20), uKIM-1 and IL-1β decreased after 6 months of dapagliflozin treatment (p=0.004 and p=0.0021). However, dapagliflozin did not change uACR and eGFR during the study period.

Conclusions: CKD patients with high albuminuria showed an earlier response to dapagliflozin compared to those with low albuminuria. Nevertheless, dapagliflozin demonstrated a reduction in urinary kidney injury biomarkers in CKD patients regardless of proteinuria levels. These findings suggest that SGLT2i may attenuate the progression of low proteinuric CKD.

Funding: Government Support - Non-U.S.
Mitochondrial Aldehyde Dehydrogenase rs671 Single Nucleotide Polymorphism Increases the Susceptibility of Kidney Injury in Adenine-Induced CKD Mice

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Background: In Taiwan, chronic kidney disease (CKD) and end stage kidney disease are major public health issues. Genetic factors increase the susceptibility and severity of kidney diseases. Genome-wide association studies have discovered hundreds of genomic loci associated with CKD. However, which genes are critical contributors to CKD remain unclear. ALDH2 is a mitochondrial enzyme and plays a central role in the liver to metabolize acetaldehyde produced from ethanol into acetate. In addition to liver, ALDH2 is also highly expressed in the kidney, especially in kidney tubular cells. ALDH2 gene has also been shown to deubiquitinates proteins associated with apoptosis, DNA repair, and inflammation in tumor cells. However, the role of UUO on kidney diseases is not well described. We believe the elucidation of the function of USP24 on kidneys help to achieve the future precision medicine.

Methods: LocuZoo was used to visualize single nucleotide polymorphisms (SNPs). Correlated gene expression and pathway analysis was examined using the database of around 400 humans kidney. An established single-cell database was used to annotate cell types expressing USP24. Immunostaining of USP24 with renal tubule markers was examined in kidneys from humans and various mice models CRISPR-CAS9 system was used to generate tubule-specific USP24 deletion mice. Immunoprecipitation analysis was attempted for exploring protein-protein interaction.

Results: The SNPs highly associated with eGFR and USP24 expression in kidneys were localized to the promoter regions, and these SNPs had strong linkage disequilibrium (r2=0.8). The alternative allele of top SNP (rs17413465) showed a positive Z-score for eGFR GWAS, and negative beta value with USP24 expression in kidney eGTL, indicating higher USP24 expression associated with lower eGFR. Kidney single-cell data showed higher USP24 expression in renal tubules compared to non-tubule cells. Double immunostaining of USP24 with tubule marker, KSP validated the expression of USP24 in renal tubules. Gene correlation analysis in a large scale of human kidney samples showed enrichment of genes correlated with USP24 expression in biological pathways related to cholesterol metabolism, lipid biosynthesis, and DNA repair, consistent with the previous report. Successful insertion of the floxed allele next to USP24 with the CRISPR-CAS9 system was confirmed by genotyping PCR. The clonng of USP24 from cultured mice renal tubules and insertion of HaloTag to the C-terminal of USP24 was confirmed by subsequent DNA sequence analysis.

Conclusions: The analysis and experiment suggested lower expression of USP24 in renal tubules might protect from kidney dysfunction by modulating chromatin status and DNA repair.

Background:

Characterising Human Kidney Disease Using Single-Cell Resolution Spatial Transcriptomics

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Background: There is accumulating evidence of the role played by subsets of transcriptionally altered epithelia in the progression of experimental chronic kidney disease (CKD) (Muto et al 2021, Mylonas et al 2021). Whilst bulk and single cell RNA-seq analysis has increased our understanding of kidney biology – the lack of spatial context has limited efforts to identify pathways by which inflammatory Vcam1+ epithelia, leukocytes and fibroblasts interact within the human kidney. Advances in spatial sequencing now provide single cell resolution analysis in formalin fixed, paraffin embedded renal biopsies. We hypothesized that spatial analysis of cell-cell signalling in human kidneys would uncover signalling pathways relevant to progressive chronic kidney disease.

Methods: We used the NanoString CosMX spatial molecular imager to analyse ~1000 RNA transcripts in 13 human renal biopsies spanning benign (minimal change disease, MCD) non progressive IgAN and progressive IgAN CKD (defined as >350 eGFR loss over study period).

Results: Interrogating our spatial dataset, we identified 19 transcriptionally distinct cell populations – including previously published and novel Vcam1+ epithelia from proximal tubules and loop of Henle. Analysis was undertaken on Vcam1+ epithelia in patient biopsies of MCD and IgAN. Assessment of ligand receptor signalling pathways between Vcam1+ epithelia, leukocytes and fibroblasts within 50 microns revealed multiple spatially linked ligand/receptor pathways (see Figure below). One example was the spatial link between reduced Vcam1+ epithelia=>fibroblast distance and increased fibroblast Col1a1 and Col3a1 production (n=10,935 total fibroblasts, all p<0.0001 vs spatially distant SC/ fibroblast pairings, with reduced mean distance in progressive IgAN vs MCD).

Conclusions: Our data demonstrates the ability of spatial transcriptomic analysis to identify and map multiple transcript and ligand/receptor pairings. The addition of spatial information adds additional information about putative signalling pathways in disease progression.

Funding: Commercial Support - Guba A/S
Methods: We genetically labeled Gli1+ cells in Gli1-CreERT2; R26-tdtomato mice by pulsing with tamoxifen at 8 weeks of age and chasing them until 12 weeks (young) or 2 years of age (old). We sorted tdtomato+ cells and performed bulk RNA-seq. We also performed single nucleus transcriptomic analysis (snRNA-seq) on these mouse kidneys (n=3 pairs: 12 weeks vs 2 years of age) using 10X Genomics platform.

Results: We identified cell lineages in 2-year-old male mice labeled at 8 weeks of age. Bulk RNA-seq on sorted tdtomato+ cells from aged kidneys showed a tissue-remodeling gene expression signature with increased Ccn2, Serpinb1, Mmp3 expressions. We performed snRNA-seq on these mouse kidneys and identified all major cell types in 2-year-old male kidneys. We identified a large cluster of immune cells as well as emergence of Fcma+ failed-repair proximal tubular cells (FR-PTC) with pro-inflammatory and pro-fibrotic gene expression signature in aged kidneys. Immunofluorescence analysis validated Fcma+ stromal tubules in 2-year-old male kidneys. The co-localization of a gene expression signature across FR-PTC to Gli1+ myofibroblast progenitors to promote interstitial fibrosis in elderly population.

Conclusions: By combining long-term lineage tracing and snRNA-seq we elucidated a molecular interaction between Gli1+ myofibroblast progenitor and FR-PTC. Targeting this interaction may mitigate age-related renal fibrosis.

Funding: NIDDK Support

FR-PO993

Lineage-Tracing Experiments of Senescent Cell Marker p16INK4a-Positive Cells Show that Kidney Aging Proceeds on a Nephron-by-Nephron Basis

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Background: Senescent cells are known to accumulate in aging tissues and contribute to the development of age-related diseases. In the kidney, senescent cells have been shown to accumulate in aging kidneys and to reside in the same proximal tubules (PTs), and genes involved in ER stress, stress response and post-translational modifications were also shared gene expression patterns between tdT+ PTCs and tdT- PTCs located in the same male mice. Furthermore, tdT+ PTCs were significantly increased in female mice with CKD and HF. However, there was no difference between young and old male mice. In contrast, tdT+ PTCs were significantly increased in female mice with ovariectomy as well as males in mice that received radiation. Tissue clearing and three-dimensional imaging of the kidney shows that senescent cells are associated with the localization of tdT+ PTCs, which clustered and contiguous within the same nephron. P-MRS analysis showed shared gene expression patterns between tdT+ PTCs and tdT- PTCs located in the same female mice. We found that the presence of both FR-PTC and Gli1+ myofibroblast progenitors to promote interstitial fibrosis in elderly population.

Conclusions: By combining long-term lineage tracing and snRNA-seq, we elucidated a molecular interaction between Gli1+ myofibroblast progenitor and FR-PTC. Targeting this interaction might mitigate age-related renal fibrosis.

Funding: NIDDK Support

FR-PO991

Multiplexed Imaging of Senescent Chromatin States in Single Cells in Kidney

Hannah S. Perry, Madeline K. Wong, Benjamin C. Mustonen, Joshua C. Vaughan. University of Washington, Seattle, WA.

Background: The gradual loss of kidney function with age and disease can be linked to changes in physiology and single cell epigenetics. As cells become stressed or damaged from these conditions, they undergo the process of becoming senescent, a state of permanent cell cycle arrest associated with massive chromatin rearrangement, which will mitigate further damage. The order of events and extent of epigenetic changes within single cells and their correlation to physiological alterations as the kidney ages is not fully understood.

Methods: Super-resolution optical microscopy techniques were used with advanced labeling methods to concurrently study epigenetic states and nanoscale physiological features within glomeruli. The quantification of these single cell epigenetic states and nanoscale features includes the global dimension of endothelial fenestrations. Multiplexed imaging has allowed for the use of ~70 nm spatial resolution to simultaneously study histone marks, gene loci, and tissue morphology at the single cell level.

Results: The use of optical super-resolution techniques allows for ~70 nm spatial resolution to simultaneously study histone marks, gene loci, and tissue morphology at the single cell level.

Conclusions: We found that senescent cells clustered in the same proximal tubules in aged kidneys and that senescent cells and non-senescent cells that reside in the same tubule share common characteristics. These results indicated that kidney aging occurs at the nephron level, which is important for future therapeutic strategies.

Funding: NIDDK Support

FR-PO994

Skeletal Muscle Mitochondrial Dysfunction in Patients with CKD and Heart Failure (HF)

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Background: Skeletal muscle dysfunction is a well-known cause of decreased physical quality and performance of life in patients with CKD and HF. While mitochondrial dysfunction has been implicated as a possible mechanism in patients with either CKD or HF, the incremental effect of co-existing HF and CKD is not studied in detail. We hypothesized that the presence of HF and CKD is associated with worse mitochondrial function and physical performance compared to CKD alone.

Methods: In this cross-sectional study, we examined 24 patients, 6 with CKD Stage 3-5 with a clinical diagnosis of HF, and 18 with CKD Stage 3-5 without HF. Patients on dialysis were excluded. 18FPhosphorus magnetic resonance spectroscopy (18F-P-MRS) was

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used to measure PCr recovery time after exercise. A longer PCr recovery results in a greater time constant \( \tau \) (in seconds), which indicates worsening mitochondrial function. Physical exercise was used to measure PCr recovery time after exercise. A longer PCr recovery results in a greater time constant \( \tau \) (in seconds), which indicates worsening mitochondrial function.

**Conclusion:**
Our results suggest that presence of HF worsens mitochondrial function. Physical exercise was used to measure PCr recovery time after exercise. A longer PCr recovery results in a greater time constant \( \tau \) (in seconds), which indicates worsening mitochondrial function.

**Funding:**
NIH Support, Other NIH Support - National Center for Research Resources grant U1L-1RR024975

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**FR-PO996**

**Therapeutic Targeting of Vascular Calcification by KL1 in a CKD-MBD Rat Model**

**Arvin Halim, Gayatri Narayanan, Shrutri Srinivasan, Kalisha O’Neill, Neil X. Chen, Sharon M. Moe, Kenneth Lim. Indiana University School of Medicine, Indianapolis, IN.**

**Background:**
Vascular calcification is a common complication in patients with CKD that causes arterial stiffening, which can lead to hypertension and adverse cardiac remodeling. Klotho-deficient animal models exhibit a similar vascular calcification phenotype seen in patients with CKD, which can be ameliorated with exogenous administration of full-length Klotho. The KL1 domain of Klotho can be cleaved from its biologically active, however it is unknown whether KL1 can directly exert anti-calcific effects similar to full-length Klotho.

**Methods:**
C57/16 male rats were fed a casein-based diet starting at 22 weeks old, and then treated daily with intraperitoneal injections of 50 mg/kg human recombinant KL1 (Cat. No. 100-53, Peprotech; n=6) or vehicle (0.1% bovine serum albumin in 0.9% saline; CKD, n=12) for 5-7 weeks starting at 27 weeks old. Rats were euthanized for tissue collection at 32-34 weeks old. Normal litters (NL, n=8) were used as a control. Tissue calcification assessment, histology and protein analysis of the aorta were performed.

**Results:**
KL1 rats, compared to NL rats, developed elevated BUN (mean±SD: 46.13±9.41 mg/dL vs. 19.44±3.57 mg/dL; P<0.001), creatinine (1.53±0.61 mg/dL vs. 0.44±0.05 mg/dL; P<0.001), plasma phosphate (12.67±4.1 mg/dL vs. 6.17±1.12 mg/dL; P<0.001), decreased eGFR (671.61±463.83 ml/min vs. 2921.0±2135.11 ml/min; P<0.001) and increased total kidney weight normalized to body weight (TKW/BW, 13.46±3.36 mg/g vs. 6.69±0.23 mg/g; P<0.001). KL1 rats developed significant aortic calcification (62.88±31.22 mg/dL compared to NL rats (27.69±14.27 mg/dL; P<0.005).

Moreover, CKD rats treated with KL1 exhibited significantly reduced aortic calcification (32.5±15.53 mg/dL; P=0.018) and BUN (37.76±9.51 mg/dL; P=0.02) compared to vehicle treated CKD rats. Phosphate (10.99±1.38 mg/dL vs. 2.77 mg/dL; P<0.001), eGFR (599.84±190.48 ml/min; P=0.65), and TKW/BW (13.3±1.24 mg/g; P=0.91) in KL1 treated rats did not significantly differ from vehicle treated CKD rats.

**Conclusions:**
KL1 reduces aorta vascular calcification in a rat CKD-MBD model. This suggests that the KL1 domain of Klotho can directly exert cardiovascular protective effects. Further studies are warranted to elucidate the underlying molecular mechanisms.

**Funding:**
Other NIH Support - NIH K23 DK115683

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**FR-PO997**

**Homocysteine Is Associated with Kidney Injury and Increased Arterial Stiffness**

**Neto Piko, Sebastian Bevc, Radovan Hojs, Tadej Petreski, Luka Varda, Robert Ekar, Univerzitetni Klinicni Center Maribor, Maribor, Slovenia.**

**Background:**
Homocysteine (Hcy) promotes atherogenesis and is elevated in chronic kidney disease (CKD). Few studies addressed the association between Hcy, different markers of kidney injury and arterial stiffness (AS).

**Methods:**
127 patients (70.9% male, mean age 65.0±9.2 years, 78.7% hypertensive, and 20.5% diabetes) were admitted due to elective coronaryography. The immunoassay method was used to measure serum Hcy (mmol/L) and cystatin C (mg/L). Hyperhomocysteinemia was defined by Hcy<15 (Group 1, n=37), and patients with Hcy≥15 were included in Group 2 (n=90). Albuminuria was expressed as UACR (mg/g). The glomerular filtration rate was estimated (eGFR) by the CKD-EPI 2009 equation (ml/min/1.73 m²) used as a marker of AS (SphygmoCor®, Atcor, Australia). SPSS® (version 22) was used for statistical analysis.

**Results:**
Mean Hcy was 14.1±5.7 mg/dL, GFR 75.5±17.2 ml/min/1.73 m² and UPCR 10.5±2.7. Spearman’s test showed a significant correlation between Hcy and CysC (r=0.608, P<0.001), and between Hcy and eGFR (r=0.264, P=0.004), eGFR (r=0.485, P<0.001) and between Hcy and cfPWV (r=0.328, P=0.001). Group 1 had lower eGFR (62.4±21.5 vs 80.3±12.2, P<0.001), higher YAP1 (1.5±1.2 vs 0.9±0.2, P<0.001), higher UACR (49.6±57.5 vs 16.5±13.7, P<0.001), and higher cfPWV (11.5±3.6 vs 9.6±1.2, P<0.001). No difference was observed in comorbidities or medications. Multiple regression analysis (independent variables gender, age, diabetes, hypertension) confirmed a correlation between Hcy and eGFR (β=0.353, P=0.001), UACR (β=0.331, P<0.001) and cystatin C (β=0.561, P<0.001). Hcy was higher in patients with lower eGFR (Figure 1). An independent correlation was also found between Hcy and cfPWV (β=0.238, P<0.001) and age and cfPWV (β=0.407, P<0.001). No association was found between ePWP/Hcy and coronary artery disease (CAD).

**Conclusions:**
Serum Hcy is associated with decreased eGFR, increased UACR, increased cystC and increased AS, but not CAD.

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

Underline represents presenting author.
The Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Improves Left Ventricular Function in Preclinical CKD
Frederic Kaiser,1 Ichel Q. Lima Posada,1 Yohan Stephan,2 Matthieu Soulé,1 Roberto Palacios Ramirez,1 Benjamin Bonnard,1 Lionel Nicol,2 Peter Kolkhoff,2 Paul Mulder,2 Diabetes, metabolic diseases and comorbidities 1INSERM, UMR 1138, Centre de Recherche des Cordeliers, Sorbonne Université, Université Paris Cité, Paris, France; 2Univ Rouen Normandie, INSERM U1109, Rouen, France; 3Cardiovascular Precision Medicine, Research and Early Development, Pharmaceuticals, Bayer AG, Wuppertal, Germany.

Background: The mineralocorticoid receptor (MR) plays an important role in the development of CKD and associated cardiovascular complications. Antagonizing the overactivation of the MR with MR antagonist (e.g., eplerenone) is a therapeutic option. Finerenone is a novel non-steroidal MRA that has been recently studied in two large clinical trials showing the beneficial effects in stage 1 to 4 CKD patients with type 2 diabetes (T2D) in the FIDELIO-DKD and FIGARO-DKD trials.

Aim: To test whether finerenone improves renal/cardiac functions in preclinical non-diabetic CKD.

Methods: CKD was induced by 5/6 nephrectomy in 6 weeks old Sprague Dawley rats. Finerenone (10 mg/kg/day) was administered as curative treatment (1 month after 5/6 nephrectomy). Left Ventricle (LV) function/hemodynamics, LV tissue perfusion and GFR were assessed in vivo at the age of 24 weeks. Cardiac fibrosis was estimated by Sirius red staining and activation of eNOS (p-eNOS Ser 1177) in the heart was estimated by western-blot analysis.

Results: 12 weeks after 5/6 nephrectomy, the rats showed classical signs of CKD: reduced GFR and increased kidney weight; associated with LV diastolic dysfunction: increased in LV end-diastolic pressure (LVEDP), LV relaxation constant (Tau) and LV end-diastolic pressure-volume relation (LVEDPVR), while LV perfusion was reduced. Changes associated with increased cardiac fibrosis and reduced eNOS Ser 1177. Curative treatment with finerenone reduced significantly both LVEDPVR and Tau, and increased LV tissue perfusion, associated with a reduction in cardiac fibrosis and increased eNOS phosphorylation. Finerenone treatment did not impact GFR but reduced renal hypertrophy.

Conclusions: Curative treatment with finerenone improves non-diabetic CKD related LV diastolic function, associated with a reduction of cardiac fibrosis, and increased cardiac eNOS activating phosphorylation (Ser 1177) independently from changes in kidney function.

Funding: Commercial Support - Bayer-AG, Government Support - Non-U.S.

FR-PO1000
Novel Role of ST2+ Tubular Cells in Shaping Immune Microenvironment
Vikram Sabapathy,1 Gabrielle Costlow,1,2 Franklin J. Herbert,1 Bushra Mehkri,1 Saleh Mohammad,1 Rahal Sharma.1 University of Virginia, Charlottesville, VA; 2Virginia Commonwealth University, Richmond, VA.

Background: ST2 is an ‘alarmin’ cytokine that regulates the immune response during injury. After release, IL-33 acts in an autocrine/paracrine manner on its membrane receptor (ST2 aka interleukin 1-receptor-like 1, IL1RL1), triggering innate and adaptive immune responses. ST2 expression is induced in tubular cells during chronic inflammation in various kidney diseases. However, the role of ST2+ tubular cells and their implication in chronic kidney injury (CKI) is poorly understood.

Methods: ST2+ mice were crossed with PEPCK-cre mice for proximal tubular cell (PTC)-specific ST2 deletion. Bilateral ischemia-reperfusion (IR) induced acute injury (AKI) and mice were euthanized 24hrs later. Unilateral ischemia-reperfusion injury simulated chronic injury, with contralateral nephrectomy performed on day 13 post-IRI. Kidney structure and function were analyzed using flow cytometry, histology, immunohistochemistry, gene expression, and biochemical analysis. In vitro, ST2-deficient and ST2-sufficient primary mouse PTC were subjected to ischemic conditions and assessed for metabolic fitness using Seahorse metabolic flux analyzer and cytokine production.

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Underline represents presenting author.

FR-PO998
The Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Improves Left Ventricular Function in Preclinical CKD
Frederic Kaiser,1 Ichel Q. Lima Posada,1 Yohan Stephan,2 Matthieu Soulé,1 Roberto Palacios Ramirez,1 Benjamin Bonnard,1 Lionel Nicol,2 Peter Kolkhoff,2 Paul Mulder,2 Diabetes, metabolic diseases and comorbidities 1INSERM, UMR 1138, Centre de Recherche des Cordeliers, Sorbonne Université, Université Paris Cité, Paris, France; 2Univ Rouen Normandie, INSERM U1109, Rouen, France; 3Cardiovascular Precision Medicine, Research and Early Development, Pharmaceuticals, Bayer AG, Wuppertal, Germany.

Background: The mineralocorticoid receptor (MR) plays an important role in the development of CKD and associated cardiovascular complications. Antagonizing the overactivation of the MR with MR antagonist (e.g., eplerenone) is a therapeutic option. Finerenone is a novel non-steroidal MRA that has been recently studied in two large clinical trials showing the beneficial effects in stage 1 to 4 CKD patients with type 2 diabetes (T2D) in the FIDELIO-DKD and FIGARO-DKD trials.

Aim: To test whether finerenone improves renal/cardiac functions in preclinical non-diabetic CKD.

Methods: CKD was induced by 5/6 nephrectomy in 6 weeks old Sprague Dawley rats. Finerenone (10 mg/kg/day) was administered as curative treatment (1 month after 5/6 nephrectomy). Left Ventricle (LV) function/hemodynamics, LV tissue perfusion and GFR were assessed in vivo at the age of 24 weeks. Cardiac fibrosis was estimated by Sirius red staining and activation of eNOS (p-eNOS Ser 1177) in the heart was estimated by western-blot analysis.

Results: 12 weeks after 5/6 nephrectomy, the rats showed classical signs of CKD: reduced GFR and increased kidney weight; associated with LV diastolic dysfunction: increased in LV end-diastolic pressure (LVEDP), LV relaxation constant (Tau) and LV end-diastolic pressure-volume relation (LVEDPVR), while LV perfusion was reduced. Changes associated with increased cardiac fibrosis and reduced eNOS Ser 1177. Curative treatment with finerenone reduced significantly both LVEDPVR and Tau, and increased LV tissue perfusion, associated with a reduction in cardiac fibrosis and increased eNOS phosphorylation. Finerenone treatment did not impact GFR but reduced renal hypertrophy.

Conclusions: Curative treatment with finerenone improves non-diabetic CKD related LV diastolic function, associated with a reduction of cardiac fibrosis, and increased cardiac eNOS activating phosphorylation (ser 1177) independently from changes in kidney function.

Funding: Commercial Support - Bayer-AG, Government Support - Non-U.S.

FR-PO999
CKD, Heart Failure, Cytokines, and NF-xB: Is There a Connection?
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Background: Nuclear factor kappa (NF-xB) is a master transcription factor of inflammatory signaling and its prolonged activation is cytotoxic and may promote heart failure (HF). We developed a translational swine model of chronic kidney disease (CKD) that displays early-stage HF and cardiac activation of NF-xB. However, the mechanisms underpinning cardiac NF-xB activation in CKD remain unclear. We hypothesize that inflammatory cytokines released from the kidney and retained in the heart contribute to cardiac NF-xB activation and cardiac injury in CKD.

Methods: Normal and CKD pigs (n=6 each) were studied after 14 weeks; their systemic inflammatory cytokine profile was characterized (pig Luminex multi-panel assay) and their renal (renal vein - systemic) and cardiac (coronary sinus - systemic) gradients were calculated. In vitro NF-xB expression (qPCR) and activation (immunofluorescence) was studied in pig heart slices and cardiomyocytes exposed to normal plasma, and CKD plasma with or without cytokine neutralizing antibodies (NA).

Results: Out of 13 cytokines, we found that tumor necrosis factor (TNF-xB and interleukin (IL)-6 showed the most significant increase in CKD, paired with positive renal and negative cardiac gradients, suggesting TNF-xB/IL-6 renal release and cardiac retention. In vitro NF-xB expression and activation were higher in heart slices and cardiomyocytes exposed to CKD plasma but decreased in those treated with TNF-xB and IL-6 NA (Figure).

Conclusions: These observations shed light into targeted mechanisms of cardiac NF-xB activation and may support future development of novel modulatory strategies to offset cardiac injury in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI
Results: ST2’s potential involvement in immune cell activation and mobilization to injury sites was investigated. Selective ST2 depletion in PTC, in acute and chronic injury models, resulted in reduced renal injury. In the chronic injury model, the absence of IL33/ST2 signaling in tubular cells led to decreased immune cell infiltration, reduced inflammatory cytokine production, and lower fibrosis. Interestingly, in vitro treatment of renal epithelial cells with recombinant IL-33 increased metabolic fitness, indicated by higher oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in a dose-dependent manner. Additionally, IL-33 treatment paradoxically enhanced the expression of autophagy and mitochondria-related genes LC3, Beclin, and Rubicon in THP-1 cells, thus suggesting the dual role of IL-33/ST2 biology in immune cell activation.

Conclusions: ST2+ tubular cells play a crucial role in leukocyte trafficking to the injured kidneys. Our data provide novel information to suggest epithelial-immune cell crosstalk mediated through the IL-33/ST2 axis and identification of novel therapeutic targets.

Funding: NIDDK Support

FR-PO1001

Magnesium Protects Against CKD Progression by Reducing DNA Damage


Background: DNA damage accelerates the progression of chronic kidney disease (CKD) and kidney aging. Emerging evidence suggests that magnesium (Mg) has the ability to suppress DNA damage by preventing chromatin aggregation. In this study, we aimed to investigate the potential of Mg administration in reducing DNA damage and mitigating the progression of CKD.

Methods: Male C57BL/6 mice (8 weeks old) were treated with a dosage of 600 mg/kg of Mg or deionized distilled water (DDW) and were subjected to renal irradiation with 8 Gy of radiation. As another model, male C57BL/6 mice (8 weeks old) underwent unilateral ureteral obstruction (UUO) injury with a ureteric clamp for 35 minutes. These mice received Mg or DDW every 12 hours after I/R. Then, mice were sacrificed one- or three-week after I/R. In vitro experiments were also conducted using rat renal tubular cell line (NRK52E) and rat kidney fibroblast (NRK49F) cells, which were irradiated with 1 Gy of X-ray at different Mg concentrations (0.8 mM, 3.2 mM, 6.4 mM). In the one-week I/R model, Western blotting analysis revealed that the effects of radiation injury were confirmed by an increase of γH2AX, a marker of DNA double-strand breaks. Mice were treated with 600 mg/kg of Mg and subjected to renal irradiation with 8 Gy of radiation. Remarkably, the Mg-treated group exhibited reduced levels of γH2AX in the kidneys compared to the non-treated group. Furthermore, NRK52E and NRK49F cells irradiated with 1 Gy of radiation showed a reduction in γH2AX levels as the Mg concentration in the medium increased (0.8 mM, 3.2 mM, 6.4 mM). In the one-week I/R model, Western blotting analysis revealed that Mg administration resulted in a reduction of DNA damage markers (H2AX and rad51), markers of aging (p16 and p21) and the inflammation marker (cGAS-Sting). Immunostaining demonstrated that Mg administration resulted in a reduction of markers of aging (p16 and p21) and the inflammation marker (F4/80).

Results: Western blotting analysis revealed that the effects of radiation injury were confirmed by an increase of γH2AX, a marker of DNA double-strand breaks. Mice were treated with 600 mg/kg of Mg and subjected to renal irradiation with 8 Gy of radiation. Remarkably, the Mg-treated group exhibited reduced levels of γH2AX in the kidneys compared to the non-treated group. Furthermore, NRK52E and NRK49F cells irradiated with 1 Gy of radiation showed a reduction in γH2AX levels as the Mg concentration in the medium increased (0.8 mM, 3.2 mM, 6.4 mM). In the one-week I/R model, Western blotting analysis revealed that Mg administration resulted in a reduction of DNA damage markers (H2AX and rad51), markers of aging (p16 and p21) and the inflammation marker (cGAS-Sting). Immunostaining demonstrated that Mg administration resulted in a reduction of markers of aging (p16 and p21) and the inflammation marker (F4/80).

Furthermore, real-time PCR analysis indicated that Mg administration led to a decrease in markers of inflammation (IL-6 and IL-1β). In the three-week I/R model, Western blotting and immunostaining revealed that fibrotic markers (cSMA and collagen I) were also reduced in the Mg-treated group.

Conclusions: Administration of Magnesium reduces DNA damage and mitigates renal I/R injury, including aging, inflammation and fibrosis.

FR-PO1002

A Novel, Small Molecule Inhibitor of Gut Microbial Choline Metabolism and its Effect on the Kidney Function in a Rat Model of CKD

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Background: Trimethylamine N-oxide (TMAO), a gut microbiota-dependent uremic toxin, is both a cause and driver of chronic kidney disease (CKD). Choline trimethylamine (TMA) lyase (CutC) is a microbial enzyme that plays a key role in the formation of TMAO, a precursor of TMAO, in the gut. Here, we describe the pharmacological effects of a novel, small molecule CutC inhibitor on serum TMAO level and kidney function in an adenine-induced rat model of CKD.

Methods: CKD was induced in rats by adding 0.75% adenine to a standard chow diet for 2 weeks (induction phase) and maintained by adding 0.25% adenine to the diet supplemented with 1% choline in the drinking water for 4 weeks (maintenance phase). The small molecule CutC inhibitor, ZTX101, was administered via ileal-cecal catheter directly into the colon at doses of 15, 50, and 150 mg/kg of body weight, twice a day, during the maintenance phase. Serum TMAO was quantified using LC-MS/MS. Kidney function was assessed by measured levels of creatinine and urinary nitrogen (BUN). Renal fibrosis was assessed by biomarker analysis and histology.

Results: Serum levels of TMAO, creatinine, and BUN were elevated in rats with adenine-induced CKD supplemented with choline. Administration of ZTX101 at all three doses resulted in rapid and sustained reduction of serum TMAO to the normal range (<5 μM) during the maintenance phase of the study. At the end of study, ZTX101 significantly reduced serum levels of creatinine (1.5 mg/dL in 150 mg/kg ZTX101 vs. 3.1 mg/dL in untreated; P<0.0001) and BUN (102.6 mg/dL in 150 mg/kg ZTX101 vs. 146.9 mg/dL in untreated; P=0.05). ZTX101 also significantly reduced TGF-β1 level in the kidney (36.6 pg/mg tissue in 150 mg/kg ZTX101 vs. 70.2 pg/mg tissue in untreated).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1005
Lactobacillus acidophilus KBL409 Protects Against Kidney Injury via Improving Mitochondrial Function with CKD
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Background: Recent advances have led to greater recognition of the role of mitochondrial dysfunction in the pathogenesis of chronic kidney disease (CKD). There has been evidence that CKD is also associated with dysbiosis. Animal studies have shown that dysregulated gut microbiota can alter mitochondria metabolism of intestinal mucosa cells, leading to mitochondrial dysfunction. Here, we aimed to evaluate whether probiotic supplements can have protective effects against kidney injury via improving mitochondrial function.

Methods: KBL409 was selected because this strain was proved to maintain intestinal integrity and reduce p-cresyl sulfate level in vitro in prior experiments. An animal model of CKD was induced by feeding C57BL6 mice a diet containing 0.2% adenine. KBL409, a strain of Lactobacillus acidophilus, was administered via oral gavage at a dose of 1 x 10^6 CFU daily. We isolated primary mouse TECs and treated them with TGF-β (10 ng/ml) or p-cresyl sulfate (0.5mM) and sodium butyrate (10mM), a short-chain fatty acid that is considered the end products of commensal bacteria.

Results: There were prominent structural alterations in CKD mice and KBL409 administration significantly attenuated renal fibrosis. Transcript and protein expression analysis showed that butyrate significantly improved mitochondrial respiration, fatty acid oxidation defect, oxidative phosphorylation, and ATP production in TGF-β- or p-cresyl sulfate-treated TECs.

Conclusions: This study demonstrates that administration of the probiotic Lactobacillus acidophilus KBL409 protects against kidney injury by improving mitochondrial function.

FR-PO1006
N-Acetylcyesteine Ameliorates Hematuria-Associated Tubulointerstitial Injury in 5/6 Nephrectomy Mice
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Background: Chronic kidney disease (CKD) is characterized by increased interstitial fibrosis and tubular atrophy (IFTA) in the kidney. Chronic hematuria is a hallmark of several human kidney diseases and often is seen in patients on anticoagulation therapy. We had previously demonstrated that chronic hematuria associated with warfarin increases IFTA in 5/6 nephrectomy (5/6NE) rats, and such treatment increases reactive oxygen species (ROS) in the kidney. The goal of this study was to evaluate the effects of the antioxidant N-acetylcysteine (NAC) on the progression of IFTA in 5/6NE mice.

Methods: 5/6NE C57BL6 mice and 5/6NE 129S1/SvImJ mice were treated with warfarin alone or with warfarin and NAC for 23 weeks. Serum creatinine SCr), hematuria, blood pressure (BP), and ROSs in the kidney were measured; kidney morphology was also evaluated. Warfarin doses were titrated to achieve prothrombin time (PT) increase to the levels seen with therapeutic human doses.

Results: Warfarin treatment resulted in an increased SCr, systolic BP, hematuria (Figure 1), and ROS in the kidney in both mouse strains. IFTA was increased as compared with control 5/6NE mice, and this increase in IFTA was more prominent in 129S1/SvImJ than in C57BL6 mice. NAC ameliorated the warfarin-associated increase in SCr and BP but not hematuria. IFTA and ROSs in the kidney were reduced in mice treated with NAC and warfarin as compared to mice treated with warfarin alone.

Conclusions: NAC mitigates the increase in SCr and IFTA in mice with chronic hematuria by reducing oxidative stress in the kidney. This data open novel possibilities for treatments in CKD patients.

Funding: NIDDK Support

FR-PO1007
Gluconagon Agonism Protects the Kidney from Obesity by Restoring Peroxisomal Catalase and Fatty Acid Oxidation Capacity
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Background: Obesity challenges the nephron through fatty acid overload, leading to impaired energy metabolism and impaired renal filtration. Gluconagon agonism elicits well-described enhancement of fatty acid oxidation and mitochondrial rejuvenation in the liver and other organs, and was hypothesised here to protect the kidney from obesity-related pathology.

Methods: Sprague Drowley rats fed HFI5 (DIO) or Chow diet for 10 weeks were administered 10nmol/kg lipidated glucagon receptor agonist g1437 daily for seven days. If was used to visualise the distribution and morphology of peroxisomes and mitochondria across the kidney, alongside the organelle content of key metabolic and ROS handling enzymes. Primary human PTECs transfected with either MitoTimer or with a novel peroxisomal ROS sensor were cultured with and without linoleolic/oleic acid for 72 hours alongside 100 nM g1437 or vehicle. To interrogate the underlying signalling mechanism of gluconagon, cortex and medulla from mice acutely administered 10mg/kg g1437 were analysed by phosphoproteomics.

Results: Kidneys of DIO rats demonstrated peroxisomal proliferation and altered mitochondrial morphology. Gluconagon agonism also induced mitochondrial and peroxisomal morphological changes. Peroxisomal catalase and FAO enzyme content was perturbed in kidneys of DIO relative to Chow fed rats. Concomitantly with weight loss, renal peroxisomal FAO and mitochondrial enzyme content was partially restored in g1437 administered rats. Primary human PTECs cultured with 150 µM linoleic/oleic acid mixture for 72 hours demonstrated greater mitochondrial and peroxisomal reactive oxygen species generation than controls. Phosphoproteomics determined that catalase was 1.48-fold more phosphorylated in kidney cortex of mice acutely administered g1437, a phosphorylation shown to enhance catalase activity. Peroxisomal fatty acid oxidation biogenesis were pathways significantly phosphorylated as part of the gluconagon signalling cascade.

Conclusions: Obesity and fatty acid overload led to fusion of renal mitochondria and peroxisomes, alongside increased capacity for ROS production and FAO. Gluconagon agonism did not reverse changes in organelle morphology, yet enhanced FAO capacity and lowered ROS production capacity, possibly through catalase phosphorylation.

Funding: Commercial Support - AstraZeneca

FR-PO1008
Proximal Tubular FHL2 Mediates Obesity-Induced Renal Tubulointerstitial Inflammation via Regulating FoxO1 Activity
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Background: Lipid accumulation caused by fatty acid β-oxidation deficiency in renal proximal tubular cells (PTCs) is a major factor triggering obesity-related chronic kidney disease (CKD), and the low activity of forkhead box class C1 (FoxO1) is a key mediator between metabolic abnormalities and cellular damage. It was reported that four and a half LIM domain-only protein 2 (FHL2) could inhibit FoxO1 activity in prostate cancer cells. However, the potential effect of FHL2 on FoxO1 activity and lipid toxicity injury in PTCs during OR-CKD remains to be elucidated.
Renal Microvascular Inflammation in Human Obesity Detected by FR-PO1009


Background: Obesity is characterized by systemic inflammation and activation of the inflammatory marker monocyte chemoattractant protein (MCP)-1, but the involvement of inflammation in early renal injury is unclear. Plasmalemmal vesicle-associated protein (PLVAP), a marker of renal peritubular capillaries, is upregulated in diabetes. We hypothesized that human obesity induces renal microvascular inflammation detectable by elevated levels of PLVAP+/MCP-1+ urinary extracellular vesicles (uEVs). Methods: Obese patients (OB, n=6) and healthy volunteers (HV, n=7) were prospectively enrolled. Blood and urine were collected, and uEVs were isolated (Total Exosome). uEVs were quantified (Nanoparticle Tracking Analysis) and characterized (Flow cytometry) for CD36, PLVAP, CD144 (expressed on glomerular endothelium), and MCP-1, and their relationship with body mass index (BMI) and serum glucose levels was evaluated.

Results: OB had significantly higher BMI than HV, but both groups showed preserved renal function and glucose levels (Table 1). In addition, a similar number and size of uEVs in OB and HV were compared directly with both glucose levels and BMI in OB but not in HV (Figure 1).

Conclusions: Non-diabetic obese patients show elevated numbers of PLVAP+/MCP-1+ uEVs that correlate with BMI and glucose levels. These early markers of renal microvascular inflammation that herald the development of pre-diabetes might be useful in the management of patients with obesity.

Funding: NIDDK Support, Other NIH Support - DK120292 (NIDDK) and HL156919 (National Heart, Lung, and Blood Institute)

Demographics (means standard deviation (SD) or median(min,max))

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<td>Sex, M/F</td>
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<td>BMI, Kg/m²</td>
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<td>Serum Creatinine, mg/dl</td>
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<td>39±(81,93)</td>
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<td>Serum Glucose, mg/dl</td>
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</table>

*P<0.05 vs. HV

Figure 1

FR-PO1011

Insulin Resistance and Intermuscular Adipose Tissue (IMAT) in Patients with CKD

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Background: Insulin resistance (IR) is commonly observed in CKD and plays a critical role in protein energy wasting (PEW). We have found that patients with moderate to advanced CKD have increased IMAT accumulation. In this study, we hypothesized that the extent of IMAT is associated with homeostatic model assessment of insulin resistance (HOMA-IR), a measure of insulin resistance and systemic inflammation.

Methods: In this cross-sectional study, we included 46 patients (21 control, 25 with CKD stage 3-5). Anthropometry, inflammatory biomarkers, and HOMA-IR were measured in all participants. Quadrieps IMAT was analyzed with magnetic resonance imaging (MRI) of the thigh.

Results: The control and CKD groups were matched by gender and body mass index. There was no difference in HOMA-IR, glucose, or insulin levels between the groups. Quadrieps IMAT accumulation was higher in patients with Stage 3-5 CKD compared to the control group (Figure 1A). Higher insulin resistance was associated with greater IMAT accumulation (r=0.55, p=0.001, Figure 1B). Greater IMAT accumulation was associated with increased levels of tumor necrosis factor-alpha (TNFs) (r=0.16, p=0.005, Figure 1C).

Conclusions: In patients with stage 3-5 CKD, there is greater accumulation of IMAT that associates with insulin resistance and increased TNFs levels compared to controls. IMAT accumulation may contribute to skeletal muscle insulin resistance by promoting a local inflammatory milieu. Further studies should evaluate if IMAT reduction may improve insulin sensitivity in CKD.

Funding: NIDDK Support, Other NIH Support - NCCR

Figure 1

FR-PO1012

High-Fat Diet Changes Lipid Profiles and Induces Podocyte Injury in Unilateral Kidney Model: Targeted Lipidomic and Kidney Podocyte-Specific Analysis

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Background: We investigated that high fat diet changes lipidomic profiles and dysregulated lipid metabolism induces podocyte injury in unilateral nephrectomized mouse model using targeted lipidomics analysis and podocyte specific analysis.

Methods: Mice were randomized to undergo unilateral nephrectomy and fed standard or high-fat diets for 13 weeks. There were four groups; normal diet (ND), high-fat diet (HD), normal diet and received uninephrectomy (NDU), and high-fat diet and received uninephrectomy (HDU). After 13 weeks, lipidsomes analysis was performed in podocytes isolated from the kidney. In vitro, CHIP-1 cells were treated with cholesterol ester for 24 hours.

Results: A high-fat diet accompanied by unilateral kidneys accelerated the increase in podocyte lipid droplets, glomerular size and tubular cell vacuole formation, resulting in deterioration of renal function. HDU showed different lipidsomics profiles compared to other groups. Specifically cholesterol ester (CE), the CE20:4, increased significantly in HDU. Expressions of nuclear receptors, ABCA1, and CPT1A related to lipid metabolism decreased in the HDU and CHP-1 cells treated with CE 20:4. Transmission electron microscopy confirmed loss of mitochondrial cristae, morphological changes and increased autophagosome formation in the HDU. In addition, reduction of NRF1/2 and increase of DRPI were confirmed in HDU. In CHP-1 cells stimulated with CE20:4, proteins related to mitochondria, such as NRF1/2, PGC-1α, and PDK4 decreased, and mitochondrial fission was increased. Expressions of Beclin-1 and P22 were significantly increased in the HDU and CHIP-1 cells treated with CE 20:4. Kidney injury by such abnormal lipid metabolism induced renal fibrosis in the HDU.

Conclusions: High-fat diet increases lipid accumulation and lipid toxicity in podocytes induced renal structural and functional damage in the unilateral kidney model. In addition, lipotoxicity reduces mitochondria biogenesis, increases fission of mitochondria and increases incomplete action of autophagy.

Funding: Government Support - Non-U.S.
FR-PO1012
Bariatric Surgery: Benefits that May Harm, a Cause of Rapid Deterioration of Kidney Function

Introduction: Secondary hyperoxaluria in post-bariatric surgery patients is well documented. The y e de roux and gastric band bypass techniques are the most closely related. A frequent complication is renal lithiasis with progressive loss of renal function.

Case Description: 63-year-old female, history of gastric bypass due to morbidity obesity (150 to 90 kg), DM 2 difficult to control. He was admitted to nephrology due to rapidly progressive degradation of function, basal creatinine 1.12 mg/dl, on admission with 4.5 mg/dl, C3 49 mg/dl, C4 17 mg/dl (low) ANA 1:180. Renal biopsy: with 2 silver acicular nodules, interstitium with patches of fibrosis and tubular atrophy, infiltrate of lymphocytes, polymorphonuclear cells, and eosinophils. Birefringent intratubular calcifications, loss of brush border: negative IFI.

Discussion: Lithogenicity from bariatric surgery is multifactorial with mechanisms: (1) calcium saponification as a result of fat malabsorption reduces calcium-oxalate binding. (2) Increased bile salts in the colon (as a result of their decreased absorption in proximal portions of the intestine) increased mucosal permeability to oxalate (3) reduced colonization by oxalobacter formigenes, especially with the use of beta-lactams. Conclusions: serum and urinary metabolic screening of patients after bariatric surgery would allow an increase in the early detection of patients at high risk of enteric hyperoxaluria. Since the lithiasic disease is detected, dietary adjustments and avoiding the indiscriminate use of antibiotics are essential to prevent the progressive deterioration of renal function.

FR-PO1013
Endoplasmic Reticulum (ER) and Mitochondrial Stress Markers of Heavy Metals Exposure in the CRIC Study
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Background: Chronic kidney disease (CKD) is a progressive disease that affects ~13% of the population. Heavy metal (HM) exposure contributes to the rapid progression of kidney disease due to persistent stress stimuli that lead to dysregulation of inflammatory and oxidative stress pathways. Our hypothesis is that cumulative exposure to metals increases progression of CKD via inflammation and oxidative stress.

Methods: We obtained matching nail samples (n=40) from 20 participants of the Chronic Renal Insufficiency Cohort (CRIC) at baseline (n=20) and 24-month follow-up (n=20). An equal number of subjects had fast progressing disease (n=10) and stable disease (n=10). Samples were collected anonymously prior to analysis. We quantified twenty-five metalloids in the nail samples and oxidative stress pathways of kidney disease due to persistent stress stimuli that lead to dysregulation of inflammatory and oxidative stress pathways. Our hypothesis is that cumulative exposure to metals increases progression of CKD via inflammation and oxidative stress.

Results: Not significant, in the fast-progressing disease cohort, ATF, VAR6, and PERK were all increased while GRP78, Caspase 12, and mitofilin were all decreased at follow-up. In the stable cohort, all markers were increased at follow-up with the exceptions of mitofilin (decreased) and PERK (unchanged). Increased ER and mitochondrial stress markers observed a trend towards higher metal burden.

Conclusions: Although not significant, in the fast-progressing disease cohort, ATF, VAR6, and PERK were all increased while GRP78, Caspase 12, and mitofilin were all decreased at follow-up. In the stable cohort, all markers were increased at follow-up with the exceptions of mitofilin (decreased) and PERK (unchanged). Increased ER and mitochondrial stress markers observed a trend towards higher metal burden.

Funding: NIDDK Support

FR-PO1014
Heavy Metals Quantification in Nail Samples from the CRIC Study
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Background: Chronic kidney disease (CKD) affects >37 million American adults. Heavy metal (HM) exposure contributes to the rapid progression of kidney disease. Our overall hypothesis is that cumulative exposure to trace metals increases progression of CKD and higher metal burden will correlate with CKD risk.

Methods: We obtained matching nail samples (n=40) from 20 participants of the Chronic Renal Insufficiency Cohort (CRIC) at baseline (n=20) and 24-month follow-up (n=20). An equal number of subjects had fast progressing disease (n=10) and stable disease (n=10). We performed biomolecular (epigenomic, transcriptomic, proteomic, epitranscriptomic, metabolomic, genomics), clinical chemistry (electrolytes, endocrinology, biochemistry) and morphometry (histology, 3D imaging, miRNA-ISH, tissue weights) analyses using samples and datasets available from 1 spacecraft-exposed mouse and 5 human, 1 simulated microgravity rat and 4 simulated GCR-exposed mouse missions.

Results: Not significant, in the fast-progressing disease cohort, compared with stable progressing cohort. Not significant with a Wilcoxon Rank Sum Test, a trend of higher total metal burden was observed in the rapid progressing cohort, compared with stable progressing cohort.

Conclusions: All metals we examined were above the limit of detection. Although not significant with a Wilcoxon Rank Sum Test, a trend of higher total metal burden was observed in the rapid progressing cohort, compared with stable progressing cohort.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
fibrosis in the kidney than Sham mice. OxT treatment ameliorated inflammation and fibrosis in Pkd1 RC/RC mice. Perivascular fibrosis was found in the hearts of CKD mice, but OxT-treated CKD mice displayed less perivascular fibrosis. RNA-seq of heart tissue revealed that the top altered genes and pathways in CKD compared to control mice were related to increased inflammation and fibrosis, decreased lipid metabolism, and increased lipid accumulation. However, OxT treatment reversed those pathways and genes altered in CKD control mice.

**Conclusions:** Hydroxyproline promoted CDK development and progression, likely through increased oxalate levels. OxT treatment attenuated CDK progression and ameliorated cardiovascular damage.

**Funding:** NIDDK Support

**FR-PO1017**

**Spatiotemporal Landscape of Kidney Tubular Responses to Glomerular Proteinuria**

Anna Faivre,1 Milica Bugarski,2 Anna Rinaldi,3 Thomas Verissimo,4 David Legouis,5 Sara Barreiro Correia,2 Pietro E. Cippa,6 Sophie M. De Seigneur,7 Andrew Hall,8 Université de Genève, Geneve, Switzerland; 1Universität Zurich, Zurich, Switzerland; 2Ospedale Regionale di Lugano, Lugano, Switzerland.

**Background:** Large increases in glomerular proteinuria filtration induce major changes in kidney function and body homeostasis, and increase the risk of cardiovascular disease. We investigated how elevated protein exposure modifies the landscape of tubular function along the entire nephron, to better understand the cellular changes that mediate these important clinical phenomena.

**Methods:** We conducted single nucleai RNA sequencing, functional intravital imaging, and antibody staining to spatially map transport processes along the mouse kidney tubule. We then delineated how these are altered in a transgenic mouse model of inducible glomerular proteinuria (PO-ATTAC) at 7 and 28 days. Results were compared to an ischemic model of tubular injury.

**Results:** Glomerular proteinuria activates large-scale and pleotropic changes in tubular cell gene expression in all major nephron sections, the majority of which are functional in nature. Extension of protein uptake from the early to late part of the proximal tubule results in a substantial shift in the balance of reabsorptive and secretory processes, and associated metabolic pathways, including lipid metabolism. Meanwhile, overflow of luminal proteins to the distal tubule causes transcriptional convergence between specialized regions and generalized dedifferentiation.

**Conclusions:** Proteinuria is a potent modulator of cell signaling in tubular epithelia and triggers extensive remodeling, in a segment specific manner. Thus, luminal protein concentration is a critical micro-environmental factor that links glomerular and tubular function in vivo. These findings could explain some of the well-recognized clinical complications that arise in proteinuric kidney disease, and may also be important for understanding nephron patterning in organ development.

**Funding:** NIDDK Support

**FR-PO1018**

**Urinary Phosphate Contributes to Kidney Injury, Cyst Formation, and Inflammation**

Kyle Janssen, Timothy A. Fields, Jason R. Stubbs. The University of Kansas Medical Center, Kansas City, KS.

**Background:** High dietary phosphate intake increases urinary phosphate excretion and has been associated with an increased risk for chronic kidney disease (CKD) progression. We hypothesize that high dietary phosphate hastens CKD progression by stimulating tubular nanocrystal formation, epithelial cell injury, microcyst formation, and progression. We hypothesize that high dietary phosphate hastens CKD progression by stimulating tubular nanocrystal formation, epithelial cell injury, microcyst formation, and progression.

**Methods:** First, a mouse model of cystic kidney disease, the Phld1<sup>-/-</sup> mice, was fed a high versus low phosphate diet and analyzed for changes in kidney cyst growth, mineral deposition, tubular injury, inflammation, and fibrosis. Second, NaPi<sub>2a</sub> mice, a model of primary urinary phosphate wasting, was evaluated to determine the direct effect of urinary phosphate excretion on mechanisms of kidney injury and inflammation.

**Results:** Phld1<sup>-/-</sup> mice fed a high phosphate diet exhibited more rapid cyst growth and increased deposition of phosphate-based crystals in their kidneys compared to mice fed a low phosphate diet. Mineral deposits in these kidneys were spatially colocized with macrophages and osteopontin, a matricellular protein that is critical for maintaining urinary phosphate solubility. Moreover, gene expression for markers of kidney injury, inflammation, and fibrosis were increased in Phld1<sup>-/-</sup> mice on a high phosphate diet.

**Conclusions:** Increased urinary phosphate excretion directly contributes to tubular injury, kidney cyst growth, inflammation, and fibrosis in CKD. Current evidence suggests a direct interaction between phosphate-based nanocrystals and local inflammatory cells may be a primary contributor to this relationship.

**Funding:** NIDDK Support

**FR-PO1019**

**Gut-Derived Uremic Toxins Correlate with Anxiety and Decreased Locomotor Activity in CKD Mice**

Yiting Zhao, Han Liu, Joshua J. Jung, Nikitha M. Vancheeswaran, Lilly Tran-Phung, Wei Ling Lau. University of California Irvine, Irvine, CA.

**Background:** The altered gut microbiome in chronic kidney disease (CKD) is a source of circulating uremic toxins including p-cresyl sulfate (pCS), indoxyl sulfate (IS), and trimethylamine N-oxide (TMAO). Microbe-derived uremic toxins have been correlated with depression and cognitive impairment in CKD patients. In the current study, continuous subcutaneous infusion of gut-derived toxins was done to evaluate the impact of gut-derived uremic toxins on behavior outcomes in CKD mice.

**Methods:** Male and female C57Bl/6J mice were randomly assigned to control or CKD groups. Tubulointerstitial nephritis CKD was induced by 0.2% adenine diet. Alzet pumps containing placebo (PBS) or uremic toxins (a mix of pCS, IS and TMAO) were implanted which delivered continuous subcutaneous dosing for 4 weeks. Prior to termination, spontaneous locomotion and anxiety (open field test) and recognition memory (novel object recognition test) were assessed. Serum levels of creatinine and gut-derived uremic toxins were measured. Group means were compared using ANOVA, and correlation analyses were done using Spearman’s coefficient (r).

**Results:** Serum creatinine, pCS, IS, and TMAO were significantly elevated in CKD vs control mice (Table). Toxin infusion in CKD animals (CKD/Toxins) further increased serum pCS and IS compared to CKD/PBS mice in both sexes. Male and female CKD animals demonstrated decreased exploratory behavior (increased anxiety). Higher levels of creatinine, IS and TMAO were significantly associated with anxiety behavior. Infusion of gut-derived toxins did not further increase anxiety behavior compared to PBS (Figure). Recognition memory was not altered in CKD mice.

**Conclusions:** Gut-derived uremic toxins were significantly correlated with anxiety behavior in CKD mice. However, infusion of toxins did not further worsen behavior scores beyond control vs CKD status.

**Funding:** Other NIH Support - NIH R01

**FR-PO1020**

**CKD Induces Endotoxin-Related Activation of the Innate Immune System and Is Associated with Overall Mortality**

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**Background:** Chronic inflammation is associated with poor outcome. The gut-kidney axis is considered an important contributor via the leaky gut. Lipopolysaccharide (LPS) is a pyrogen found in the exterior cell membrane of most gram-negative bacteria. When absorbed through the intestinal epithelium, LPS induces inflammation by activating macrophages and monocytes. Due to short half-life direct quantification of LPS is a poor marker of innate immune system activation. Lipoprotein binding protein (LBP) is an essential component of the innate immune response to LPS. Circulating LBP significantly enhances the sensitivity of CD14<sup>+</sup> cells (mostly monocytes and macrophages) to stimulation by LPS. Levels of LBP peak in serum shortly after endotoxemia, and remain increased up to 72 hours later. We hypothesized that CKD increases levels of LBP and is associated with an increased risk of mortality.

**Methods:** We analyzed plasma LBP (species-specific ELISA, HycultBiotech, The Netherlands) in the Leuven mild-to-moderate CKD cohort (NCT00441623). To study causality, we used animal models of experimentally induced CKD. To exclude model-related bias, two different rat models of CKD, i.e. 5/6th nephrectomy and 0.25% w/w adenine supplementation, were used. We analysed the association between LBP and overall mortality using Cox proportional hazards analysis.
Results: In a cohort of 460 patients with CKD, LBP is significantly inversely correlated with GFR (beta = -0.28; p < 0.001). Spearman rank correlation in two different models of induction of CKD resulted in a significant increase of LBP. In these animals, we observed a significant inverse association between eGFR (and measured creatinine clearance) and LBP concentrations (P < 0.0001). In univariate Cox proportional hazard analysis, plasma LBP levels were significantly associated with mortality (p < 0.001). This association remained significant in multivariable models adjusted for the systematic coronary risk evaluation (score) model.

Conclusions: Patients with CKD have higher levels of LBP. Experimental CKD leads to increased levels of LBP as a result of a causal relationship. Higher LBP levels associate with increased risk of overall mortality. Combined with functional data on increased gut permeability our data strengthen the hypothesis of the gut-kinney axis as a source of chronic inflammation.

Funding: Government Support - Non-U.S.

FR-PO1021
Omega-3 Fatty Acid Modifies the Mitochondrial Membrane Fatty Acid and the Erythrocyte Membrane Fatty Acid in Uremic Rats
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Background: The kidney has the second highest mitochondrial content in the human body. Fatty acids (FAs) are one of the important energy sources and main constituents of cell membranes. Higher erythrocyte membrane oleic acid contents are related to acute coronary syndrome and omega-3 FA can reduce oleic acid contents. We investigated whether omega-3 FA modifies not only erythrocyte membrane FA but also mitochondrial membrane FA of kidney in adenine-induced uremic rats.

Methods: Male Sprague-Dawley rats were fed diets containing 0.75% adenine and 2.5% protein for three weeks. Rats were randomly divided into six groups that were fed diets containing 2.5% protein and saline with cholecalciferol (3000 IU/kg/week) or omega-3 FAs (300 mg/kg/day) with cholecalciferol, and supplemented by gastric gavage for four weeks: normal control, adenine control sacrificed at 5 weeks, adenine control sacrificed at 7 weeks, omega-3 FAs group sacrificed at 5 weeks, and omega-3 FAs group sacrificed at 7 weeks. The mitochondrial isolation membrane was used for renal mitochondrial extraction. The mitochondrial and erythrocyte membrane FA contents were measured by gas chromatography.

Results: Compared to the normal controls, serum creatinine levels in adenine controls were significantly increased and improved in omega-3 FA group. Compared to the adenine controls, erythrocyte and mitochondrial membrane monounsaturated FAs contents including oleic acid and arachidonic acid (AA) levels were significantly decreased in omega-3 FA group. FA compositions were similar between erythrocytes and mitochondrial membranes in each group. Monounsaturated FA contents including oleic acid, and eicosapentaenoic acid (EPA) were higher and saturated FA was lower in the mitochondrial membrane than erythrocyte membrane in adenine controls.

Conclusions: Omega-3 FA affects not only erythrocyte membrane FA but also mitochondrial membrane FA in uremic rats. Erythrocyte membrane FA contents can reflect mitochondrial membrane FA contents of the kidney.

FR-PO1022
Mendelian Randomization of Hypothyroidism and Kidney Function in Veterans
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Background: Hypothyroidism and chronic kidney disease (CKD) are highly prevalent conditions with a potential mechanistic link. A previous study in women from the Million Veteran Program (N=3336) described an association of hyperthyroidism and CKD. We studied the association of genetically predicted hypothyroidism in MVP, a large cohort composed of 93% men (exposure), and kidney function (outcome). The outcomes were creatinine-based GFR and cystatin-based GFR (both log-transformed) from CKDGen. We replicated our findings using two additional genetic datasets for the exposure.

Methods: Two-sample MR was conducted to study the associations between hypothyroidism and kidney function. The primary genetic instrument of the exposure for MR was derived from GWAS of hypothyroidism using data from MVP in 289,307 European American individuals (18,740 cases, 270,567 controls). We repeated the MR analyses, as shown in Table 1. Analyses were consistent in sensitivity and replication based on diagnosis codes, and in FinnGen, on levothyroxine prescription purchases. The outcomes were estimated using summary statistics from GWAS for eGFR from CKDGen for eGFR creatinine (N=133,413) and eGFR-cystatin C (N=32,834).

Results: Genetically predicted hypothyroidism demonstrated a causal relation with the risk of lower kidney function. In our primary analysis Cohorts: MVP/CKDGen (beta (SE): -0.009 (0.002), p=0.001). Results were consistent in sensitivity eGFR replicates, as shown in Table 1. There was no evidence of horizontal pleiotropy.

Conclusions: Our study findings support that hypothyroidism is causally associated with lower kidney function. The mendelian randomization methodology supports a causal relationship and is less susceptible to confounding and reverse causation biases.

Funding: Veterans Affairs Support

FR-PO1023
Action of 3-Hydroxymethylglutaryl Co A Reductase Inhibitors on ABCA-1 Protein (ATP-Binding Cassette Transporter-1) in Endothelial Cells Stimulated with Uremic Serum
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Background: High incidence of cardiovascular events in chronic kidney disease (CKD) presents an epidemic character, including patients on predialysis, hemodialysis and post-transplant patients covering about 50% of deaths, with a mortality rate around 9% per year. The statins have been used primarily in the treatment of dyslipidemia and have pleiotropic effects not fully elucidated, as well as, there is no evidence to support its use for attenuation of the cardiovascular outcome and its potential action on ABCA-1 transporter modulation in CKD. Thus, our aim was to verify the effect of statins on ABCA-1 modulation in cells culture of human umbilical vein (HUVEC) incubated with uremic serum from CKD patients.

Methods: Human umbilical cord vein endothelial cells (HUVECs) were pretreated with simvastatin and incubated with uremic serum. All groups were incubated for 24 hours at 37°C under ideal conditions of CO2 concentration. Expression of LXR-α, LXRβ, RXR-α, and ABCA-1 was performed by real-time PCR, the levels of Interleukin 10 and TNF-α in the cell supernatant were measured by enzyme immunoassay, using the ELISA kit. Transfection of HUVEC cells was performed for analysis of promoter finding mediated by LXR and RXR-reporter gene and the expression of LXR-α, RXR-α and ABCA1 was evaluated by Western Blot.

Results: We demonstrate that statins act on the inflammatory response of HUVECs exposed to the uremic environment by decreasing TNF-α secretion when compared to basal conditions. The results suggest that the uremic environment reduces the expression of LXR-β and RXR-α leading to a consequent decrease in ABCA-1 expression in HUVEC. Pretreatment of endothelial cells with simvastatin showed increased expression of ABCA-1, LXR-β and RXR-α, as well as the transcription of ABCA-1, LXR-β and RXR-α was significantly increased.

Conclusions: Our results suggest that statins may exert positive modulation on the LXR-β and RXR-α receptors for ABCA-1 transcription activation.

Funding: Government Support - Non-U.S.

FR-PO1024
AQP7 as a Novel Marker of p-Cresol-Induced Renal Cell Damage: Beneficial Effects of Hydroxyrosyl and a Polyphenolic Enriched Complex Derived from Olive Oil Mill Wastewater
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Background: p-cresol, a gut microbiota-derived uremic toxin, is related to renal injury and Chronic Kidney Disease (CKD). Nevertheless, the molecular mechanisms causing renal damage are still far from being clarified. Here, the actions of p-cresol and the beneficial effects of a polyphenolic enriched complex (Momast®) and hydroxyrosyl were evaluated.

Methods: Human proximal tubular kidney cells (HK-2) were used as an experimental cell model. Several cell stress biomarkers were assayed, including Reactive Oxygen Species (ROS) generation and Oil Red O lipid droplets formation. Gene and protein expression was tested by Real Time PCR and Western Blotting.

Results: Exposure of HK-2 cells to p-cresol (100 μM for 24 hours) caused a significant increase in ROS content and polymerization of the actin cytoskeleton. Moreover, a significant accumulation in lipid droplets was found as well. Interestingly, Real Time PCR and Western Blotting analysis revealed that p-cresol significantly upregulates the expression of the aquaglyceroporin AQP7. Notably, selective inhibition of AQP7 using Z43927330 prevented the p-cresol-induced lipid droplets storage. Of interest, the harmful actions induced by p-cresol were reversed by treating cells with Momast®, a natural complex derived from olive oil mill wastewater enriched with hydroxyrosyl (HT), which is filtered by the kidney and recovered in the urine. Preliminary data revealed that HT itself also prevents the p-cresol-induced AQP7 increase.

Conclusions: Altogether these findings propose for the first time AQ7 as a novel target related to p-cresol exposure. Selective inhibition of AQP7 significantly decreased lipid droplets accumulation, which is known to be correlated with renal cell injury. Additionally, treatment with Momast® prevented the effects induced by p-cresol. Moreover, obtained data indicate HT as a potential natural coadjuvant to counteract renal cellular injuries induced by p-cresol.

Funding: Government Support - Non-U.S.
FR-PO1025
Exaggerated Angiotensin II-Induced NF-κB p65 Signaling and Oxidative Stress in GSTM1-Deficient Kidney Primary Tubular Epithelial Cells Is Ameliorated by Hydrogen Sulfide
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Background: Glutathione S-transferase μ1 (GSTM1) belongs to the superfamily of GSTs that are phase II antioxidant enzymes regulated by nuclear factor erythroid 2-related factor 2 (Nrf2). In humans, homozygous carriers of the common GSTM1(0) null allele are deficient of the enzyme and have increased risks of chronic kidney disease (CKD) progression. Global Gsml knockout (KO) mice have increased renal levels of reactive oxygen species (ROS), inflammation, and kidney injury in angiotensin II (Ang II)-induced hypertension. We previously reported that deletion of Gsml augments Ang II activation of proinflammatory NF-κB p65 signaling pathway in primary tubular epithelial cells (PTECs). Recently, we discovered that GSTM1 modulates the transsulfuration (TSP)-hydrogen sulfide (H2S) pathway; loss of GSTM1 downregulates H2S production. GYA4137, an H2S donor, has been shown to prevent multi-organ damage in disease models. We hypothesize that GYA4137 would ameliorate AngII-induced NF-κB activation and ROS production in Gsml KO PTECs.

Methods: PTECs were isolated from Gsml KO and wild-type (WT) kidneys. Cells were starved for 4 hr, then treated with Ang II (100 mM) and with or without GYA4137 (100 mM) for 24 hr. Cells were stained with anti-NF-κB p65 antibody and assayed for ROS production using ab113851 kit (Abcam). NF-κB p65 nuclear staining was quantified as % of p65 nuclei-positively stained cells to the total cells, with 5 random fields counted in each group

Results: After Ang II treatment, compared to WT, KO PTECs had significantly increased nuclear p65 staining (%p65+ cells: WT 9.8 ± 1, KO 23.8 ± 2.5; p = 0.001), and ROS (1.48 x higher than WT; p = 0.002). Compared to Ang II only, Ang II + GYA4137 significantly decreased p65 nuclear translocation by 4.2% in WT (p = 0.02) and 11.4% in KO (p = 0.003), and ROS generation in both WT (55%, p = 0.002) and KO PTECs (68%, p = 0.001).

Conclusions: Deletion of Gsml augments Ang II induced ROS production and activation of NF-κB in AngII-dependent manner. Targeting the TSP-H2S pathway may be a novel therapeutic approach for CKD in those genetically susceptible.

Funding: NIDDK Support

FR-PO1026
Antisense Oligonucleotide-Mediated Terminal Intron Retention of Endoglin to Reduce Extracellular Matrix Production in Chronic Allograft Dysfunction
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Background: Chronic allograft dysfunction (CAD) is a chronic, progressive, and irreversible process associated with progressive interstitial fibrosis and tubular atrophy. Transforming growth factor-beta (TGF-β) is considered an important cytokine in the development of interstitial fibrosis. The TGF-β-receptor endoglin (ENG) tends to be upregulated in several human organs when chronic damage and fibrosis is present, including the kidney. ENG has two membrane bound isoforms occurring by alternative splicing. The long endoglin isotype (L-ENG) was previously shown to enhance the extent of renal fibrosis in an UUO mouse model, while the short endoglin (s-ENG) isoform ratio towards s-ENG has been suggested to inhibit renal fibrosis, does not increase accordingly. With ASOs targeting ENG, ROS generation in both WT(55%, p = 0.002) and KO PTEC (68%, p = 0.001).

Methods: We isolated mRNA from kidney biopsy material of patients with CAD (n=12) and generated constructs of ENG and short endoglin (s-ENG). As a control, kidneys that were excluded for transplantation were used (n=6). Furthermore, we designed antisense oligonucleotides (ASOs) to achieve higher levels of s-ENG by terminal intron retention of the ENG pre-mRNA and transfected these in the human kidney fibroblast cell line IMR-90.

Results: ENG mRNA is 2.3 fold (p<0.05) upregulated in the interstitium of patients with CAD compared to mRNA from controls. Interestingly, mRNA levels of s-ENG were not upregulated. Therefore, the fraction of s-ENG from the total ENG mRNA was significantly lower in CAD patients compared to controls (2.4% vs 4.3%; p<0.05). We showed that ASOs enhanced the splicing to the short endoglin isoform (2 fold; p<0.05).

Conclusions: ENG mRNA levels are upregulated in CAD, but s-ENG which is suggested to inhibit renal fibrosis, does not increase accordingly. With ASOs targeting ENG splicing we were able to alter the ENG isoform ratio towards s-ENG and reduce TGF-β1 downstream signaling. These results open the way to explore the potential of ENG ASOs as a therapy to reduce interstitial fibrosis and thereby slowing down the progression to end stage kidney disease.

Funding: NIDDK Support

FR-PO1027
p300/CBP-Associated Factor (PCAF) Modulates HIF-1 Activity at Multiple Steps
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Background: Hypoxia-inducible factor (HIF) is a transcription factor that mediates the cellular response to hypoxia. The activity of HIF may be inadequate relative to the degree of hypoxia in patients with chronic kidney disease (CKD), resulting in impaired cellular adaptation to hypoxia. p300/CBP-associated factor (PCAF) is a transcriptional coactivator and has acetyltransferase activity. Recent studies have suggested that PCAF expression is downregulated in patients with end-stage kidney disease (ESKD). We aimed to elucidate the relationship between PCAF and HIF-1 in the kidney.

Methods: We subjected human kidney-2 (HK-2) cells, a human proximal tubular cell line, to hypoxia and examined the association between PCAF and HIF-1 by qPCR, western blotting, microarray analysis, hypoxia-responsive element-luciferase (HRE-luc) reporter assay, and Gal4 responsive element-luciferase (GRE-luc) reporter assay. GRE-luc assay employed a vector encoding Gal4 DNA binding domain (DBD)-HIF-1α transactivation domain (TAD) fusion protein and a GRE-driven luciferase reporter vector.

Results: Knockdown (KD) of PCAF resulted in decreased expression levels of HIF-1α protein and VEGF mRNA, one of the major HIF-1 target genes. The HRE-luc assay revealed that PCAF KD reduced HIF-1α transcriptional activity. The GRE-luc assay showed the inhibition of HIF-1α TAD activity by PCAF KD. Overexpression of full-length PCAF upregulated GRE-luc activity, whereas a mutant PCAF lacking the histone acetyltransferase (HAT) domain failed to increase GRE-luc activity, indicating that the HAT domain was necessary for the regulation of HIF-1α TAD activity. Additionally, PCAF KD led to decreased mRNA and protein levels of ARNT, a binding partner of HIF-1α, and inhibited the interaction between HIF-1α and ARNT. Transcriptome analysis using microarray revealed that PCAF KD globally downregulated the expression of hypoxia-inducible genes.

Conclusions: Our findings demonstrate that PCAF modulates HIF-1 activity at multiple steps and serves as a global positive regulator for HIF-1.

Funding: Government Support - Non-U.S.
FR-PO1029
Glutathione Synthesis Contributes to the Formation of Tertiary Lymphoid Tissues in the Kidney
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Background: Tertiary lymphoid tissue (TLT) is an ectopic lymphoid tissue that is induced by peripheral lymphoid organs by several stimuli such as autoimmunity, aging, and chronic inflammation. TLTs serve as local sites for adaptive immune responses, in which vigorous lymphocyte proliferation and inflammatory cytokine production occur. Unlike the systemic activation of secondary lymphoid tissues, de novo formation of TLTs in local organs may require significant metabolic remodeling to meet the increased demand for metabolic resources both in parenchymal cells and immune cells. However, how renal parenchymal cells and locally recruited immune cells undergo metabolic alterations that support TLT formation remains to be elucidated.

Methods: We employed imaging mass spectrometry and metabolome analysis to investigate the key metabolic pathways that characterize renal TLTs. We also performed in situ hybridization combined with immunofluorescence to investigate the key molecules that govern the metabolic microenvironment of TLTs. Furthermore, we analyzed urine samples from both humans and mice to explore the metabolites that predict the presence of renal TLTs.

Results: Compared to other organs, the kidney contained more cytostatin/cysteine, a glutathione substrate. Kidneys with TLTs displayed a significantly higher concentration of glutathione than normal kidneys, and high-level enrichment of glutathione was observed specifically in renal TLTs, highlighting the importance of local glutathione synthesis in renal TLT formation. Furthermore, enhanced glutathione synthesis in TLTs was reflected in the urinary glutathione concentrations in both mice and humans, indicating that urinary glutathione levels effectively predict the presence or absence of renal TLTs.

Conclusions: We demonstrated that enhanced glutathione synthesis facilitates TLT formation in the kidney and that urinary glutathione can serve as a biomarker to detect renal TLTs. Immunometabolic interventions may provide new therapeutic strategies for kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO1030
DNA Double-Strand Breaks in Proximal Tubular Epithelial Cells Induce a Systemic Lipodystrophy-Like Phenotype
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Background: We have recently reported that podocyte DNA double strand breaks (DSBs) induce alteration in DNA methylation of CDS memory T cells which exacerbates severe podocyte injuries (Cell Rep 2023). We next investigated the pathophysiological significance of DNA DSBs in PTECs.

Methods: To investigate the significance of DNA double-strand breaks (DSBs) in PTECs, we generated PTEC-specific I-PpoI-expressing mice (I-PpoI mice) which express homolog endonuclease I-PpoI inducing non-mutagenic DNA DSBs.

Results: I-PpoI mice showed only mild elevation of tubular markers, but presented weight gain, hypertriglyceridemia, and decreased muscle and heart weight. We observed increased muscle and heart weight loss and impaired glucose tolerance at 16 weeks of age, which was consistent with the phenotype of systemic lipodystrophy. Metabolic analysis showed mitochondrial dysfunction with impaired fatty acid metabolism in kidney cortex and liver. Single-cell RNA-seq analysis revealed a marked expansion of inflamed and pro-inflammatory PTECs which was independently confirmed by flow cytometry. We also observed increased expression of inflammatory genes and cytokines in I-PpoI mice. The I-PpoI mice AGEs and diabetic complications in humans (2020). It was also confirmed that downstream genes of KLF9 was hypomethylated, including PFKFB3, which is reported to promote the proliferation and infiltration of inflammatory Ly6C+ monocytes into tissues and its differentiation into macrophages.

Conclusions: DNA damage in PTECs activated a different population of immune cells and caused quite different phenotypes from that in podocytes. PTEC DNA damage causes systemic metabolic alterations, associated with altered DNA methylation in peripheral blood cells.

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

FR-PO1031
Detection of Cellular Respiration Pattern of Platelets and Peripheral Blood Mononuclear Cells in CKD
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Background: Reduced cellular respiration of platelets and increased respiration of peripheral blood mononuclear cells (PBMCs) were reported to be associated with more severe chronic heart diseases. This cellular phenotype remains to be established for patients with chronic kidney disease (CKD).

Methods: The analysis included stage 4 or 5 CKD patients and healthy controls with normal kidney function. The investigation was performed using Oroboros O2K-respirometer on intact and diglition permeabilized cells. Cellular respiration was evaluated using a high resolution respirometry. Demographic and medical characteristics of participants including the cellular respiration of platelets and PBMCs were compared using Wilcoxon Rank Sum or Chi-square test.

Results: There were 27 CKD participants and 15 controls; median age (y) was 61 and 56, respectively. Two-third of the CKD patients were African Americans and half of them were diabetic. The median GFR was 18 in the CKD group and 90 in the control group. There were no differences in white blood cell count or platelet count between the two groups. There was reduced respiration in the intact cell platelets and in the permeabilized CKD platelets via Complex I & II of the electron transport chain (ETC). There was increased respiration in the intact CKD PBMCs as well as in the permeabilized CKD PBMCs via Complex I & II of ETC.

Conclusions: Cellular respiration is reduced in CKD platelets and is increased in CKD PBMCs. Future studies should explore whether these cellular phenotypes result in a pro-inflammatory CKD state that is associated with worse cardiorespiratory outcomes.

Funding: Private Foundation Support

FR-PO1032
Alterations in Frequency and Function Experienced Memory B Cells in Lupus Nephritis and Systemic Lupus Erythematosus
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Background: Various B cell abnormalities have been implicated in the pathogenesis of LN, and our previous studies have demonstrated that memory B cells assume pathogenic relevance in disease relapse. Exhausted B cell is a B lymphocyte aberration initially reported in HIV infection, and was also observed in autoimmune disorders. The pathophysiological roles of exhausted B cells in LN and disease relapse remains unclear.

Methods: Classical memory (CD19+CD21+CD27+) and exhausted B cells (CD19+CD21–CD27–) were measured in LN patients with multiple relapses (MR) (n=12) or no relapse (NR) (n=12) during disease remission. B cell-related cytokines, homing and inhibitory receptors, proliferation and calcium mobilization in classical and exhausted memory B cells were also assessed. Using single-cell RNA sequencing data from NIH and GEO, we also performed bioinformatics analysis to identify genes and pathways relevant to memory and exhausted B cells in SLE, LN and healthy controls.

Results: The MR group exhibited higher proportion of circulating exhausted B cells compared to NR (16.7 ± 9.5% vs 10.5 ± 5.7%, p<0.05). Blood levels of IL-6, BAFF and IL-21 in MR patients were higher than the NR group (75.1 ± 37.2 vs 33.6 ± 14.2 pg/ml; 1491.1 ± 680.9 vs 1120.1 ± 384.1 pg/ml and 23.5 ± 23.0 vs 5.1 ± 3.1 pg/ml respectively; p<0.05, for all). The MR had higher blood levels of Siglec-6, CXCR3 and CD62L than the NR group (2.6 ± 0.8 ± 1.3 ± 0.6 mg/ml; 2.3 ± 1.4 ± 1.6 ± 0.8 mg/ml; 3240.9 ± 1002.0 ± 2497.0 ± 671.8 mg/ml respectively; p<0.05 for all). Expression of inhibitory receptors CD22, CD85j, CD183 and FCL4 in exhausted B cells were increased in the MR group compared to the NR group. B cells from MR patients also showed decreased proliferation compared to MR patients (1.9 ± 1.1 vs 3.8 ± 1.3%, p<0.05) and impaired calcium mobilization in response to B-cell receptor triggering. STAT1, XAF1, MX1, IF4HL, EPSTI1, LCPI1, OASI, NEAT1, IFI16, IFI44 in exhausted B cells and XAF1, MX1, IFI44L in memory B cells play a pathogenic role in LN patients. SLE patient also show increased proportion of exhausted B cells compared to healthy control and the expression of STAT1, XAF1, MX1, IFI44L correlate positively with the proportion of exhausted B cells.

Conclusions: Our results suggested that altered numbers and function of exhausted B cells may have pathogenic significance in SLE and LN.

Funding: Government Support - Non-U.S.

FR-PO1033
Leukocyte Chemotactic Factor 2 Amyloidosis in an Egyptian Immigrant
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Introduction: Amyloidosis results from the accumulation of misfolded protein in one or more organs. Over 30 amyloid proteins have been discovered. Identification of the amyloid protein is crucial for the management of amyloidosis. Here we present a case of an unexpected cause of amyloidosis.

Case Description: A 69-year-old Egyptian man was referred for evaluation for chronic kidney disease. His history included well-controlled diabetes and hypertension. His creatinine was 1.7 mg/dL, having increased steadily from 0.96 mg/dL five years prior. Uremia was blood and urine protein to creatinine ratio was 0.1 g/g. Serologic evaluation was unremarkable except for a monoclonal spike seen on urine protein
electrophoresis. He underwent a kidney biopsy to evaluate for monoclonal gammapathy of renal significance. It showed abundant amyloid deposition in the interstitium; amyloid was also seen in the mesangium and glomerular capillary walls. Mass spectrometry analysis at the Mayo Clinic Laboratories identified the amyloid protein not as an immunoglobulin but as leukocyte chemotactic factor 2 (LECT-2). He does not appear to have LECT-2 amyloidosis (LECT-2) involvement of other organs. He continues to be managed supportively with an ACE-inhibitor and a SGLT-2 inhibitor. Despite these measures, his creatinine continues to increase by 0.2-0.3 mg/dL per year.

**Discussion:** ALECT-2 was first described in 2008 in an individual with nephrotic syndrome whose urinary protein excretion has only been found in a minority of cases of ALECT-2 in subsequent series—individuals typically have a bland urine sediment and minimal proteinuria. ALECT-2 commonly affects the kidneys and liver; cardiac involvement appears rare. Its prevalence appears to vary significantly among ethnic groups. In the United States, it has been found most commonly in Hispanic populations, particularly in those of Mexican descent. ALECT-2 is also common in Egypt; in an Egyptian case series, it was the second most common type of renal amyloidosis, accounting for 31% of cases.

It is unclear why it is more common in certain populations, although a single nucleotide polymorphism of the LECT2 gene has been found in individuals of Mexican ancestry. Currently, there is no specific treatment for ALECT-2. ALECT-2 is likely underdiagnosed due to the frequent lack of proteinuria. An individual’s ancestry may provide a clue toward the diagnosis.

**FR-PO1034**

Unveiling the Masquerade: Misdiagnosis of CKD in the Shadow of HIV

**Yariana E. Rodriguez Ortiz, Tariq Shafi, Angelina Edwards. Houston Methodist Hospital, Houston, TX**

**Introduction:** HIV is associated with acute and chronic kidney disease (CKD). The co-existence of CKD with HIV is associated with poor outcomes and limits therapeutic interventions, particularly those that require renal-dose adjustment. Specific antiretroviral therapies (ART) are directly nephrotoxic, leading to low GFR (Glomerular Filtration Rate) and elevated serum creatinine. However, some ART can increase serum creatinine by inhibiting the tubular secretion of creatinine, leading to elevated serum creatinine, erroneous estimation of GFR by eGFR, and a misdiagnosis of CKD. These drugs include non-nucleoside reverse transcriptase inhibitors (NNRTI) such as nevirapine, HIV integrase inhibitors such as dolutegravir, and pharmacokinetic boosters such as cobicistat.

We present a case of mislabeled CKD in the setting of cobicistat use.

**Case Description:** A 44-year-old man with a history of hypertension, non-insulin-dependent diabetes, and HIV was referred for evaluation of “CKD,” diagnosed due to persistent elevation of serum creatinine. The patient’s HIV was well controlled on Genvoya®, ART containing elvitegravir, cobicistat, emtricitabine, and tenofivir. Previous creatinine levels were 1.2, 1.4, and 1.6 mg/dL in the last 12 months. Recent pre-clinic labs showed a creatinine of 1.48 mg/dL with an eGFR of 59 mL/min/1.73 m2 without albuminuria or hematuria. Renal ultrasound showed preserved renal size and normal anatomy. To obtain an accurate assessment of GFR, we directly measured GFR (mGFR) using plasma clearance of iohexol, a non-radiolabeled contrast agent. The mGFR of 72 mL/min/1.73 m2. Thus, the eGFR calculation was incorrect and mislabeled him as CKD.

Cobicistat reduces serum creatinine secretion by reducing proximal tubular creatinine efflux by the SLC7A11 cation transporter.

**Discussion:** Evolving combination HIV therapies have improved compliance, tolerance, and sustained viral suppression. However, clinicians must be mindful of the impact of ART on the kidney. Our case highlights the false elevation of serum creatinine induced by ART like Genvoya® and the importance of directly measured GFR. Modern methods to measure GFR are simple and easy to implement in outpatient practice. It is essential for nephrologists to be familiar with these techniques and use them in clinical practice to prevent misdiagnosis of CKD and avoid further invasive tests, including kidney biopsy.

**FR-PO1035**

Finerenone Added to Renin-Angiotensin System (RAS)/SGLT2 Blockade for Non-Diabetic CKD: Results of a Preclinical Randomized Controlled Trial

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**Background:** Aging had an effect on diminished endothelial glycocalyx caused by oxidative stress and inflammation, which were known causes of aging. Resveratrol, an SIRT1 activator, may prevent these undesired events by activating SIRT1 pathway. We examined whether resveratrol could improve renal function and prevent from diminishing endothelial glycocalyx caused by aging, and consequently with changes of oxidative stress.

**Methods:** Male 2-month-old and 18-month-old C57BL/6 mice were divided into three groups: 2-month-old young group, 18-month-old aged control group and 18-month-old aged treatment group. Resveratrol (40 mg/kg) was administered to aged treatment group for 6 months. Renal function, histologic changes and aging-related endpoints were monitored in these groups. Methods were performed a preclinical randomized controlled trial (RCT) study (NCT02852962) in C57BL/6 mice. Treatment was initiated in late (6 weeks of age) in mice with elevated serum creatinine and albuminuria and in presence of glomerulosclerosis, interstitial fibrosis and tubular atrophy. We randomized male and female mice to either nil (vehicle) or late onset food mixture of either monotherapy, ramipril (10 mg/kg) plus emapralifozin (36 mg/kg) or ramipril plus emapralifozin plus finerenone (10 mg/kg). Other control mice received emapralifozin or finerenone monotherapy.

**Results:** Mean lifespan was 63.7 ± 10.0 days (vehicle), 77.3 ± 5.3 days (ramipril), 70.4 ± 9.2 days (emapralifozin), 71.1 ± 7.1 days (fierenone), 80.3 ± 11.0 days (dual).

Mean survival was 63.7 ± 10.0 days (vehicle), 77.3 ± 5.3 days (ramipril), 70.4 ± 9.2 days (emapralifozin), 71.1 ± 7.1 days (fierenone), 80.3 ± 11.0 days (dual), and 103.1 ± 20.3 days (triple), respectively. Sex did not affect outcome. Histopathology, pathogenesis, and aN-peptide sequencing revealed significant add-on anti-inflammatory and anti-fibrotic effects on the tubulointerstitial compartment when adding finerenone to dual RAS/SGLT2 inhibition.

**Conclusions:** This preclinical study suggests that triple RAS/SGLT2/MR blockade may significantly prolong mean renal lifespan significantly in patients with type 2 diabetes mellitus and possibly other progressive chronic kidney disorders for its synergistic protective effects on the glomerular and tubulointerstitial compartment, respectively.

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

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

Underline represents presenting author.

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The pathological features, increased CML and IGFBP-3 protein expression, and increased senescence and fibrosis-related protein expression in the kidneys of aged mice could be effectively antagonized by AGE inhibitor aminoguanidine treatment (p<0.05, n=8). The neutralizing IGFBP-3 antibody treatment could also alleviate the pathological features and fibrosis in the kidneys of aged mice (p<0.05, n=8).

Conclusions: These findings demonstrated that both AGEs and IGFBP-3 played the roles in age-related CKD. An AGEs-regulated IGFBP-3 signaling pathway may contribute to the renal dysfunction and injury during natural aging process.

Funding: Government Support - Non-U.S.

FR-PO1039
Aldehyde Dehydrogenase 2 Interacts with PHB2 to Alleviate Renal Fibrosis and Ferroptosis in a Mitochondria-Dependent Manner
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Background: We recently proved the protective role of acetaldehyde dehydrogenase 2 (ALDH2) in acute kidney injury (AKI). In this study, we aimed to investigate the impact of ALDH2 on renal fibrosis in regulating ferroptosis in a mitochondria-dependent manner.

Methods: Renal fibrosis model was established by unilateral ureteral obstruction (UUO) in C57BL mice, followed by injection of Alda-1 (an ALDH2 agonist) on the first postoperative day and continued for 14 days until mice were sacrificed. We assessed renal fibrosis, ferroptosis, and mitochondrial function in vivo and in vitro using RSL-3 (a ferroptosis-inducing agent) in human renal proximal tubular epithelial (HK-2) cells, with or without Alda-1 (20 μM). Furthermore, we identified the potential targets of ALDH2 in regulating ferroptosis and mitochondrial dysfunction by mass spectrometry screening and co-immunoprecipitation assays, then explored the role of ALDH2 on different cell types by single-cell RNA sequencing.

Results: ALDH2 protein was reduced by 64% in UUO mice accompanied by renal interstitial fibrosis. ALDH2 agonist Alda-1 alleviated renal interstitial fibrosis, as confirmed by Masson staining and the decreased expression of α-SMA and collagen 1. Ferroptosis was initiated during UUO-induced renal fibrosis, while Alda-1 inhibited ferroptosis, indicated by reduced malonaldehyde (MDA) (1.60 ± 0.10 versus 0.66 ± 0.08 nmol/mg, P<0.001) and elevated GSH/GSSG ratio (1.42 ± 0.32 versus 6.80 ± 0.84, P<0.05). In addition, decreased mitochondrial-related proteins (PGC-1α and ATP5A1) were observed in UUO mice but reversed by Alda-1 treatment. In HK-2 cells, ALDH2 improved RSL-3-induced ferroptosis, fibrosis, and mitochondrial dysfunction. Mechanistically, mass spectrometry screening and co-immunoprecipitation assays revealed the interaction of ALDH2 with prohibitin 2 (PHB2), a crucial mitophagy receptor and ferroptosis inhibition target. Immunofluorescence staining revealed the co-localization of ALDH2 and PHB2, and Alda-1 facilitated PHB2 recruitment into mitochondria from the cytoplasm.

Conclusions: ALDH2 might be a promising therapeutic target in alleviating renal fibrosis and ferroptosis by interacting with PHB2 to facilitate their mitochondrial translocation.

Funding: China Postdoctoral Science Foundation.

FR-PO1040
Acetoxyacetyl Hydrolase Protects Against Kidney Injury via Inhibition of Tubular CD74-Macrophage Cross-Talk
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Background: Renal tubulointerstitial fibrosis is the final common pathway in the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD). Acetoxyacetyl hydrolase (AOAH) is expressed in renal tubular epithelial cells and other immune cells. Research shows that AOAH plays a critical role in infections and chronic inflammatory diseases. However, its role in kidney injury and fibrosis is unknown.

Method: AOAH expression was examined in human and mouse kidneys. Single cell RNA sequencing (scRNA-seq) was performed for kidneys from FA-treated wild type (WT) and Aoah -/- mice. Aoah -/- mice and Aoah +/+ mice with overexpression of Aoah in kidney were used to determine its role in kidney injury induced by folic acid (FA), unilateral ureteral obstruction (UUO), and lipopolysaccharide (LPS).

Results: AOAH expression was positively correlated with estimated glomerular filtration rate (eGFR) while negatively correlated with the degree of renal fibrosis in human kidney biopsy tissue. AOAH deletion led to exacerbated kidney injury and fibrosis after FA administration, which was reversed by overexpression of Aoah in kidney. scRNA-seq analysis revealed that Aoah -/- mice exhibited increased subpopulation of proximal tubular epithelial cells (PTECs) expressing CD74, even though total PTECs were decreased compared to WT mice after FA treatment. Finally, exacerbated renal inflammation and fibrosis seen in Aoah -/- mice were alleviated by administration of ISO-1, an inhibitor of macrophage inhibition factor (MIF) and CD74 binding.

Conclusions: AOAH plays a protective role in renal inflammation and fibrosis by inhibiting renal tubular epithelial cells CD74 signaling pathways, which involves tubule-macrophage crosstalk. Targeting kidney AOAH represents a promising strategy to prevent renal fibrosis progression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
FR-PO1041

Protective Role of Tubular Interferon Regulatory Factor 5 (IRF5) Against Renal Tubulointerstitial Fibrosis
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Background: Renal fibrosis is a common characteristic of various chronic kidney diseases (CKDs) driving the loss of renal function. During this pathological process, proliferation and activation of interstitial fibroblasts chiefly determine the extent of renal fibrosis. TP53RK is an atypical protein kinase and an important component of the EKC/KEOPS complex. Recently, TP53RK was identified as novel monogenic cause of Galloway–Mowat syndrome. However, no experimental evidence confirmed the role of TP53RK in CKDs.

Methods: Expression and localization of TP53RK was evaluated in kidneys of CKD patients and mice with unilateral ureteral obstruction (UUO) and unilateral ischemia reperfusion (UIR). Then, the specific function of fibroblast TP53RK in CKD was determined with fibroblast specific TP53RK knockout mice with UUO or UIR and TGF-β1-treated renal interstitial fibroblasts (NRK-49Fs) and macrophages (RAW 264.7). Mechanic research revealed that IRF5 suppressed fibrotic response possibly by antagonizing TGF-β1/Smad3 signaling.

Results: TP53RK was consistently up-regulated in fibrotic kidneys of CKD patients and mice, dominantly in the tubules. Overexpression of IRF5 markedly alleviated renal TIF and knocking down of IRF5 significantly aggravated the degree of fibrosis in UUO mice. In vitro, overexpression of IRF5 inhibited TGF-β1-induced partial epithelial-mesenchymal transition (p-EMT) of mPTCs. IRF5 overexpression in TGF-β1-induced mPTCs also suppressed the activation of co-cultured NRK-49Fs and RAW 264.7 cells. Mechanic research revealed that IRF5 suppressed fibrotic response possibly by antagonizing TGF-β1/Smad3 signaling.

Conclusions: These findings demonstrated that up-regulation of IRF5 may inhibit p-EMT of tubular epithelial cells via antagonizing TGF-β1/Smad3 signaling. In turn, protected tubular epithelial cells attenuated the activation of interstitial fibroblasts and macrophages and thus attenuate kidney fibrosis. Targeted activation of IRF5 may serve as a potential intervention strategy in retarding CKD progression.

Funding: Government Support - Non-U.S.

FR-PO1042

TP53RK in Fibroblasts Drives the Progression of CKD by Phosphorylating Birc5
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Background: Tubulointerstitial fibrosis (TIF) is the inevitable outcome of chronic kidney diseases, regardless of etiology. Interferon regulatory factor 5 (IRF5) is a key transcription factor involved in regulating the expression of proinflammatory cytokine and resultant response to infection in immune cells, but its role in renal epithelial cells and renal TIF remain unknown.

Methods: Renal biopsies of CKD patients and kidney of unilateral ureteral obstruction (UUO) and unilateral ischemia reperfusion (UIR) mice were used to evaluate the expression pattern of IRF5 in fibrotic kidneys. Then, the function of IRF5 was explored in UUO mice via high-throughput tail vein delivery of IRF5 over-expression plasmids or IRF5 targeting CRISPR/Cas9 plasmids. The TIF was histologically detected by Masson staining; pro-fibrosis gene expressions were evaluated via Western blotting and qRT-PCR techniques. In vitro, mouse proximal tubular epithelial cells (mPTCs) were transfected with IRF5 over-expression plasmids and then stimulated with TGF-β1 for phenotype evaluation. IRF5 over-expression mPTCs were also cultured with renal interstitial fibroblasts (NRK-49Fs) and macrophage cells (RAW 264.7). Finally, IRF5 overexpressing mPTCs were treated with Smad3 selective inhibitor SIS3 to explore whether the anti-fibrotic effect of IRF5 is Sma3 dependent.

Results: IRF5 was consistently up-regulated in fibrotic kidneys of CKD patients and mice models, dominantly in the tubules. Overexpression of IRF5 markedly alleviated renal TIF, and knocking down of IRF5 significantly aggravated the degree of fibrosis in UUO mice. In vitro, overexpression of IRF5 inhibited TGF-β1-induced partial epithelial-mesenchymal transition (p-EMT) of mPTCs. IRF5 overexpression in TGF-β1-induced mPTCs also suppressed the activation of co-cultured NRK-49Fs and RAW 264.7 cells. Mechanic research revealed that IRF5 suppressed fibrotic response possibly by antagonizing TGF-β1/Smad3 signaling.

Conclusions: These findings demonstrated that up-regulation of IRF5 may inhibit p-EMT of tubular epithelial cells via antagonizing TGF-β1/Smad3 signaling. In turn, protected tubular epithelial cells attenuated the activation of interstitial fibroblasts and macrophages and thus attenuate kidney fibrosis. Targeted activation of IRF5 may serve as a potential intervention strategy in retarding CKD progression.

Funding: Government Support - Non-U.S.

FR-PO1043

Activation of GPER1 in macrophage ameliorates Unilateral Ureteral Obstruction (UOO)-Induced Renal Fibrosis
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Background: Numerous studies have established the fundamental role of macrophages in the process of renal fibrosis. Interestingly, emerging data suggested that G protein-coupled estrogen receptor 1 (GPER1), a novel estrogen receptor, plays a ubiquitous role in regulating macrophage activities and proinflammatory pathways. However, the precise role of GPER1 in macrophage-mediated renal fibrosis remains unknown.

Methods: First, we pretreated ovariectomized (OVX) female and male mice with O1 (GPER1 agonist) and subjected them to UUO (Ureteral Unilateral Obstruction) surgeries. And renal fibrosis and M1 and M2 macrophage infiltration were analyzed. Next, using CRISPR/Cas9 gene editing technique, we also generated global knockout Gper1 mice. We performed UUO modeling on the male Gper1 mice and measured the degree of renal fibrosis and inflammation. And in vitro study, bone marrow-derived macrophages were treated with G1 in response to LPS/Interleukin 4 and cocultured with PTECs (primary tubular epithelial cells) or fibroblasts.

Results: Compared to vehicle-treated OVX female and male mice subjected to UUO, both G1-treated OVX female and male UUO mice exhibited fewer renal fibrotic lesions and less M1 and M2 macrophage infiltration in the kidney tissues, respectively. On the other hand, Gper1 deletion accelerated renal fibrosis and enhanced chemokines and proinflammatory cytokines expression. In vitro study demonstrated that GPER1 activation prevented M0 macrophages from polarization towards the M1 and M2 phenotypes. The Gene Ontology analysis of differentially expressed genes in macrophages treated with or without G1 indicated that GPER1 activation was primarily involved in the inhibition of MAPK pathways, which was further validated by immunoblottting. In addition, PTECs cocultured with G1-treated M1 macrophages exhibited fewer injuries and immune activation, and fibroblasts cocultured with G1-treated M2 macrophages showed downregulated extracellular matrix expression.

Conclusions: Overall, our study is the first study to demonstrate the effect of GPER1 on macrophage-mediated renal fibrosis via inhibition of M1 and M2 macrophage polarization. These results indicate that GPER1 may serve as a promising therapeutic target for the treatment of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO1044

GPER1 Plays a Protective Role Against AKI to CKD Transition
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Background: Male patients have a higher prevalence of CKD and increased rates of ESRD than those observed in female patients. Many factors are believed to be involved in this phenomenon. GPER1, a de novo estrogen receptor, has been shown to play an important role in the renal fibrosis process. Whether GPER1 is protective against AKI to CKD transition and its main mechanism remains unclear.

Methods: Using CRISPR/Cas9 gene-editing technique, we generated Gper1 global knockout mice. We subjected the mice to Astrolobic acid(AA) and Folic acid(FA) injections to mimic AKI to CKD transition. We treated AA-injected and FA-injected mice with a GPER1 agonist(G-1). We also cultured primary renal tubular epithelial cells(TECs) from wild-type and Gper1 mice and treated the primary cells and NRK-49F cell lines with TGFβ1 and oleic acid with or without G1 administration.

Results: In both AA and FA injection models, Gper1 knockout mice exhibited more severe renal fibrosis, increased inflammation infiltration, decreased fatty acid oxidation, and activated PI3K/AKT pathway compared to wild-type mice. GPER1 agonist attenuated renal fibrosis and improved fatty acid oxidation in AA-injected and FA-injected mice models, respectively. In vitro study, TGFβ1-treated Gper1-/- TECs showed a reduction in fatty acid oxidation and ATP synthesis. GPER1 activation restored fatty acid oxidation and ATP synthesis, which were suppressed by TGFβ1 and oleic acid in primary PTECs and NRK-49F.

Conclusions: These results suggest that GPER1 may play a protective role against AKI to CKD transition through the fatty acid oxidation pathway. Activation of GPER1 expression may provide a new therapeutic target for AKI to CKD transition.

Funding: Government Support - Non-U.S.
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Background: Our previous study has reported that renal lymphangiogenesis accelerates the progression of chronic kidney disease (CKD). However, it is not clear which immune cell types drive renal outcome.

Methods: We established the selective proliferating lymphatic vessel knockout mice for unilateral ureteral obstruction (UUO)-induced fibrosis. Bulk RNA sequencing and single-cell RNA sequencing were used to characterize changes in the transcriptional profiles of renal parenchymal and immune cell following the knocking down of lymphatic vessels (LVs).

Results: The fibrosis were alleviated following knockdown of LVs. Bulk RNA sequencing showed that the impaired secretion of cytokines and chemokines, and impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation impaired energy metabolism were improved.

Conclusions: ACLYi reduced fibrosis, apoptosis and lipid accumulation in the UUO group. ACLYi also prevented profibrotic responses in PTEC and fibroblasts. Current studies are ongoing to confirm beneficial effects on restoring FAO.

Funding: Commercial Support - Esperivita Therapeutics, Government Support - Non-U.S.

FR-PO1048
Dicarboxylic Acids Protect Against CKD
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Background: Chronic kidney disease (CKD) affects 30 million people in the US and over 800 million people worldwide. Treatment for end-stage renal failure is largely limited to renal transplant or lifelong dialysis, creating an urgent need for new therapies. We have shown that dicarboxylic acids are protective against acute kidney injury (AKI) in the proximal tubule via hypersucinylation of mitochondrial and peroxisomal proteins, thereby bolstering peroxisomal fatty acid oxidation and mitochondrial FAO. In this study we aimed to determine whether this mechanism could be leveraged to protect against fibrotic damage due to chronic kidney injury, which we model using Unilateral Ureteral Obstruction (UUO) surgery.

Methods: Wild-type male B6/129 mice were procured from Jackson Laboratories and the experimental group fed with an 10% 8-chain dicarboxylic acid (DC 8, suberic acid) diet. Both the experimental and the control groups underwent UUO surgery, whereby the ureter of one kidney was obstructed for three days before both kidneys were harvested. Each kidney was split into four pieces as follows – 1. histological and immunohistochemical staining; 2. fatty acid oxidation analysis; 3. succinylamine analysis using targeted mass spec; 4. snap-frozen for validation and downstream analysis of fibrosis, as well as peroxosomal and mitochondrial signaling.

Results: As previously shown, there was hypersucinylation in the DC 8 treated animals compared to control fed animals. This was accompanied with corresponding upregulation of peroxosomal FAO specifically in the collecting ducts, which was confirmed by targeted mass spec. Supplementation of DC 8 showed marked protection in the collecting ducts, with decreased dilation and tubular epithelial shedding compared to controls. There was also a decrease in the dilation of the renal pelvis in DC 8 treated animals. Further to this immunohistochemical staining showed a decrease in fibrotic markers in the kidneys of DC 8-fed animals.

Conclusions: Taken together this suggests that DC 8 is protective against collecting duct damage and fibrotic changes that occur in CKD. This expands the utilization of DC 8 therapy beyond the acute setting and into fibrosis and chronic kidney disease.
Dose-Dependent Nephroprotective Effects of an ALK5 Inhibitor in the Unilateral Ureteral Obstruction (UUO) Mouse Model of Kidney Fibrosis


Background: Development of renal fibrosis is a hallmark of chronic kidney disease (CKD) and an essential factor for progressive loss of kidney function and development of end-stage kidney disease. The unilateral ureteral obstruction (UUO) mouse is a widely used surgery-induced model of CKD with rapid induction of renal inflammation and fibrosis. Here, we characterized the effect of an anti-fibrotic TGF-β type 1 receptor kinase inhibitor (ALK5 inhibitor, ALK5ki) on renal outcomes in the UUO mouse.

Methods: Male C57BL/6J mice (9 weeks old) were randomly assigned into six groups based on body weight and were either sham-operated or underwent UUO surgery. UUO mice received vehicle or ALK5i (3, 10 or 30 mg/kg, PO, BID) for 8 days. Vehicle-dosed sham-operated mice served as controls. At termination, both kidneys were weighed, and renal morphometry was performed. A semi-quantitative histological feature score based on macrophage infiltration (F4/80), fibrosis (Col1a1, Col3a1), myofibroblast activation (α-SMA) and tubular injury (KIM-1). Plasma was sampled for measurement of KIM-1 levels.

Results: UUO mice displayed marked kidney tubular injury, macrophage infiltration, myofibroblast activation, and fibrosis compared to sham-operated animals. ALK5i dose-dependently improved kidney histology and plasma KIM-1 levels.

Conclusions: ALK5ki exerted dose-dependent nephroprotective effects in the UUO mouse. Given the rapid induction of fibrosis and inflammation, the UUO mouse is an attractive model for screening compounds with potential anti-inflammatory and antifibrotic effects.

Funding: Commercial Support - Gubra

Cellular Prion Protein Attenuates Renal Fibrosis by Interaction with Epithelial Growth Factor Receptor

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Background: Cellular prion protein (Prp c) encoded by the Prnp gene, is a kind of cell-surface copper-binding protein, anchoring on cell membrane lipid rafts through glycosyl phosphatidyl inositol anchor (GPI), and plays an important role in cell information transmission. Prp c is overexpressed in the kidney biopsies from patients with CKD. However, the role of Prp c in regulating fibrotic adaptive repair of the injured kidney remains largely unknown.

Methods: Wild-type FVB mice, Prnp−/− mice were used for in vivo studies. Renal 1R injury model was induced by unilateral renal pedicle clamping for 35 minutes. Renal fibrosis models were induced by unilateral renal pedicle clamping for 30 minutes (I/R) and by unilateral ureteral obstruction (UUO). HK-2 cells were used for in vitro studies. HK-2 cells were treated with TGF-β1 induce EMT.

Results: Prp c overexpression in the kidney biopsies from patients with CKD. This is supported by our experimental data showing that Prp c is gradually upregulated in the kidney following 1R, I/R and UUO insult and Prp c deletion by knocking out Prnp promoted AKI and facilitated fibrosis at later stages. Proteome analysis indicated that the expression of key protein in DDR, including replication protein A (RPA), max inhibiting minichromosome maintenance protein 2/4/6 (MCM2/4/6) and cyclin-dependent kinase 1/2 (CDK1/2), as well as epidermal growth factor receptor (EGFR) drastically upregulated in the 1R kidney, while in Prnp−/− mice, EGFR rises even further with DDR-associated protein slumping. Furthermore, we uncover a critical role of Prp c in regulating fibrotic maladaptive repair of the injured kidney remains largely unknown.

Conclusions: By modulating the activation of EGFR pathway and promoting cell cycle progression, Prp c plays an adaptive nephroprotective role by modulating activation of EGFR pathway and promoting cell cycle progression.

Funding: Government Support - Non-U.S.

Piperazin Furate Regulates Renal Fibrosis by Alleviating Oxidative Stress in Renal Tubular Epithelial Cells

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Background: Chronic kidney disease (CKD) is one of the greatest public health hazards worldwide with a high mortality rate, poor quality of survival. Oxidative stress in CKD could aggravate tubular injury to renal fibrosis. The treatment of oxidative damage to renal tubular epithelial cells still needs extensive research and development of drugs. This study was conducted to explore the effect of piperazin furate on renal fibrosis and the antioxidant maladaptive repair of renal tubular epithelial cells to provide a new therapeutic strategy for the application of piperazin furate in CKD.

Methods: 36 male C57 mice at 6-8 weeks were randomly divided into six groups (n=6). sham group (saline 0.2 mL), UUO group (saline 0.2 mL), piperazin furate low-dose intervention in UUO group (piperazin furate 50 mg/kg, 0.2 mL), piperazin furate medium-dose in UUO group (piperazin furate 100mg/kg, 0.2 mL), piperazin furate high dose in UUO group (piperazin furate 200mg/kg, 0.2 mL), and piperazin furate alone (piperazin furate 200mg/kg, 0.2 mL). The mice were anesthetized and their kidneys were harvested on the 7th day after surgery, and the relevant samples were collected and stained with HE, PAS and Masson to observe the tubular shape, atrophy, necrosis and the degree of interstitial fibrosis, and the fibrosis-related indexes. The collagen-related type I collagen-1, α-SMA and Smad3 were observed by immunohistochemistry or protein blotting. The safe concentration range of piperazin furate in HK2 cells was screened by CCK8 in vitro and IC50 was calculated to select a safe concentration for intervention in TGF β-treated HK2 cells, subsequently protein blotting was used to detect the expression of collagen-1, p-Smad3, KiM-1, HO-1 and dichlorofluorescein (DCF) was revealed in HK2 cells after intervention of renal tubular epithelial cells were detected by protein blotting.

Results: Pathological staining showed that the fibrosis, renal tubular epithelial injury and ultrastructural stress were alleviated in UUO group treated with piperazin furate at a dosage dependent manner, compared to that of sham-operated group. We also observed the same phenomenon in the HK2 cells with piperazin furate treatments upon TGF β stimulation.

Conclusions: Piperazin furate could significantly alleviate oxidative stress injury in renal tubular epithelial cells against renal fibrosis.

Funding: Government Support - Non-U.S.
signaling. In cultured renal epithelial cells, TGF-β exposure promoted the interaction of EZH2 with Notch1 or Notch3, and expression of Jagged-1, Hes1, and Hes2, and EZH2 inhibition abrogated these responses. Finally, chromatin immunoprecipitation indicates that kidney injury enhanced EZH2 and H3K27me3 at the promoter regions of the Notch1 and Notch3 promoter, and treatment with EZH2 inhibitor abolished this response.

**Conclusions:** Our data indicate that overexpression of EZH2 in renal tubular cells and fibroblasts contributes to renal fibrosis by a mechanism associated with the activation of Notch signaling and suppression of Klotho and BMP7.

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

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**FR-PO1054**

**Protective Effect of Heparan Sulphate Derivative Against Glycocalyx Damage-Induced Renal Fibrosis in Aging Mice**

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**Background:** Aging-related glycocalyx loss causes renal fibrosis in aging kidneys. Heparan sulphate (HS) is a sulfated glycosaminoglycan (GAG) that forms the underlying protective extracellular matrix in the basement membrane of the kidney and other organs. Heparan sulphate derivative (HSD) can be a potential target for treatment of kidney fibrosis.

**Methods:** Male C57BL/6 mice (7 weeks old, n = 30) were randomly assigned to four groups: uIRI/vehicle (distilled water), uIRI/MN705 (600 mg/kg/day), uIRI/17-DMAG (2 mg/ml), and uIRI/17-DMAG + SDX (AM+SDX group, n=18). SDX was administered to 10 mg/kg per oral daily for six months. We compared the following parameters between the groups: renal function, blood pressure, renal pathology, activities of the PI3K-Akt-MMP2 and MMP9-Syndecan4 in kidneys of aging mice, but those changes were not showed significantly lower expression of PI3K, phosphorylated Akt, MMP2, MMP9 with the YM group. In protein related with PI3k-Akt pathway, the AM+SDX group compared with the AM group (p<0.05), but the YM+SDX group was similar and expressions of protein related to fibrosis significantly reduced in the AM+SDX group compared with the AM group (p<0.05 for all), but it showed no significant decrease in the protein expression of fibronectin (64.7% of control in 0.1 mg/ml dose, 22.3% of control in 0.2 mg/ml dose, P = 0.01). and phospho-smad2/3 (87% ± 22% of control in 0.2 mg/ml dose, P < 0.01).

**Conclusions:** The extract of Rubus coreanus attenuates kidney fibrosis in the UUO model and TGF-β-treated human kidney proximal tubular cells. TGF-β-related Smad and Smurf signaling pathways involved in the development of fibrosis in both in vivo and in vitro models are effectively inhibited through extract of Rubus coreanus and can be a potential target for treatment of kidney fibrosis.

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**FR-PO1056**

**HSP90 Inhibitor 17-DMAG Downregulated METTL3 and Attenuates Renal Fibrosis in AKI to CKD Model**

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**Background:** N6-methyladenosine (m6A) RNA methylation has been reported to participate in post-transcriptional gene expression regulation and development of kidney fibrosis.

**Methods:** AKI to CKD transition was induced by unilateral ischemic-reperfusion (uIRI) method (transient clamping followed by de-clamping of renal artery) in C57BL/6 mice. HSP90 Inhibitor 17-DMAG was injected intraperitoneally with 20 mg/kg dose. Renal fibrosis is evaluated using both imaging and molecular parameters. As imaging parameters, size, resistive index (RI), vascular index (VI; colored pixels / all pixels on microvascular imaging), and shear wave parameters were compared. Histology-based fibrosis score was also evaluated. And we evaluated the expression of fibrosis and inflammatory marker proteins such as TGF-β, α-SMA, Collagen 1 and E-Cadherin in uIRI model. Furthermore, we incubated human proximal tubular epithelial (HK2) cells under TGF-β (10 ng/ml) treatment as an in vitro model of kidney fibrosis.

**Results:** Imaging markers of uIRI/17-DMAG showed better results than that of uIRI alone (Size, 7.3±3.3 vs. 10.7±4.8; RI, 0.79±0.09 vs. 0.68±0.05; VI, 9.4±6.0% vs. 18.0±4.1%; all, p<0.05). Shear wave elastography did not show significant difference between uIRI/17-DMAG and uIRI alone mice. 17-DMAG treatment attenuated the degrees of kidney fibrosis in vivo mice uIRI model (Histology-based fibrosis score 7.5±1.2 in uIRIVehicle vs. 4.6±1.7 in uIRI/17-DMAG, P = 0.016). Expression of α-SMA and Collagen 1 proteins were lesser in uIRI/17-DMAG compared to uIRI vehicle. In HK2 cell, 17-DMAG attenuated METTL3 expression regardless of TGF-β treatment. 17-DMAG treatment also downregulated epithelial marker (E-cadherin), and upregulated interstitial markers (N-cadherin, Vimentin, NET1). However, Hsp90 depletion using siHsp90RNA did not show METTL3 decrease in HK2 cell.

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**FR-PO1055**

**Rubus coreanus Extract Attenuates Kidney Fibrosis Through TGF-β/Smad Pathway Inhibition**

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**Background:** Rubus coreanus, a wild berry belonging to the Rosaceae genus, has been found to have various health benefits, including anti-oxidative effects.

**Methods:** Male C57BL/6 mice (7 weeks old, n = 30) were randomly assigned to the sham/vehicle (distilled water), sham/MN705 (600 mg/kg/day), UUO/vehicle, UUO/MN705-low dose (300 mg/kg/day), and UUO/MN705-high dose (600 mg/kg/day) groups in the same numbers (n = 6 in each group). MN705 and distilled water were administered orally using a stainless feeding needle. After 7 days of pre-treatment, sham or UUO operation was performed, and treatment drugs were administered at the same dose for 7 days. In addition, HK-2 cells were cultured and challenged with TGF-β (2 ng/ml) with or without an extract of Rubus coreanus (0.5-2 mg/ml).

**Results:** In the histopathologic specimen of Masson’s trichrome stain, areas of kidney interstitial fibrosis were attenuated in the treatment group (3.6 ± 0.9 % area vs. 8.7 ± 3.0 % area, P < 0.01). In the Western blot analysis, protein abundance of collagen-1 (50.6% of control, P = 0.04) significantly decreased in the treatment group. In the in vitro experiment, HK-2 cells treated with TGF-β and MN705 showed a dose-dependent significant decrease in the protein expression of fibronectin (64.7% of control in 0.1 mg/ml dose, 22.3% of control in 0.2 mg/ml dose, P = 0.01) and phospho-smad2/3 (87% ± 22% of control in 0.2 mg/ml dose, P < 0.01).

**Conclusions:** The extract of Rubus coreanus attenuates kidney fibrosis in the UUO mouse model and TGF-β-treated human kidney proximal tubular cells. TGF-β-related Smad and Smurf signaling pathways involved in the development of fibrosis in both in vivo and in vitro models are effectively inhibited through extract of Rubus coreanus and can be a potential target for treatment of kidney fibrosis.
Conclusions: 17-DMAG treatment attenuated renal fibrosis both in vitro TGF-β-challenged HK2 cell model and in vivo AKI to CKD mice model. METTL3 expression was diminished by 17-DMAG treatment.

FR-PO1057
Omega 3 Fatty Acids Attenuated AKI to CKD Transition and Renal Fibrosis: Identification of Anti-Fibrotic Metabolites

Background: Renal fibrosis, recognized as a histological hallmark of CKD, has become an object of interest as a prospective therapeutic target. Recent meta-analyses showed that the patients with AKI are at high risk of developing CKD, and the concept of AKI to CKD was established. ω3 fatty acids (ω3PUFA) were reported to exhibit renal protective effects. However, their renal protective mechanism has remained unclear.

In this study, we aimed to investigate the effect of ω3PUFA on AKI to CKD and to identify the active fatty acid metabolites against renal fibrosis.

Methods: Mice were fed a normal diet or an ω3PUFA diet. After 4 weeks of feeding, bilateral renal ischemia-reperfusion (IR) was performed. The activity of fatty acid metabolites was assessed by using human monocyte-derived cell lines (THP-1 cells) and human tubular epithelial cell lines (HK-2 cells) and rat renal fibroblasts cell lines (NRK49F cells).

Results: The normal or ω3PUFA diet was fed for 4 weeks, and IR (35 min) was performed to induce severe AKI. ω3PUFA diet improved the survival after AKI as compared to the normal diet. Next, AKI to CKD model (IR; 30 min) was subjected to evaluate the effect of ω3PUFA. ω3PUFA group exhibited the suppression of tubular damage and fibrosis at day 14 after renal IR. Renal fatty acid metabolites were measured, and multivariate analysis showed a significant increase in eicosapentaenoic acid (EPA) and its metabolites (18-HEPE, 17,18-EpETE, 17,18-diHETE) in the ω3PUFA group. When THP-1 cells were stimulated with LPS and the supernatant was added to HK-2 cells, an increase in IL-6 expression was observed, whereas when THP-1 cells were co-treated with EPA’s metabolites, IL-6 expression was suppressed. In NRK-49F cells, TGF-β1-stimulated production of α-SMA expression was suppressed by the presence of EPA and its metabolites.

Conclusions: Feeding ω3PUFA improved the survival after severe AKI and reduced tubular damage and renal fibrosis in AKI to CKD. The anti-inflammatory and anti-fibrotic effects of EPA and its metabolites were shown.

FR-PO1058
Inhibition of HDAC1 Attenuates Renal Fibrosis Through Blocking Partial Epithelial-Mesenchymal Transition
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Background: HDAC1 is the only member of the class IV histone deacetylases (HDACs) and is highly expressed in brain, heart, kidney et al and participates in diverse physiological processes, such as tumor growth, immune regulation, oxidant stress injury et al. However, it remains unclear whether HDAC1 involves in renal fibrosis.

Methods: In this study, we assess the role of HDAC1 in the development of renal fibrosis in Unilateral Ureteral Obstruction (UUO) mouse model. To examine the efficacy of HDAC1 in renal fibrosis after UUO injury, FT895 at 5mg/kg in 50 ul. DMSO was given intraperitoneally after ureteral ligation and then administered for 7 days. The mice were euthanized and kidney was collected on day 7.

Results: Masson trichrome staining results showed collagen fibrils were extensively deposited within the interstitial space in the kidney after UUO injury. Immunoblot analysis of kidney tissue lysate demonstrated increased expression of α-SMA, collagen I, and fibronectin in the kidney after UUO injury. However, administration of FT895 significantly reduced ECM deposition and significantly decreased the expression levels of α-SMA, collagen I, and fibronectin. To determine the effect of HDAC1 inhibition on the arrest of epithelial cells at G2/M and partial epithelial-mesenchymal transition (EMT), we examined the expression of pH3Ser10, a hallmark of cells arrested at G2/M and Snail and Twist, key transcription factors that drive EMT development in the obstructed kidney. Immunoblot analysis results showed that administration of FT895 significantly reduced the expression of pH3Ser10, Snail and Twist.

In addition, we further visualize the immune cell infiltration by immunohistochemistry analysis of F4/80, a macrophage marker. FT895 treatment decreased infiltration of F4/80 macrophages in the interstitial areas of the obstructed kidneys.

Conclusions: These data provide strong evidence that inhibition of HDAC1 attenuates development of renal fibrosis in vivo through suppression of several events associated with partial EMT development. Therefore, inhibition of HDAC1 would be a promising therapeutic strategy for the treatment of renal fibrosis.

FR-PO1059
Neutrophil-1, the Co-Receptor of TGF-β and TNF-α, Is a Novel Therapeutic Target for Renal Injury and Renal Fibrosis
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Background: Renal fibrosis is the ultimate common pathway of a variety of progressive kidney diseases, in which TGF-β plays an important role. However, current strategies targeting TGF-β showed poor clinical efficacy. One of the reasons for its futility is the co-receptor surroogy. Neutrophil-1 (NRPI) is a transmembrane glycoprotein acting as a co-receptor of TGF-β and TNF-α, which is recently identified as a potential therapeutic target for pulmonary fibrosis. However, its role in kidney injury and renal fibrosis remains unclear.

Methods: Kidney samples from patients with transplanted renal insufficiency and ischemia-reperfusion mice were analyzed. NRPI-KSP mice were generated to delete NRPI in renal tubular epithelial cells (TECs). The molecular mechanisms of NRPI1 in kidney injury and renal fibrosis were explored via multi-omics analysis of single cell sequencing, transcriptomics and proteomics.

Results: NRPI expression is upregulated in TECs in transplanted renal insufficiency patients and mice with IR induced AKI, which is co-expressing with receptors of TGF-β and TNF-α. Knockdown of NRPI in TECs reduced IR-induced kidney injury and fibrosis in mice. NRPI1 distal tubular cells secreted collagen and cytokines, and communicated with myofibroblasts, exacerbating renal fibrosis by activating the SMAD pathway in TECs in a TGF-β receptor dependent manner. Meanwhile, in TGF-β receptor negative distal TECs, NRPI1 upregulated TNF-α and its target gene NFKB1 via TNRIA (TNF-α receptor), thereby inhibiting ETV6-related crotonylase expression, which led to downregulation of lysine crotonylation on key glucose metabolic enzymes, exacerbating renal injury, inflammation and fibrosis.

Conclusions: NRPI is a key molecule promoting kidney injury and fibrosis via activation of SMAD3, TECs-myofibroblasts crosstalk and inhibiting crotonylation of key glucose metabolic enzymes, which promotes the pro-fibrotic and pro-inflammatory effects in both TGF-β receptor negative and positive TECs. Therefore, NRPI1 is a novel therapeutic target for kidney disease.

Funding: Government Support - Non-U.S.
Daphnepedin A, a Natural Small Molecule, Targets Cdc42-Mediated Lipocalin Signaling to Combat Renal Fibrosis

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Background: Renal fibrosis is a common fate in various chronic kidney diseases (CKD), eventually leading to dysfunction. So far there is no effective treatment for this pathological process. Wikstroemia chamaedaphne, a shrub endemic in China, is a medicinal plant that have been used in folk medicines to treat edema, but its application and mechanism in kidney-related diseases are unknown.

Methods: The inhibitory effects of extractive fractions of Wikstroemia chamaedaphne on the activation of renal fibroblasts were identified in the in vitro model of rat renal fibroblast cell line stimulated by transforming growth factor-β1. A phenotypic screening was conducted to identify the most potent diterpenoid isolated from Wikstroemia chamaedaphne in the in vitro model of renal fibroblast activation. Unilateral ureter obstruction mouse model of renal fibrosis was utilized to confirm the anti-fibrotic activity of the diterpenoid. The drug efficacy of the diterpenoid was compared with pifredione, the anti-fibrotic drug undergoing clinical phase 2 trial. RNA-sequencing was employed to explore the underlying pharmacological mechanism. By incorporating cellular thermal shift assay with quantitative mass spectrometry (MS-CETSA), the direct target of the diterpenoid was identified. Surface plasmon resonance and active GTP-binding cdc42 pull-down experiments was performed to verify the target protein. Small interfering RNA was used to knock down the target protein in NRK-49F cells and the drug efficacy of the diterpenoid was identified.

Results: In our bioassay-guided chemical investigation on the medicinal plant Wikstroemia chamaedaphne, the daphne diterpenoid daphnepedin A (15) was identified as a promising anti-fibrotic lead. 15 showed significant anti-fibrosis effects both in vitro and in vivo, much more potent than the clinical trial drug pifredione. Leveraging MS-CETSA, we identified cell division cycle 42 (cdc42), a GTPase, as the direct target of 15. Mechanistically, 15 inhibited the activity of cdc42, disrupting cdc42-dependent glycan synthase kinase-3β (GSK-3β) serine 9 phosphorylation, which in turn activates GSK-3β and downregulates downstream β-catenin pro-fibrotic signaling. Using RNA-sequencing, we identified a core set of stromal and injury genes, which shared transcriptional identity with DNTSs of the relevant UIR and UUO murine models. We used two clinically relevant UIR and UUO murine models. The study may aid in identifying patients with a disease relevant phenotype at risk for progression and will complement our target identification and validation focused on maladaptive tubular repair.

Funding: Government Support - Non-U.S.

Identification of Surrogate Biomarkers Reflecting Tubular Failed Repair in CKD

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Background: Intertitial fibrosis, tubular atrophy and inflammation (IFTA) are common final pathways to end-stage kidney disease (ESKD), contributing to progressive nephron loss and functional decline in most chronic kidney diseases (CKD), including those typically glomerular in origin. Disease-associated failed repair proximal tubule cells (FR-PTs) have been described in rodent models and are characterized by a pro-inflammatory and profibrotic phenotype that contributes to IFTA severity. We have recently demonstrated that accumulation of FR-PTs in humans predicts reduced event-free survival in multiple CKD etiologies. Here we used multi-omics analysis of patient-matched kidney biopsies and biofluids from the NURTURE CKD cohort to discover biomarkers associated with an accumulation of FR-PTs to non-invasively identify patients at risk for progression.

Methods: Serum (n = 99) and urine samples (n = 22) from multiple etiologies from the NURTURE biobank were assayed using Olink and SomaScan proteomics platforms, respectively. Patient-matched kidney biopsies for each of the samples were analyzed via RNA-Seq and scored for a gene signature reflecting FR-PTs. Correlation analyses of biofluid protein abundance with kidney mRNA expression and FR-PTs signature scores suggested candidate non-invasive biomarkers for further validation (r ≥ 0.4 and p ≤ 0.05).

Results: Proteinomic analysis identified 78 serum and 79 urine proteins significantly correlated with the kidney biopsy FR-PT score in CKD patients. Strong positive correlation of 14/78 serum and 9/79 urine proteins with kidney mRNA expression suggests these proteins originate from the kidney or share a common regulatory mechanism. Importantly, expression of the respective genes was negatively correlated with eGFR and enriched in FR-PTs and immune cells, likely reflecting the kidney inflammatory and fibrotic microenvironment.

Conclusions: This study identified potential surrogate biomarkers associated with the accumulation of FR-PTs in subjects with different CKD etiologies from the NURTURE cohort. These may aid in identifying patients with a disease relevant phenotype at risk for progression and will complement our target identification and validation focused on maladaptive tubular repair.

Funding: Commercial Support - Chinook Therapeutics, Evotec SE

The Renal Damage Induced by an Experimental Model of Early CKD Is FR-PTs-dependent

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Background: In chronic kidney disease (CKD), the progressive decline in renal function is accompanied by inflammatory and fibrotic processes. These processes can contribute to the increasing levels of proteinuria, which is recognized as a risk factor in patient morbidity and progression. Neutrophil gelatinase-associated lipocalin (NGAL) is an accepted biomarker for assessing renal damage in CKD patients and experimental animals. However, it is still uncertain whether NGAL actively promotes proteinuria in the context of early CKD, and whether this phenomenon is related to the type of renal injury. The objective of this study was to determine whether the progression of nephrectomy (Nx) at 5 days in mice is associated to renal dysfunction and to the pro-inflammatory/fibrotic damage, and whether this is NGAL-dependent.

Methods: Male C57BL/6 Wild type (WT) and knock-out for NGAL (NGAL-KO) mice (8-12 weeks), underwent a model of Nx for 5-days (n=4-6), to evaluate function and kidney damage.

Results: The Nx model at 5 days in WT and NGAL-KO mice resulted in a significant reduction in glomerular filtration rate, with 56.1% and 58.2%, respectively. Notably, the increase in blood area levels was significantly higher in WT mice compared to NGAL-KO (43.0±2.15 vs. 29.5±3.02 arbitrary units). Also, the ratio protein/creatinine in urine exhibited NGAL-dependency (10.29±3.0 vs. 7.09±0.6 arbitrary units in NGAL-KO). Concerning the renal damage, the early CKD model induced tubular lumen dilation in WT mice (13.6±0.9 vs. 8.0±0.3mm in Sham), which was prevented by the NGAL ablation. Additionally, the normalized fibrosis area in remnant kidney was significantly 2.3 times lower in the NGAL-KO mice with respect to WT animals, which correlated with the mRNA abundance of interleukin-6 (P<0.01). Finally, we found an increased protein production of macrophage (M) monocyte chemotactant (CCL2) in kidneys of WT mice due to Nx model, which was not observed in NGAL-KO mice (P>0.05).

Conclusions: Our results show that renal overexpression of IL-6 and CCL2 after 5-days of Nx are NGAL-dependent. This pro-inflammatory phenotype correlates with the tubular remodeling, fibrosis and the proteinuria, suggesting a possible role of NGAL for the CKD progression from the early stages.

Funding: Government Support - Non-U.S.
AKI-CKD transition. Reduces G2/M cell cycle arrest, cellular senescence, and secretion of profibrotic mediators. Treatment, with increased activation of growth arrest genes p53 and p21. shRNA-induced the initiation of G2/M cell cycle arrest. Effect of BRCA1 on arresting the cell cycle would exacerbate maladaptive repair through the role of BRCA1 in renal fibrosis has been largely unexplored. We hypothesized that the adaptation in many pathologies, notably in the prevention of carcinogenesis. Until recently, FR-PO1065?

**CKD Mechanisms: Progression, Fibrosis, and Beyond**

**FR-PO1065**

**BRCA1 Potentiates Maladaptive Repair and Fibrosis Through Induction of Proximal Tubule G2/M Arrest and Senescence**

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**Background:** DNA damage is a major contributing factor in the progression of fibrotic renal disease. Proximal tubular (PT) epithelial cells are particularly vulnerable to toxic, ischemic, and obstructive injury in the kidney, leading to replication fork arrest and DNA double-strand breaks (DSBs), triggering the DDR, a protective adaptation in many pathologies, notably in the prevention of carcinogenesis. Until recently, the role of BRCA1 in renal fibrosis has been largely unexplored. We hypothesized that the effect of BRCA1 on arresting the cell cycle would exacerbate maladaptive repair through the initiation of G2/M cell cycle arrest.

**Methods:** Shc34al-Cre mice were crossed with Brca1<sup>fl</sup> mice yielding mice with PT Brca1 exon 11 gene deletion. Mice were subjected to bilateral ischemia/reperfusion (BIRI) or aristolochic acid (AA)-induced injury. Markers of DNA damage, cell cycle arrest, senescence and fibrosis were evaluated by immunofluorescence staining and western blot analysis of tissue sections and patient-derived PTs subjected to AA or cisplatin. HKC8 cells were transfected with shRNA and treated with either cisplatin or AA to investigate the role of BRCA1 in injury-associated apoptosis, growth arrest and senescence.

**Results:** BRCA1 protein expression was increased in human CKD kidneys. The expression of Brca1 exon 11 was increased following BIRI or AA. PT Brca1 deletion protected mice from fibrosis, as shown by Sirius red staining, fibronectin, collagen I, and a-smooth muscle actin (α-SMA) following BIRI or AA. PT-Brca1 depleted mice had fewer pH3+ cells, a G2/M cell cycle phase marker and reduced S-p-Gal, a senescence marker. Primary PTs displayed increased p-BRCA1<sup>Ser1524</sup> after 48h AA or cisplatin treatment, with increased activation of growth arrest genes p53 and p21. shRNA-induced reduction of BRCA1 in HKC8s decreased the percentage of cells in the G2/M cell cycle phase and significantly reduced cell viability.

**Conclusions:** BRCA1 induces fibrosis after tubular injury. Loss of BRCA1 from PTs reduces G2/M cell cycle arrest, cellular senescence, and secretion of profibrotic mediators in vivo and in vitro. Thus, transient inhibition of BRCA1 can be beneficial for preventing AKI-CKD transition.

**Funding:** NIDDK Support, Other NIH Support - American Heart Association

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**FR-PO1067**

**The Adenine-Induced Mouse Model of CKD Shows Rapid Development of Impaired Kidney Function, Renal Fibrosis, Muscle Wasting, and Anemia**


**Background:** Translational rodent models are essential to identify more efficacious treatment options for patients with chronic kidney disease (CKD). However, most preclinical CKD models do not demonstrate impaired kidney function as determined by decreased glomerular filtration rate (GFR). Here, we characterize an adenine diet-induced (ADI) mouse model of CKD that enables clinical translational studies of CKD.

**Methods:** Male C57BL/6j mice (11 weeks old) were randomized into study groups (n=8-10 per group) based on body weight. ADI mice received a control diet from study day -2 and a CKD-inducing diet containing 0.2% adenine from study day 1, while control mice received a control diet from day -2 and continued with it throughout the study period. All groups received oral vehicle dosing once daily starting from day 1 until termination. Transdermal GFR (tGFR), urine creatinine-to-albumin ratio, and plasma cystatin C (pCyC) were evaluated at week 3 and 5. Blood was collected for glycated haemoglobin analysis, and gastrocnemius muscle and kidney tissue were sampled and weighed. Kidneys were collected for RNA sequencing or processed for histological evaluation of markers of macrophage infiltration (F4/80) and fibrosis (Coll1a1).

**Results:** Compared to controls, ADI mice showed a significant tGFR decline correlating with an increased pCyC and marked albuminuria at 3 and 5 weeks after commencement. At termination, ADI mice showed significantly decreased glycated haemoglobin (14.7 vs 17.6 g/dL) and gastrocnemius muscle weight compared to mice receiving the control diet (0.12 vs 0.15 g). Furthermore, Quantitative kidney histomorphometric analysis demonstrated an increase in kidney fibrosis (Coll1a1) and macrophage infiltration (F4/80) in ADI mice. Consistent with GFR decline and kidney injury, the renal transcriptome signature in ADI mice indicated upregulation of gene expression markers of fibrosis (e.g. Col1a1, Grem1), inflammation (e.g. Il6, Il1b), and angiogenesis (e.g. Edna, Agrp).

**Conclusions:** ADI mice rapidly develop functional, biochemical and histological hallmarks of CKD complicated by anaemia and muscle wasting. Consequently, ADI mice are highly relevant in preclinical target and drug discovery for CKD.

**Funding:** Commercial Support - Guba
Annexin A2 Promotes Tubular Epithelial Trans-Differentiation and Kidney Fibrosis

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Background: Annexin A2 is a Ca2+- and phospholipid-binding protein widely expressed in various cells and tissues. It acts as a cell surface receptor for tissue plasminogen activator (tPA) and plasminogen, regulating the homeostasis of blood clotting, coagulation, and thrombocyte degradation. However, its role in kidney fibrosis remains largely unknown. Our previous in vitro work has shown that annexin A2 mediates NF-κB activation and promotes macropage M2 to M1 phenotypic change, suggesting a critical role of annexin A2 in kidney fibrogenesis.

Methods: Unilateral ureteral obstruction (UUO) was induced in a novel annexin A2 knockout mice and their wildtype counterparts. Renal histology was evaluated. Kidney fibrosis, renal annexin A2 level, and epithelial transdifferentiation were examined in these mice.

Results: Annexin A2 was dramatically induced in the obstruction-induced fibrotic kidneys in a time-dependent manner, and its induction correlated with the extent of fibrotic injury as indicated by fibronectin deposition. Intriguingly, double immune staining analysis found that annexin A2 was dramatically induced in the interstitial F4/80-positive macrophages. It was further found that, after obstructive injury, annexin A2 knockout mice displayed significantly reduced tubular epithelial damage and dramatically decreased deposition of matrix components such as collagen and fibronectin than that of their control littermates. Additionally, obstruction-induced epithelial transdifferentiation was significantly reduced in annexin A2 knockout mice as indicated by increase of E-cadherin and decrease of de novo induction of SMA.

Conclusions: Thus, it is clear that annexin A2 promotes epithelial transdifferentiation and kidney fibrosis after obstructive injury. Additionally, our results indicate a role of macrophages in annexin A2-mediated epithelial damage and transdifferentiation.

Funding: Other U.S. Government Support, Private Foundation Support

Alveolar Type II Cell-Specific Mitofusins Modulate Kidney Fibrosis and Associated Lung Injury

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Background: Chronic kidney disease (CKD)-associated lung injury and implications of deleterious lung-kidney crosstalk on the progression of kidney fibrosis are under-recognized. Mitochondrial fusion proteins, mitofusin (MFN)1 and MFN2, play critical roles in regulating mitochondrial physiological function, which is essential for kidney homeostasis. We studied the effects of type II alveolar epithelial cell (AEC) II-specific loss of MFN1 or MFN2 on kidney fibrosis and associated lung injury during CKD.

Methods: AEC II (Spc-Cre−/−)specific Mfn1fl/fl (Mfn1−/−) or Mfn2fl/fl (Mfn2−/−) knockout (KO) and control (Spc-Cre−/−) mice were subjected to unilateral ureteral obstruction (UUO) or sham surgery (7-days) or fed with ademine (AD) or control diet (28-days). Kidneys, lungs, blood, and bronchoalveolar lavage (BAL) fluid were analyzed by western blot, Masson’s trichrome staining, and flow cytometry. Serum creatinine (Scr) and blood urea nitrogen (BUN) were measured.

Results: Mfn1 and Mfn2 in AEC II (EpcCam+ CD45−), lungs, and kidneys decreased while iron mononuclear monocytes (CCR2+ Ly6C+ CD11b+) in blood, kidneys, lungs, and BAL fluid increased after UUO or AD. AEC II-specific Mfn1 or Mfn2 KO mice displayed higher expression of fibronectin, arginase-I, galectin-3, IL-1β, and TGF-β1, and collagen deposition in the kidneys and lungs after UUO or control mice. Mfn1−/− Mfn2−/− loss in AEC II resulted in increased kidney macropages (KM, CD11b+ F4/80+ CD11c−) and in obstructed kidneys increased and alveolar macrophages (AM, siglecF+ F4/80+ CD11c+ CD45+) in the lungs and BAL fluid after UUO. KM and AM from AEC II-specific Mfn1 or Mfn2 KO mice exhibited higher mitochondrial-specific reactive oxygen species and galectin-1 after UUO than control mice. Moreover, AEC II-specific Mfn2 KO mice displayed a lower number of proximal tubular cells (melolin+ CD45−) in obstructed kidneys, and higher BUN and Ser levels than control mice after UUO.

Conclusions: In 2 models of kidney fibrosis, we show downregulation of Mfn1/2 in both the lungs and kidneys. AEC II-specific loss of Mfn1/2 increased inflammatory and fibrotic responses in KM and AM during CKD, suggesting the role of macrophages in inter-organ crosstalk. Mitochondrial-derived damage-associated molecular patterns from AM and injured AEC II may be involved in deleterious lung-kidney crosstalk and aggravate kidney fibrosis.

Funding: Other NIH Support - NIH T32 HL134629; NHLBI; P01 HL114501; K08 HL157728

The Uremic Toxin Indoxyl Sulfate Contributes to Renal Fibrosis via mTORC1 Signaling Pathway

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Background: Activation of mTORC1 in renal tissue has been reported in chronic kidney disease (CKD)-induced renal fibrosis. This suggests that the regulation of renal mTORC1 activity represents a potential therapeutic target for the treatment of renal fibrosis. However, the molecular mechanisms responsible for regulating mTORC1 in kidney fibrosis pathology are not well understood. The purpose of this study was to identify the uremic toxin involved in mTORC1-induced renal fibrosis.

Methods: Human renal proximal tubule epithelial cells (HK-2 cells), rat renal interstitial fibroblast (NRK-49F cells), and human monocytes (THP-1 cells) were used in in vitro studies. Adenine-induced CKD mice were used in in vivo studies.

Results: Among the seven protein-bound uremic toxins, only indoxyl sulfate (IS), an indole-containing compound, caused significant activation of mTORC1 in HK-2 cells. This IS-induced mTORC1 activation was inhibited in the presence of an organic anion transporter inhibitor, a NADPH oxidase inhibitor, and an antioxidant. IS also induced mitochondrial damage in epithelial cells, differentiation of fibroblasts into myofibroblasts, and inflammatory response of macrophages, which are associated with renal fibrosis, and these effects were inhibited in the presence of rapamycin (mTORC1 inhibitor). IS in vivo experiments, IS-overload was found to activate mTORC1 in interstitial fibroblasts. The administration of AST-120 or rapamycin targeted to IS or mTORC1 ameliorated renal fibrosis in CKD mice.

Conclusions: The findings reported herein indicate that IS activates mTORC1, which then contributes to renal fibrosis. Therapeutic interventions targeting IS and mTORC1 could be effective against renal fibrosis in CKD.

Funding: Government Support - Non-U.S.

The Role of SRy-box transcription Factor 4 in Renal Fibrosis

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Background: Chronic kidney disease (CKD) is a widely prevalent disorder around the world that affects over 10% of adults. The pathological feature of CKD is characterized by the excessive production and deposition of extracellular matrix (ECM). The production and accumulation of ECM is partly due to tubular epithelial cell (TEC) dedifferentiation. However, the molecular mechanisms underlying TEC dedifferentiation are not fully understood. In this study, we investigated the role of SRy-box transcription factor 4 (SOX4) in regulating TEC dedifferentiation during the development of CKD.

Methods: We generated SOX4 conditional knockout mice by crossing SOX4 floxed mice with tamoxifen-inducible CAG-CreER mice. CAG-Cre′ SOX4flox mice were given tamoxifen to induce SOX4 deletion (SOX4−/−). CAG-Cre′ SOX4flox mice received the same dose of tamoxifen and used as controls (SOX4−/−). Both SOX4−/− and SOX4fl/fl mice were subjected to unilateral ureteral obstruction (UUO). Kidneys were harvested at 10 days after UUO injury. Kidney sections were prepared and stained for histological and immunohistochemical analysis. Western blot analysis and immunostaining were performed to detect the levels of signaling molecules, fibronectin, collagen type I, and alpha-SMA in the kidneys. Sirius red staining was performed to detect total collagen deposition in the kidney. Cultured TECs were employed to examine the role and molecular mechanisms of SOX4 in the regulation of TEC dedifferentiation in vitro.

Results: The expression of SOX4 was increased in TEC after UUO injury. In response to obstructive injury, SOX4−/− mice exhibited TEC dedifferentiation with senescence and G2/M arrest, fibroblast activation and developed substantial total collagen deposition and ECM protein production in the kidney. Global SOX4 deficiency significantly alleviated TEC dedifferentiation, suppressed fibroblast activation, and reduced total collagen deposition and ECM protein production in the kidney with UUO injury. Furthermore, knockdown SOX4 by shRNA inhibited TEC dedifferentiation in cultured TEC in response to UUO. Mechanically, SOX4 facilitated TGF-β1-Smad3 signaling to promote TEC dedifferentiation.

Conclusions: Our results demonstrate that SOX4 plays an essential role in the development of renal fibrosis by regulating TEC dedifferentiation and fibroblast activation. Therefore, SOX4 may serve as a novel therapeutic target for CKD.

Funding: NIDDK Support, Veterans Affairs Support

Cell-Specific Iron Metabolism in Kidney Fibrosis


Background: Chronic kidney disease (CKD) affects 10-15% of the adult U.S. population. Our recent data indicate that in CKD, most kidney macrophages (KMq) have pathologically depleted cellular labile iron pool, which induces their pro-fibrotic responses. However, the mechanism of intracellular iron deficiency of KMq and iron metabolism in other cell types that participate in fibrosis, particularly in tubulal epithelial cells (TEC) have not been elucidated in CKD.

Methods: We used two models of kidney fibrosis, adenine diet and unilateral ureteral obstruction (UUO). We analyzed expression of iron-related genes (Tfrc, iron importer, transferrin receptor 1 [TFR1], a marker of cellular iron deficiency or overload; Fth1 and Fli; ferritin heavy and light chains; Slc40a1, iron exporter; and Ncoa4, a marker of ferritinophagy) and respective proteins in whole kidney tissue, as well as in sorted KMq and TEC (isolated using CD11b and CD133 magnetic microbeads). We also analyzed expression of these genes in publically available single cell/nuclear transcriptomic mouse and human kidney fibrosis datasets.

Results: In contrast to KMq, Tfrc gene was suppressed in whole kidney tissue and in the proximal TEC of UUO kidneys, suggesting iron excess in some (e.g., proximal tubules) and labile iron deficiency in other (e.g., KMq) cell types during kidney fibrosis. Importantly, ferritin depilation in KMq was observed despite suppression of Fpt in CD11b-positive KMq, while both Slc40a1 gene and Fpt protein were induced in whole kidney tissue during fibrosis. This suggests that regulation of Fpt is independent of systemic iron treatment.
hepcidin in most kidney cells (but not in KM)) during fibrosis. Fih1 and Fgf genes were suppressed while Fih2 and Fgf21 were induced in whole kidney tissue, KMs, and in TEC during fibrosis. Taken together with TIR1/Tiec data, this suggests excessive expression of Fih in KMs and insufficient in TEC during fibrosis. Cell-specific ferritin dysregulation in kidney fibrosis may owe to disrupted ferritinophagy. Indeed, NCOA4 expression was drastically reduced in KMs and had only a trend toward reduction in TEC during fibrosis.

Conclusions: Cellular iron status varies among different cell types participating in kidney fibrosis, which likely differentially modulates fibrotic responses of these cells and may inform novel cell-specific therapeutic targets.

Funding: NIDDK Support, Private Foundation Support

FR-PO1073

IRhom2 Promotes Kidney Fibrosis Through Activation of EGFR in Fibroblasts

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Shirong Pan Promotes Kidney Fibrosis Through Activation of EGFR in Fibroblasts

Background: In the kidney, tubulointerstitial fibrosis can result from incomplete recovery from acute kidney injury (AKI). Activation of the epidermal growth factor receptor (EGFR) has been implicated as a potential mediator of interstitial fibrosis. IRhom2, an inactive member of the Rhomboid intramembrane protease family, can regulate EGFR signaling pathway via activation of ADAM17 (TACE) and secretion of EGFR ligands, including amphiregulin and HB-EGF as well as secretion of TNF-α. The current studies were designed to investigate the potential role of IRhom2 in the development of kidney fibrosis.

Methods: IRhom2 knockout (IRhom2-/-) and WT mice (C56/Bl6, male, 12-18 weeks old) were used for all experiments. Models of kidney injury included ischemia-reperfusion (IRI) and unilateral ureteral obstruction (UUO). Kidney myeloid cells and fibroblasts/microfibroblasts were isolated with corresponding microbeads.

Results: In the UUO model, IRhom2 mRNA expression increased in total kidney, isolated myeloid cells, and isolated kidney fibroblasts/microfibroblasts. Immunofluorescence staining confirmed IRhom2 expression in renal macrophages (F4/80+) and microfibroblasts (α-SMA+ IRhom2+ cells). Although the numbers of α-SMA+ cells and p-EGFR (α-SMA+) cells were minimal under normal condition, they markedly increased after UVO for 8 days. In IRhom2-/- mice, both the numbers of α-SMA+ myelofibroblasts and p-EGFR+ (indication of EGFR activation) α-SMA+ myofibroblasts decreased, with the percentage of p-EGFR expressing myofibroblasts decreasing from 43% to 17%. Quantification of Picrosirius red staining clearly showed less kidney interstitial fibrosis in IRhom2-/- mice. Four weeks after ischemic injury, IRhom2-/- mice also developed less fibrosis, as indicated by reduction in kidney profibrotic and fibrogenic gene and protein expression as well as expression of Picrosirius red staining. In addition, IRhom2-/- mice had preserved kidney function, as indicated by higher glomerular filtration rate 4 weeks after ischemic injury.

Conclusions: These studies provided evidence for a potential role of IRhom2 in development of kidney fibrosis in response to kidney injury, due at least in part by stimulating EGFR activation in fibroblasts/microfibroblasts. Targeting IRhom2 may provide a new strategy for prevention of kidney interstitial fibrosis.

Funding: NIDDK Support

FR-PO1075

LCn2 Plays a Key Role in Dot1l-HDAC2-ET1-Mediated Kidney Fibrosis

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Background: Kidney fibrosis is a hallmark of chronic kidney disease. The genetic and epigenetic factors regulating kidney fibrosis are largely unknown. Kidney injury marker Lipocalin 2 (Lcn2) is involved in kidney fibrosis. We reported that Agp2Cre mice express Cre specifically in Agp2+ progenitor cells, which generates at least 5 types of cells forming distal convoluted tubule 2 (DCT2), connecting tubule (CNT) and collecting duct (CD). Our recent studies also indicated that disruption of histone H3 K79 remodeling in Dot1 loss in Agp2+ progenitor cells, leading to upregulation of cell adhesion (ET1) and kidney fibrosis through histone deacetylation (HDAC2) during normal aging. Here, we hypothesize that Lcn2 is a new component of this process and upregulates HDAC2, which in turn increases ET1 and facilitates kidney fibrosis.

Methods: Using the Agp2Cre driver, we developed three conditional knockout mice: 1) Dot1l-CNT/CD-specific Dot1l conditional knockout mice (Dot1l+ Agp2Cre or Dot1l+); 2) DCT2/CNT/CD-specific Dot1l conditional knockout mice (Dot1l+ Edn1f/f Agp2Cre or Dot1l+); 3) DCT2/CNT/CD-specific Dot1l conditional knockout plus Lcn2 global knockout mice (Dot1l+ Agp2Cre Lcn2-/- or Dot1l+ Lcn2-/-). WT and the three knockout mice were analyzed at the age of 15 months. A variety of approaches including immunofluorescence staining coupled by high-resolution confocal microscopy, metabolic assays, real-time RT-qPCR, and Western blotting were used to assess kidney fibrosis, kidney function, and/or expression of HDAC2, Lcn2, and ET1 in mice, in IMCD3 cells overexpressing Lcn2, or in IMCD3 cells treated with various doses of recombinant Lcn2.

Results: Like Dot1l+ vs. Dot1l+ mice, Lcn2-/- vs. Dot1l+ mice displayed less pronounced kidney fibrosis and improved kidney function. While high Lcn2 expression remained in Dot1l+ vs. Dot1l+ mice, significantly reduced HDAC2 and ET1 levels were observed in Dot1l+ vs. Dot1l+ mice. In IMCD3 cells, silencing Dot1l in IMCD3 cells led to upregulation of Lcn2, and addition of recombinant Lcn2 or overexpression of Dot1l increased expression of HDAC2 and ET1.

Conclusions: Dot1l-Lcn2-HDAC2-ET1-kidney fibrosis may be considered as a new fibrogenesis pathway. That is, disruption of Dot1l in Agp2+ progenitor cells not only directly upregulates ET1, but also indirectly through Lcn2, which positively regulates HDAC2, further facilitating ET1-mediated kidney fibrosis.

Funding: NIDDK Support, Other NIH Support - Capital Region Medical Research Institute

FR-PO1076

Stimulator of Interferon Genes (STING) Mediates Endoplasmic Reticulum Stress Activation Causing Renal Fibroinflammation

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Background: Endoplasmic reticulum (ER) stress plays a pivotal role in kidney disease pathogenesis, yet the mechanisms leading to ER stress are largely unexplored. Viruses are known to manipulate ER-related processes, potentially aiding their replication or pathogenesis. The adaptor molecule STING, known for detecting double-strand DNA in pathogenic infections. In light of these insights, we investigated the relationship between STING, ER stress, and the development of kidney disease.

Methods: We utilized STING N153S mice, exhibiting constitutive STING activation, and mice with a conditional deletion of STING from kidney tubules. We performed in vitro experiments, including the silencing of STING or ER stress pathways, and analyzed molecular events through immunofluorescence, qPCR, western blot, and immunoprecipitation techniques. Gene expression data was scrutinized through RNA sequencing from human control and diseased samples, as well as mouse kidney disease models.

Results: In both the cisplatin and UUO models, we identified a consistent activation of STING and the ER stress–activated eEF2a kinase (PERK) pathway. Interestingly, STINGdependent pathway involved physically interact with and activate PERK, leading to ER stress and, subsequently, renal fibroinflammation. On the contrary, deletion of STING or PERK inhibition showed a protective effect against disease development. Further, transcriptomic

Mechanism of the involvement of IGFBP-5 in renal fibrosis

FR-PO1074

IGFBP-5/TGF-β1-Induced Cell Cross-Talk Between Endothelium and Tubular Epithelia Promotes Renal Fibrosis

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Background: Renal fibrosis is a common pathophysiological characteristic of chronic kidney disease (CKD) for which there is no effective treatment. The mechanism of renal fibrosis is complicated and remains unclear. Our previous study revealed that Insulin-like growth factor binding protein 5 (IGFBP-5) induces glycolytic activation in ECs and ultimately aggravates renal inflammation in diabetic kidney disease (DKD). These findings suggest that IGFBP-5 may be a new pathogenic factor in renal fibrosis and a potential new therapeutic target in CKD.

Funding: Government Support - Non-U.S.
Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is a key player in angiogenesis and vasculogenesis. In the context of chronic kidney disease (CKD), VEGFR2 plays a crucial role in neovascularization and neangiogenesis. This process is essential for tissue repair and regeneration, but dysregulated angiogenesis can contribute to renal fibrosis and progression of kidney disease.

Our findings suggest that VEGFR2-mediated angiogenesis is upregulated in CKD models, leading to an imbalance between pro- and anti-angiogenic factors. This imbalance disrupts the delicate balance required for optimal renal repair. The interplay between VEGFR2 and other angiogenic factors, such as VEGF, is critical in guiding this process.

To further understand the role of VEGFR2 in CKD, we conducted a comprehensive analysis of various CKD models, including rodents with experimental CKD and human biopsy samples. In all models, we observed a significant increase in VEGFR2 expression and activity, associated with enhanced angiogenesis.

Moreover, we identified specific genetic and molecular mechanisms that regulate VEGFR2 expression and function in the context of CKD. These findings have important implications for the development of targeted therapeutic interventions aimed at modulating angiogenesis in CKD.

In conclusion, VEGFR2-mediated angiogenesis is a critical mediator of renal repair in CKD. Understanding the molecular mechanisms that regulate this process could pave the way for novel therapeutic strategies to improve renal function and prevent progression of kidney disease. Further research is needed to validate these findings and to explore the potential of VEGFR2 as a target for clinical intervention in CKD.
Results: Administering CH-223191 to rats after nephrectomy prevented the harmful effects of IS on the kidneys. CH-223191 restored H2S levels, reduced IS accumulation, and reversed the changes in H2S-producing enzymes and the transcription factor Sp1 (Fig1). It also decreased oxidative stress and lipid peroxidation in the nephrectomy rats (Fig2). These findings indicate that CH-223191 protects against kidney damage by mitigating IS-induced effects, preserving H2S generation, and reducing oxidative stress.

Conclusions: Impaired H2S generation caused by IS renders the kidney susceptible to oxidative stress damage, representing one of the mechanisms underlying IS-mediated kidney function loss.

activated pericytes into myofibroblasts, the expression of peritubular capillaries (PTC) (VEGF and CD31) were normalized to baseline; and 3) the activation of pericytes into myofibroblasts was decreased and would not be recovered; 4) the population of M2 macrophages marked by F4/80 + CD206 and CD11b + ly6C low was increased; and 5) the expression of inflammatory factors (TNF-α, IL-1β, IL-6 and IL-10), TGF-β, and HIF-1α and HIF-2α, and the population of inflammatory cells; 2) the expression of pro-inflammatory factors was low, but the expression of anti-inflammatory factors was high; 3) the expression of the components of autophagy was decreased and would not be recovered; 4) the population of PTC maintained at low level; 5) pericytes were constantly be activated into myofibroblasts to form fibrosis, and 6) the expression of HIF-1α and HIF-2α was initially increased, then decreased to baseline (normal) level but increased again in the late stage.

Conclusions: With our new RUUO mouse model, we confirm that renal adaptive repair occurs in 5-days-RUO kidneys to simulate the complete recovery of AKI, whereas renal maladaptive repair occurs in 10-days-RUO kidneys to simulate the progression from AKI to CKD.

FR-POI084

Clinical Characteristics and Renal Outcome of Patients with Thrombotic Thrombocytopenic Purpura from a Large Multicenter Cohort (USTMA Registry)

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Background: Thrombotic thrombocytopenic purpura (TTP) is a rare hematological disease caused by autoimmune deficiency of ADAMTS13 and responds to urgent plasma exchange therapy. Renal dysfunction is typically mild and severe clinical scores have incorporated creatinine (Cr) level < 2.0 mg/dL to differentiate TTP from other thrombotic microangiopathies. However, renal dysfunction and outcomes are not well studied in TTP. Therefore, we used the United States Thrombotic Microangiopathies (USTMA) TTP registry, the largest US TTP registry, to evaluate clinical characteristics of patients with severe renal dysfunction at presentation and estimate loss of kidney function over time.

Methods: The USTMA TTP registry contains data on TTP episodes between 1985 to 2019 from 14 centers across the US. We compared the clinical characteristics of patients with severe renal dysfunction at presentation to the general TTP population.

FR-POI083

Establishment and Application of a Novel Reversible Unilateral Ureteral Obstruction (RUUO) Mouse Model and in Mechanism Study of AKI to CKD

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Background: Acute kidney injury (AKI) is a worldwide health problem. About 35-71% of AKI cases progress to chronic kidney disease (CKD) due to renal repair failure. Studies on the progression of AKI to CKD are focused on animal models of prerenal and renal AKI. It is necessary to establish an animal model to investigate the progression of postrenal AKI to CKD.

Methods: We established a RUUO mouse model. In brief, we ligated the left ureter to create a ureteric obstruction in mice. After 5 or 10 days, ureteral obstruction was removed by the coindication of the ureter and bladder. Three days later, we performed right nephrectomy and then observed renal function and molecular mechanisms on the left kidney with IF and IHC staining, scanning electron microscopy and flow cytometry analysis.

Results: We observed adaptive and maladaptive repairs in 5 and 10 days RUO kidneys. During the complete recovery of AKI in 5 days RUUO kidneys, 1) the infiltration of M2 macrophages marked by F4/80 + CD206 and CD11b + ly6C low was increased; and 2) the expression of inflammatory factors (TNF-α, IL-1β, IL-6 and IL-10), autophagy components (Beclin-1, Bcl-2, BNP3, LAMP2, LC3BII/I and P62), and HIF-1α and HIF-2α, and the population of peripheral capillaries (PTC) (VEGF and CD31) were normalized to baseline; and 3) the activation of pericytes into myofibroblasts was blocked and alleviated as examined by PDGFRβ+ SMA staining. In the process of AKI to CKD in 10 days RUO kidneys, 1) M1 macrophages marked by F4/80 + iNOS and CD11b + ly6C high were dominant at the beginning, and then gradually transformed into pro-fibrotic CD11b + Ly6C low cells; 2) the expression of pro-inflammatory factors was high, but the expression of anti-inflammatory factors was low; 3) the expression of the components of autophagy was decreased and would not be recovered; 4) the population of PTC maintained at low level; 5) pericytes were constantly be activated into myofibroblasts to form fibrosis, and 6) the expression of HIF-1α and HIF-2α was initially increased, then decreased to baseline (normal) level but increased again in the late stage.

Conclusions: With our new RUUO mouse model, we confirm that renal adaptive repair occurs in 5-days-RUO kidneys to simulate the complete recovery of AKI, whereas renal maladaptive repair occurs in 10-days-RUO kidneys to simulate the progression from AKI to CKD.

FR-POI082

The Pathogenic Role of C5a/C5aR Axis in AKI-to-CKD Transition

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Background: Activation of complement C5a/C5aR axis contributes to the pathogenesis of acute kidney injury (AKI). However, whether it plays a role in the transition to chronic kidney disease (CKD) after AKI remains unclear. In this study, we investigated the chronic effects of bilateral ischemia-reperfusion injury on C5aR deficient mice and dissected C5aR-dependent mechanisms during AKI-to-CKD transition.

Methods: Wild type C5aR+ and knockout C5aR-/- mice were subjected to bilateral ischemia and sacrificed at day 3 and 7 after reperfusion. Kidney damage was assessed by evaluating kidney function, histopathological changes and expression levels of pro-inflammatory, fibrotic, oxidative and injury markers.

Results: Compared to the C5aR+ controls, C5aR-/- mice showed significant decrease in serum creatinine and reduced expressions of Kim1 and Ngal in both the 3-day and 7-day BIRI models. The improvement in kidney injury in BIRI C5aR-/- mice was further confirmed by PAS staining. The expression levels of MCP-1, TNF-α, IL-6 were significantly decreased in C5aR-/- mice after BIRI. In particular, there was decreased infiltration of M1 macrophages with an increase in M2 macrophage number in C5aR-/- mice on day 7 after reperfusion. Sirius red and Masson Trichrome staining demonstrated a progressive development of interstitial fibrosis in C5aR-/- mice after BIRI, which were suppressed in C5aR+ mice with less deposition of collagen 1 and collagen 3 in the post-ischemic kidneys. Moreover, the oxidative stress markers NO2 and 8-OHdG were significantly reduced in C5aR-/- mice after BIRI.

Conclusions: C5aR deficiency protected mice from kidney inflammation and fibrosis by reducing oxidative stress during AKI-to-CKD transition.

Funding: Research Grants Council of Hong Kong (General Research Fund, grant no. 17108222), Hong Kong Society of Nephrology Research Grant (2021)
upon presentation between patients presenting with mild (Cr ≤ 2 mg/dl) versus severe (Cr >2 mg/dl) renal dysfunction. To model eGFR loss over time with TTP episodes, we used longitudinal linear mixed-effects models.

Results: Between 1985-2019, there were 1257 TTP episodes (771 patients) and the majority of episodes had mild renal dysfunction (n=1115, 88.7%). Compared to mild renal dysfunction, patients with severe renal dysfunction had more severe symptoms, lower platelets and higher lactate dehydrogenase (LDH). There were 285 unique patients with multiple TTP episodes to evaluate for eGFR loss over time. Overall, we found a mean slope of eGFR per year of -0.70 (95% CI -0.84, -0.56). There were no differences in eGFR slopes according to the number of TTP episodes a patient experienced. LDH level was associated with eGFR loss between episodes, with a modestly sized effect (change in eGFR per year slope 0.02 (95% CI 0.008-0.032) per 2-fold increase in LDH).

Conclusions: Severe renal dysfunction is uncommon in TTP but it is more likely to be present in patients with multi-organ dysfunction. Hence, existing clinical prediction scores are likely to less accurately in more severe TTP episodes. Loss of eGFR over time is consistent with previous estimates of age-related eGFR, hence we conclude that subsequent TTP episodes do not significantly affect eGFR loss and likely confirms previous findings that most patients with TTP recover normal renal function with modern treatment.

FR-PO1085
Chromatin Remodeling Factor, INO80, Inhibits PMAIP1 in Renal Tubular Cells Through Exchange of Histone Variant H2A.Z for H2A.

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Background: Epigenetic modifications such as histone modifications and chromatin structures in the kidney contribute towards the progression of chronic kidney disease (CKD). In this study, the role of chromatin remodeling factor, inositol requiring 80 (INO80) was investigated because INO80 has been reported to be associated with renal function in a genome-wide analysis. Although INO80 regulates transcription by altering the chromatin structure at the nucleosome level, its role in the kidney remains unknown. Our aim of this study is to clarify the pathophysiological role of INO80 in the kidney.

Methods: We evaluated the expression level of INO80 using UUO (unilateral urethral obstruction) model rats. We also investigated INO80 mRNA expression in a proximal tubular cell line (HK2) under hypoxia. To identify the downstream target genes of INO80, we performed RNA-seq using sRNA of INO80. We examined the effects of INO80 on apoptosis of tubular cells.

Results: The mRNA level of INO80 extracted from uo group (n = 6) was significantly reduced compared to the control group. INO80 knockdown promoted apoptosis, suggesting that INO80 plays a role in inhibiting tubular cell apoptosis. The expression levels of INO80 in HK2 cells under 1% hypoxic condition significantly decreased than those under normoxia. We identified 32 down-regulated genes and three up-regulated genes. These genes were suspected to be INO80 downstream target genes. As a result of gene ontology (GO) apoptosis-related genes such as TP53 (tumor protein p53), E2F1 (E2F transcription factor 1), and PMAIP1 (phobol-12-myristate-13-acetate-induced protein 1) were significantly associated with INO80 functions. PMAIP1 is a member of pro-apoptotic subfamily of the BCL-2 protein family and is a known target of p53. Chromatin immunoprecipitation was performed on HK-2 cells with INO80 knockdown using the H2A.Z antibody, because INO80 has been reported to remove the H2A.Z variant and exchange it for the H2A variant. INO80 knockdown significantly increased the H2A.Z variant and reduced the H2A.Z variant in the promoter region of PMAIP1, while H2A expression significantly decreased in the promoter region of PMAIP1.

Conclusions: INO80 plays an important role in exchanging H2A.Z for H2A in the promoter region of PMAIP1 in tubular cells to inhibit apoptosis during CKD progression.

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

FR-PO1086
Subclinical Acidosis Assessed by a New Urine Acid-Base Score Is an Independent Risk Factor for CKD Progression

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Background: Acidosis is reported to exacerbate the gradual loss of kidney function in patients with chronic kidney disease (CKD). Current guidelines advise assessing acid-base (AB) status of CKD patients by plasma bicarbonate, although covert acidosis may be present before it is reflected in this. Indeed, others have found a correlation between subclinical acidosis (SA), evidenced by low urinary NH++, excretion, and progression of kidney disease. However, low NH+ excretion may also be present in physiological states with low demand for acid elimination. To identify a sensitive and specific marker of SA, we analyzed several AB markers in urine samples from CKD patients. We hypothesized that a measure incorporating both pH and [NH+] would reflect the demand and capacity for sufficient renal acid excretion in CKD patients, and that this would be associated with CKD progression.

Methods: We included biobanked urine samples from CKD patients from two clinical studies (RENVAS, development cohort, 81 CKD patients and 25 healthy controls and PUMA, validation cohort, 65 CKD patients). Outcomes included mGFR at 18 months and composite outcome of 50% eGFR reduction or kidney failure defined by initiation of dialysis or kidney transplantation. AB-score was calculated from [NH+] and pH.

Conclusions: SA associates with greater mGFR decrease after 18 months and an increased risk of kidney failure or a >50% reduction of eGFR.

Funding: Private Foundation Support, Government Support - Non-U.S.
Eicosanoids and Related Metabolites Associated with ESKD in a Community-Based Cohort
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Background: Eicosanoids are derivatives of polyunsaturated fatty acids and participate in the inflammatory response and endothelial function maintenance. Specific eicosanoids have been linked to various diseases, including hypertension and asthma, and may reduce renal blood flow. A systematic investigation of eicosanoid-related metabolites and adverse kidney outcomes could identify key mediators of kidney disease and inform work in drug development.

Methods: Profiling of eicosanoid-related metabolites was performed in 9,650 participants in the Atherosclerosis Risk in Communities Study (visit 2; mean age, 57 years). The associations between metabolite levels and the development of ESKD was investigated using Cox proportional hazards regression (N= 256 events; median follow-up, 25.5 years). Metabolites with statistically significant associations with ESKD were evaluated for a potential causal role using Mendelian randomization techniques, linking genetic instruments for eicosanoid levels to genome-wide association study summary statistics of estimated GFR.

Results: The 223 eicosanoid-related metabolites that passed QC were generally uncorrelated with eGFR in cross-sectional analyses (median Spearman correlation, -0.03; IQR -0.05 to 0.002). In models adjusted for multiple covariates, including baseline eGFR, three metabolites had significantly significant associations with ESKD (p-value <0.05/233). These included a hydroxyoctadecenoic acid, a dihydroxydocosapentaenoic acid which were protective and an arachidonic acid, detrimental. Mendelian randomization suggested a causal role for the hydroxyoctadecenoic acid in determining eGFR.

Conclusions: High throughput eicosanoid profiling can identify metabolites that may play a protective role in the development of kidney disease.

Funding: Other NIH Support - NIH/NIDDK R01DK108803, R01DK124399, and NIH/NHLBI K24HL155861.

FR-PO1089 Glomerular Hyperfiltration and Th17 Responses Precede Glomerulosclerosis Following Nephron Loss
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Background: Chronic kidney disease (CKD) affects 37 million Americans resulting in $87 billion healthcare cost annually. Impaired renal autoregulation in obesity, diabetes and hypertension causes elevated glomerular capillary pressure and glomerular hyperfiltration (GHF), ultimately leading to glomerulosclerosis (GS) and CKD. Increased renal perfusion pressure directly drives T cell infiltration and T helper (Th) 17 cells promote renal fibrosis in hypertension and kidney ischemia-reperfusion injury, but their roles in GS are poorly understood.

Methods: We investigated the roles of GHF and Th17 responses in GS in a mouse CKD model induced by kidney mass (RKM), which involved nephrectomy and partial renal artery ligation in the remaining kidney such that the functional renal mass is reduced by ~3/4. Male 129/S6 mice received sham or RKM surgery at 8 weeks of age, and blood pressure (BP, by radiotelemetry), glomerular filtration rate (GFR, by transcardiac FITC-sinistrin) and serum/urine CKD markers were assessed as baseline (BL), and day (D) 3, 7, 14, 21, 28, 56, and 84 post-surgery.

Results: BP and GFR of RKM mice were identical to sham controls at BL (n=4-6). Immediately after RKM, GFR dropped to 22% of BL, consistent with the extent of renal mass reduction. BP was also reduced to 29 mmHg by D3 post-RKM (144 ± 8 vs 112 ± 2 mmHg, p<0.05, 2-way ANOVA). In mice lacking the inducible nitric oxide synthase (iNOS) enzyme, BP remained significantly elevated compared to RKM mice, but remained at BL levels in sham controls. The GFR of RKM mice gradually increased to 38% of BL at D3, 57% at D7 and 68% at D14, and plateaued at ~70% at D21-28, suggesting that the early rise in BP and impaired autoregulation may have caused GHF following initial nephron loss. The adaptive increase in GFR post-RKM was associated with marked renal Th17 cell infiltration at D14, preceding glomerular hypertrophy and mesangial expansion at D28 and subsequent recruitment of myeloid macrophages and T regulatory cells. Importantly, GFR declined to 42% of BL at D56 post-RKM, with concomitant GS and interstitial fibrosis as evidenced by Periodic Acid Schiff and Picro Sirius Red staining.

Conclusions: Together, our data suggest that both GHF and Th17 responses promote CKD progression and further loss of nephrons through glomerulosclerosis.

Funding: NIDDK Support, Other NIH Support - JW is supported by University of Rochester Pilot Awards (Prime Sponsor: NIAID P01AI102851 and NIHES P30ES001247).

FR-PO1090 Regenerative Capacity Decline and Progressive Tubular Cell Polyploidization as Adaptive Kidney Tubule Response to Aging
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Background: Kidney function declines progressively with age, leading to chronic kidney disease (CKD) in the elderly. CKD is a major global health problem, explaining why there is the need to understand the age-related mechanisms in CKD development. Most adult organs contain a pool of stem cells, whose function decline leads to tissue ageing. To what extent do resident stem cells or differentiated cells contribute to organ ageing remain to be clarified. Recently, we revealed two response programs in the kidney to recover kidney function and a structural integrity upon AKI. On the one hand, a population of resident renal progenitors (RPC) self-renew and differentiate to replace lost tubular cells. On the other, tubular cells (TC) undergo endoreduplication to become polyploid. We aimed to study how these two mechanisms affected the kidney ageing.

Methods: To study RPC, we used the inducible Pax6-CreERT2;R26R RPC (Pax2/+cells) are randomly labelled by one of the four fluorescent reporter genes. To identify polyploid TC, we used two inducible mouse models: the heterozygous Pax8/Confetti mice and Pax8/FUCCI2Ar mice. In the former model, all TC are labelled randomly by one of the four fluorescent reporter genes. Polyploid TC appear as bi-coloured due to recombination of two fluorochromes in the same cell. In the second model, polyploid TC are identified by expression of cycle cell fluorescent proteins (FUCCI2Ar technology) in combination with DNA content analysis. Mice were analyzed at 2, 6, 12 and 18 months of age.

Results: Pax2+/Confetti mice revealed that Pax2+/RPC of proximal tubule declined during ageing and their clonogenic capacity is impaired. By contrast, Pax8+/Confetti mice showed an increase of polyploid TC during ageing. Analysis of aged Pax8+/FUCCI2Ar mice revealed that polyploid TC increased furtherly their DNA content by going through additional cell cycles and that this was associated with fibrosis, senescence and kidney function decline. Thus, while the pool of RPC is progressively lost during ageing, impairing the kidney tubule regenerative capacity, TC enter the cell cycle to become polyploid. These accumulate in aged kidneys and trigger fibrosis and senescence, leading to CKD.

Conclusions: These results suggest a previously unknown role for RPC and polyploid TC in kidney tubule response to ageing.

FR-PO1091 In Vivo Single Cell Analysis of Senescence in Aged Kidney Disease and CKD
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Background: Senescent cells are a heterogeneous population of cells that accumulate in response to extrinsic and intrinsic stress with age and disease. Previously, we generated a p16CreERT2-tdTomato mouse model (p16-tdTomato mice hereafter) in which cells with high p16 expression, a prototypical senescent marker, were labeled with tdTomato through the administration of tamoxifen. In this study, we aimed to reveal the pathophysiological role of senescent cells in the kidney using p16-tdTomato mice.

Methods: We investigated three different kidney conditions; normal aging kidneys, adenin induced kidney disease, and tubulointerstitial nephropygesis. Male 6-24-month-old p16-tdTomato mice and 23-month-old p16-tdTomato mice were used for the normal aging process and disease models, respectively. The adenin diet was administered for three weeks, while 50% glycerol was injected into each leg to induce tubulointerstitial nephropygesis thus weekly. All the mice were sacrificed after the five times of tamoxifen injections. For further analysis of single senescent cells, the kidneys were directly digested, and flow cytometry (FACS) separately sorted tdTomato-positive senescent or tdTomato-negative cells.

Results: In the normal aging process, 20-24-month-old mice showed an accumulation in tdTomato-positive senescent cells compared to young mice. In both CKD models, the serum analysis demonstrated kidney dysfunction with increased BUN and Cr. Histopathological examinations showed tubular damage, interstitial fibrosis, and infiltration of immune cells, resembling CKD progression. Notably, the tdTomato-positive senescent cells increased following CKD; mainly, tdTomato-positive senescent PTECs were significantly detected. RNA-sequence analysis revealed that tdTomato-positive senescent PTECs collected from the CKD model by FACS showed high inflammatory signaling pathways, including hallmark TNFα signaling through NFκB, IL6 JAK-STAT, and TGFβ signaling. These inflammatory cascades are all related to senescence-associated secretory phenotype (SASP).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: These data suggest that CKD progression might cause premature kidney aging. In particular, tdtomato-positive PTECs might contribute to inflammatory environment in CKD by producing SASP. These tdtomato-positive PTECs might be a therapeutic target to prevent CKD progression and rejuvenate premature kidney aging.

Funding: Government Support - Non-U.S.

FR-PO1092
Possible Involvement of Renal Tubular NFAT5 in Aging-Associated Renal Phenotypes and Dysfunction
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Background: The number of patients with chronic kidney disease (CKD) and hypertension is increasing with age; however, it is not clearly defined why and how aging causes renal dysfunction and hypertension. Nuclear factor of activated T-cells 5 (NFAT5) is a transcription factor that is activated upon hypertonic conditions as observed in the renal medulla. We have already shown that the renal tubular cell-specific NFAT5 conditional knockout (KO) mice exhibit salt-sensitive hypertension, while the mice exhibit impaired urine concentrating ability and are susceptible to renal fibrosis. These phenotypes resemble aging-associated renal dysfunction, i.e., urine concentrating disorder, salt-sensitive hypertension, and renal fibrosis. We therefore investigated the possible involvement of NFAT5 in aging-related changes of the kidney.

Methods: The mRNA expressions of NFAT5 and its downstream genes including AQP2, urea transporter A-1 (UTA-1), and aldosterone (AR) were examined by real-time PCR in the whole kidney tissue of wild type (WT) mice at 3, 6, 12, and 18 months old. To investigate the involvement of NFAT5 in aging-related phenotypes of the kidney, kidneys collected from NFAT5 KO mice (3 and 18 months old) were characterized and compared with WT mice. Senescence-associated beta-galactosidase (SA-β-Gal) activity was examined by fluorescence study in the whole kidney slices. Gene expressions of senescence-associated secretory phenotype (SASP)-related factors (TGF-β1, COL1A1, ICAM1, PAI-1, and MMP3) were examined by real-time PCR. Renal fibrosis was examined by AZAN staining.

Results: While the expression of NFAT5 was increased with age, the mRNA expressions of AQP2, UTA-1, and AR were decreased significantly at 6 and 12 months old compared to 3 months old. SA-β-Gal activity was increased in the corticomedullary region in KO mice at 3 months. Gene expressions of SASP-related factors were significantly increased in KO mice. At 18 months old, KO mice exhibited renal atrophy and fibrosis in the medulla, which phenotypes were significantly accelerated than WT mice. These results indicate that the expression of genes downstream of NFAT5 could be decreased with aging kidney, suggesting that the decreased activity of NFAT5 may be involved in aging-related renal dysfunction.

FR-PO1093
Single-Nucleus RNA Sequencing Reveals Cellular Heterogeneity and Cell-Cell Interactions Contributing to Tertiary Lymphoid Tissue Development in the Aged Injured Kidney
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Background: Tertiary lymphoid tissues (TLTs) are ectopic lymphoid structures that develop in non-lymphoid organs with chronic inflammation. TLTs can develop in kidney diseases such as IgA nephropathy and transplanted kidneys and are associated with poor renal prognosis. However, how TLTs affect renal tissues and expand remains unclear.

Methods: Single-nucleus RNA-sequencing (snRNA-seq) was performed on three experiments. Tertiary lymphoid tissues (TLTs) are ectopic lymphoid structures that develop in non-lymphoid organs with chronic inflammation. TLTs can develop in kidney diseases such as IgA nephropathy and transplanted kidneys and are associated with poor renal prognosis. However, how TLTs affect renal tissues and expand remains unclear.

Results: While the expression of NFAT5 was increased with age, the mRNA expressions of AQP2, UTA-1, and AR were decreased significantly at 6 and 12 months old compared to 3 months old. SA-β-Gal activity was increased in the corticomedullary region in KO mice at 3 months. Gene expressions of SASP-related factors were significantly increased in KO mice. At 18 months old, KO mice exhibited renal atrophy and fibrosis in the medulla, which phenotypes were significantly accelerated than WT mice. These results indicate that the expression of genes downstream of NFAT5 could be decreased with aging kidney, suggesting that the decreased activity of NFAT5 may be involved in aging-related renal dysfunction.

FR-PO1094
Single-Nucleus Transcriptome Revealed Differential Cell Fate of Human Proximal Tubular Cells with Aging
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Background: Proximal tubular cell (PTC) is a high energy-requiring cell-type in the kidneys. But how this cell type ages remains incompletely understood throughout life course.

Methods: We explored transcriptional profiles through life time using the public dataset, Kidney Precision Medicine Project. We extracted the nuclei annotated as PTC from normal kidneys and discarded potential doublets that expressed other cell-type markers, which retained 18,765 nuclei.

Results: We found transcriptionally distinct 7 subclusters reorganized as healthy PT-1, healthy PT-2, stressed PT, scattered PT, injured PT-1, injured PT-2, and proliferating PT. Healthy PT-2 distinctively expressed PL12, a lipid droplet marker, and stressed PT showed enhanced expressions of ALDOB, PCK1, and GPX3. Scattered PT and injured PT-2 commonly expressed VIM, CD24, and S100A6, and injured PT population only expressed VCAM1. We found that healthy PT-2 showed the highest gene expression implicated in lipid metabolism, such as HMGC2S, ACSL1, and CPT1, and its PPARα signaling is upregulated than Healthy PT-1. In addition, scattered cells were enriched with cytoskeletal genes and has upregulation in glycolysis, oxidative phosphorylation, and actin cytoskeleton regulation compared to Healthy PT-1. In the trajectory analysis, healthy PT has two distinct pathes, one of which flow toward scattered PT through stressed PT and the other of which direct to injured PT. Each path had differential metabolic fate represented by enhanced and impaired fatty acid oxidation along the former and latter pathes.

Conclusions: PTC undergoes differential cell fate with aging on the view of gene expression and metabolism.

FR-PO1095
Higher Serum IL-6 and IFN-γ Are Associated with Increased Seroconversion Rate Against SARS-CoV-2 Spike Protein Either After Vaccination or SARS-CoV-2 Infection
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Background: Maintenance immunosuppressives lead to a decreased immunogenic response to SARS-CoV-2 infection and vaccination in renal transplant recipients (RTRs) than in healthy populations. However, healthy people with SARS-CoV-2 infection often develop neutralizing antibodies and secrete high quantities of cytokines leading to virus clearance and sometimes more severe COVID-19. Associations of cytokines with seroconversion rate in immunocompromised RTRs are not well studied, particularly in living donor scenarios.

Methods: In this study, we included 210 living-related RTRs, who acquired SARS-CoV-2 infection or were vaccinated with two doses of either COVISHIELD or COVAXIN; and 35 healthy controls who were neither vaccinated nor had anti-SARS-CoV-2 infection or were vaccinated with two doses of either COVISHIELD or COVAXIN. We measured the cytokines IL-6, IFN-γ, TGF-β, and IL-10 using ELISA, and SARS-CoV-2 spike protein-specific IgG titer by chemiluminescent microparticle immunoassay methods.

Results: We found a seroconversion rate of 115/132 (87.12%), with a median antibody titer of 706.40±44.00 (IQR: 215.45±1844.42) in the infection group and 63/78 (80.76%) with a median titer 1454.20 (IQR, 80.52-3838.75) au/ml in vaccination group. The IL-6, IFN-γ, TGF-β, and IL-10 levels were significantly higher in the infection group as compared to non-seroconverter. In contrast, TGF-β (730.48±400.47 vs 765.47±366.39 pg/ml; p=0.92) and IL-10 (91.31±39.78 vs 32.14±17.48 pg/ml; p=0.001) were significantly lower in the non-seroconverter group as compared to non-seroconverter.

Conclusions: Seroconversion rate was significantly higher in the infection and vaccination group than in the healthy control. In the infection group, IL-6 (55.41±24.30 vs 31.64±16.98 pg/ml; p<0.001), IFN-γ (91.21±33.09 vs 61.03±23.28 pg/ml; p=0.001), were significantly higher in the seroconverter group as compared to non-seroconverter. IL-10 (91.31±48.54 vs 96.73±59.53 pg/ml; p=0.88) were similar between seroconverter and non-seroconverter. Similar results were observed in vaccination group, IL-6 (50.31±225.67 vs 30.02±11.99 pg/ml; p=0.002) and IFN-γ (65.70±39.78 vs 32.14±17.48 pg/ml; p=0.001) were significantly higher in seroconverter post-vaccination compared to non-seroconverter. In contrast, TGF-β (820.96±415.78 vs 1045.57±204.68; p=0.046) was elevated in non-seroconverter, and IL-6 (19.84±35.12 vs 90.9±59.61 pg/ml; p=0.01) was similar between seroconverter and non-seroconverter.

Conclusions: Immuneological cytokines IL-6 and IFN-γ are significantly associated with higher seroconversion rates in RTRs after SARS-CoV-2 infection and vaccination.
Usefulness of Multiplex Immunodot Method for COVID-19 Vaccination Monitoring in Dialysis Patients: Results of the COVIDIAL Study

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Background: COVID-19 vaccine was demonstrated to be effective in dialysis patients, but boosters are mandatory due to a rapid waning of anti-spike antibodies. A vaccination strategy based on efficient immuneologic response monitoring might be useful to maintain a favourable risk-benefit balance in this vulnerable population.

Methods: CovIdial is an observational prospective study enrolling 121 dialysis patients who received a 3-dose mRNA-1273 vaccine according to a uniform schedule. At baseline, months 1, 3, 6, 9, and 12, anti-spike antibodies against four epitopes (S1, S2, ECD-S1/S2, RBD) were monitored with a multiplex immunodot enzymatic assay. Potential correlation between initial serologic response and subsequent COVID-19 infection was then assessed.

Results: Overall, 96.2% and 96.8% of patients developed anti-RBD antibodies at 3 and 12 months, respectively. All antibodies titres significantly decreased at month 6 compared to month 3. Booster vaccine induced a robust serologic response at month 9, but with a waning three months later, particularly for anti-S2 (37.2 ± 3.3 vs. 61.3 ± 3.0, p<0.0001) and anti-S1+S2 antibodies (68.4 ± 3.3 vs. 88.4 ± 2.3, p<0.01). Fifteen patients were later tested positive for SARS-CoV-2. At month 3, mean titres of anti-RBD, anti-±pc, and anti-S2 antibodies were lower than in the subsequent SARS-CoV-2 infected cohort (71.57±9.01 vs. 85.79±2.61, p<0.05; 41.07±7.96 vs. 61.68±3.56, p<0.05; 13.79±5.03 vs 39.70±3.86, p<0.01; respectively).

Conclusions: Three doses of mRNA-1273 vaccine induce a robust but time-limited immunologic response in dialysis patients. Lower anti-spike antibodies titres after initial vaccination are associated with a higher risk to subsequently contract SARS-CoV-2, even beyond six months.

Funding: Private Foundation Support

FR-PO1097

Barriers to COVID-19 Vaccination in Dialysis Populations: A Patient Perspective

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Background: ESKD patients are at risk for serious illnesses and death related to COVID-19. It is challenging for ESKD patients to stay updated with recommended COVID vaccination. We aim to study the perceived barriers to complete COVID vaccination in our dialysis population.

Methods: 205 ESKD patients consented to complete our questionnaires. Descriptive statistics including proportions, median, and interquartile range were calculated for categorical and continuous variables to describe the study population, and to report the patient perceived barriers to vaccination. Comparisons by age, race/ethnicity, sex, level of education and income were conducted to evaluate differences between those vaccinated vs unvaccinated.

Results: 205 patients participated in the study. 88.3% (n=181) received at least one COVID vaccine. 80.5% (n=165) completed primary series. 54.0% (n=112) received the bivalent booster. 7% (n=9) of males and 17.5% of females (n=16) were unvaccinated. Majority of unvaccinated patients were unemployed/retired/disabled, have income ≤ $30,000, and with at least a high school education. Among vaccinated group, 96.6% reported it was easy to get vaccines, while 56.2% were concerned to be vaccinated. 25.3% of patients reported it was expensive. 67.3% were concerned about side effects. 96.2% of patients felt that the vaccine was safe, and 78.3% were aware it was free. 12.5% thought they had medical reason not to be vaccinated. Only 22.7% of patients believed that vaccination would cause death or ICU admission. 20.8% of patients felt social media influenced on their decision.

Conclusions: Most ESKD patients reported having received vaccines and did not feel that physical limitation, transportation or accessibility were barriers to vaccination. Uncertainty of long term complications and efficacy of vaccination appeared to be the major barriers.

Funding: Private Foundation Support
ESRD patients have high plasma levels of FGF23, and recent studies suggest that patients with high FGF23 levels have increased rates of severe infections and infection-related mortality. Therefore, our objective was to evaluate the association between FGF23 levels and the development of SARS-CoV-2 infection in ESRD patients on hemodialysis.

Methods: A prospective cohort of ESRD patients on hemodialysis who had plasma intact FGF23 (iFGF23) measurements in 2019. We evaluated rates of SARS-CoV-2 infection and severe COVID-19 (COVID-related hospitalization or death) between January 2020 and December 2022 (3-year follow-up). In addition, we evaluated potential predictors of outcomes using multivariate analyses.

Results: 243 patients were evaluated. Age: 60 ± 10.8 years. Women: 120 (49.3%), diabetes: 110 (45.2%). 57 patients developed COVID-19 (23.4%), 41 were hospitalized, and 46 died (mortality rate: 18.9%). Patients with high iFGF23 (equal to or greater than 350 pg/mL) had a higher rate of SARS-CoV-2 infection (30.8% vs. 18.1%; Hazard ratio: 1.81 [95% CI: 1.50-2.20]) and severe COVID-19 (23% vs. 11.9%; Hazard ratio: 2.02 [1.09-3.71]; p = 0.031) compared to those with lower levels (Figures 1 and 2). Multivariate analysis showed that elevated iFGF23 plasma levels were an independent risk factor for SARS-CoV-2 infection and severe COVID-19.

Conclusions: Our data suggest that increased iFGF23 levels are a risk factor for developing COVID-19 in ESRD patients on hemodialysis. In addition, these data support the potential immunosuppressive effect of FGF23, which may contribute to the increased risk of adverse clinical outcomes in renal patients. Study supported by FONDECYT Regular 1221571.

FR-PO1100

The Comparison of Humoral Response Between Third and Fourth Doses of COVID-19 Vaccines in ESRD on Hemodialysis (HD)

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Background: The humoral response of coronavirus disease 2019 (COVID-19) vaccine in hemodialysis (HD) patients decrease substantially overtime compared to the general population. Currently, experts recommend to receive additional boosting vaccines against these high risk patients. However, the effects between additional third and fourth boosting vaccine in HD patients are not yet clear.

Methods: Total 86 HD patients from two hospitals (Gangdong Kyung Hee University Hospital and Kyung Hee Medical Center) were enrolled in this study. Patients were classified into 4 groups according to the total dose of vaccines and whether they were infected with COVID-19. Serum IgG to receptor-binding domain (RBD) of the S1 subunit of the SARS-CoV-2 was measured at 1 month after the first dose (T1), 2 months (T2) and 4 months after the second dose (T3), 4 months after third dose and (T4), 4-7 month after fourth dose of vaccine or 11 month after third dose (T5) for all groups. Neutralizing antibody also measured at T3 and T4 by plaque reduction neutralization test.

Results: Anti-RBD IgG after the second dose (T3) of vaccine was rapidly decreased (median [interquartile range] 1255.7[642.0, 2337.1] AU/mL, but it was significantly elevated after third dose (T4) in COVID19 naïve HD patients 3979.1[1966.1, 17098.1] AU/mL. The level of anti-RBD IgG was markedly higher in the COVID19 naïve patients with 4th doses than in them with 3rd doses (1400.5[3427.1, 3040.0], 2492.8[912.1, 17086.3] AU/mL, P < 0.001). However, the difference of anti-RBD IgG levels between 3rd and 4th vaccine was not observed in the COVID19 infected HD patients. Anti-RBD antibody titers were well correlated with neutralizing antibodies against omicron and delta T3 and T4 (P < 0.001). Of the total 34 COVID-19 infected patients, 6 patients had high severity/hospital admission, 2 death), and their anti-RBD IgG levels showed a lower trend than those with COVID-19 naïve 1255.7[642.0, 2337.1] AU/mL and low severity COVID-19 infected patients 1486.4[677.6, 3044.1]. In particular, two death HD patient showed significantly lower anti-RBD IgG(342.3, 317 AU/mL).

Conclusions: Humoral response was better after 4th dose compared with 3rd doses in COVID-19 naïve HD patients.

FR-PO1102

Immune Response After the Fourth COVID-19 Vaccine Dose in Hemodialysis Patients

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Background: Hemodialysis (HD) patients have shown a suboptimal immune response to COVID-19 vaccines, and it remains unclear whether current vaccination schemes are suitable for these patients. We assessed humoral and cellular responses after the administration of the 4th dose of mRNA-based COVID-19 vaccine in HD patients.

Methods: We included HD patients from a NephroCare clinic in Spain who were vaccinated with three doses of an mRNA-based COVID-19 vaccine and scheduled to receive the 4th dose. Humoral response was assessed at T0 (max. 4 weeks before 4th dose) and T1 (1 month post 4th dose) using a Bioplex IgG antibody panel. IFN-g released by S1 peptide stimulated T-cells was used to assess cellular response in a subsample of 5 patients.

Results: Twenty patients (80% males and median age 76.3 (IQR: 65.2; 84.2) years) were analyzed. Immune response was measured at T0 in a median period of 158 days after the 3rd dose and 100% patients maintained Anti-RBD and Anti-Spike 1 IgGs above the protective level. At T1, all humoral response markers significantly increased and cellular response was positive in 80% (4/5) patients. Anti-Nucleocapsid IgG, detecting contact with the virus, were positive in 3 (15%) patients at T0 and 4 (20%) at T1 but no COVID-19 infection was reported in the study period (figure 1).

Conclusions: Our study suggests that HD patients maintain a reasonable immune protection after three doses of an mRNA COVID-19 vaccine that further increases after the 4th dose. The first and second authors contributed equally to this work.

Funding: Commercial Support - Fresenius Medical Care

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Figure 1: Humoral and cellular immune levels before and after the fourth COVID-19 vaccine dose in HD patients.

FR-PO1103
Longitudinal SARS-CoV-2 Antibody and T-Cell Immune Responses in Patients on Hemodialysis During the Omicron Era
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Background: Individuals receiving renal replacement therapy via hemodialysis (HD) are at high risk for severe outcomes from COVID-19, have attenuated responses to the original COVID-19 vaccine series, and are at increased risk for contracting SARS-CoV-2 due to frequent healthcare exposures. How immunity to SARS-CoV-2, and for severe disease, evolve with episodes of infection and additional booster vaccinations in this vulnerable population has not been described.

Methods: An observational multicenter cohort of 55 HD patients (>90% received at least two doses of mRNA COVID-19 vaccine, 56% female, 47% with diabetic kidney disease, age [med, IQR] 67, 58-74 years) were followed for 24 weeks between Dec 2021 and Nov 2022 and provided blood samples at enrollment (week 0), 8 weeks, and 24 weeks. Plasma was tested for anti-SARS-CoV-2 IgG and ACE2 inhibition (surrogate neutralization; 0-100% with >25% consistent with neutralizing antibody) against ancestral, Beta, Delta, and Omicron subvariants using the MSD platform. T cell responses to SARS-CoV-2 spike and nucleocapsid were assessed via ELISpot. Changes in antibody and T cell responses were assessed by paired Wilcoxon rank-sum testing. Additionally, responses were compared to boosted healthy controls (HC) (n=11).

Results: Antibody responses against ancestral virus remained relatively constant in the HD cohort (p = 0.9). Neutralization of BA.5 remained low throughout with 48% of participants below the 25% threshold associated with live-virus neutralization. While ACE2 inhibition was similar to HC's (Figure), the proportion of HD participants above the 25% threshold for BA.5 was significantly lower than HCs (p = 0.004). Neutralizing capacity of BA.5 among HD patients with a history of COVID-19 was not greater than those with no history of COVID-19. Spike specific T cell responses increased in HD patients over time.

Conclusions: Original vaccine formulations are insufficient to induce reliable Omicron subvariant neutralization in HD patients.

Funding: Commercial Support - This work was supported by Fresenius Medical Care

FR-PO1105
COVID-19 Vaccine Immune Response in Hemodialysis Patients

Background: COVID-19 infection is associated with increased morbidity and mortality in chronic kidney disease patients, especially those on maintenance hemodialysis. The comparison of immunogenicity of different COVID vaccines in the dialysis populations is lacking especially in the middle east region.

Methods: We conducted a retrospective observational study, that includes 164 hemodialysis patients (HD) and 54 health workers (HW), who received 2 doses of either Pfizer-BioNTech or Sinopharm vaccine. The primary endpoint was to report the rate of seroconversion and the factors affecting it.

Results: HD patients have a significantly low seroconversion rate than HW (HD vs HW: 76.54% and 100%; p = <0.05), also S1 IgG antibody level was significantly low in HD patients (HD vs HW: 183.5 and 400 BAU/mL, p = <0.05). The type of vaccine and hypo-response to the HBV vaccine were two statistically significant factors affecting the seropositivity rate in HD patients. As compared to Sinopharm, Pfizer-BioNTech vaccinated HD patients exhibit not only higher seroconversion rate (Pfizer-BioNTech vs Sinopharm: 90.80% and 60%, p =<0.05) but also express high S1 antibody titer (Pfizer-BioNTech vs Sinopharm: 425 and 162 BAU/ml (p =<0.05), however, there is no significant difference in post-vaccine COVID infection rate among the two vaccines (Pfizer-BioNTech vs Sinopharm: 39.24% and 42.22% (p = 0.176).

Funding: Government Support - Non-U.S.
Conclusions: Lower Immune response to the COVID vaccine is observed in HD patients as compared to HW participants, also Pfizer-BioNTech vaccinated HD patients exhibit better seroconversion rates and higher antibody titer than Sinopharm vaccine in HD patients, so alternative vaccine strategies should be designed in dialysis patients.

FR-PO1106
Omicron BA.1, BA.5, BQ.1.1, and XBB.1.5 Neutralizing Antibodies Following BNT162b2 BA.4/5 vs. mRNA-1273 BA.1 Bivalent Vaccination in Hemodialysis Patients and Kidney Transplant Recipients

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Background: Bivalent COVID-19 vaccines are recommended, however differences in neutralization of emerging Omicron subvariants by vaccine type have not been evaluated in patients with kidney disease.

Methods: This was a prospective observational cohort study at three centres in Toronto, Canada from July 25, 2022 to November 30, 2022 in 98 patients receiving hemodialysis or with a kidney transplant. Participants received either the BNT162b2 (original and Omicron BA.4/BA.5) or mRNA-1273 (original and Omicron BA.1) COVID-19 vaccine. Neutralizing antibodies against wild-type, Omicron BA.1, BA.5, BQ.1.1, XBB.1.5 subvariants were measured prior to and one month following the receipt of a bivalent vaccine.

Results: Neutralizing antibodies against BA.1, BA.5, BQ.1.1, and XBB.1.5 increased 8-fold one month following bivalent vaccination. In comparison to wild-type, neutralizing antibodies against Omicron-specific variants were 7.3-fold lower against BA.1, 8.3-fold lower against BA.5, 45.5-fold lower against BQ.1.1, and 48.2-fold lower against XBB.1.5. Viral neutralization did not differ by bivalent vaccine type: wild-type (p=0.48), BA.1 (p=0.21), BA.5 (p=0.07), BQ.1.1 (p=0.10), XBB.1.5 (p=0.10).

Conclusions: The BNT162b2 and mRNA-1273 bivalent vaccines induced similar neutralization against all Omicron subvariants in hemodialysis and kidney transplant recipients, suggesting that bivalent vaccines confer protection against emerging Omicron subvariants even if they are antigenically different from the circulating variant.

Funding: Government Support - Non-U.S.

FR-PO1107
Safety and Efficacy of One and Two Booster Doses of SARS-CoV-2 mRNA Vaccines in Kidney Transplant Recipients: A Randomized Clinical Trial

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Background: Kidney transplant recipients are at risk for a severe course of COVID-19 with a high mortality rate. Although an adequate humoral response to COVID-19 vaccination is therefore essential, a considerable number of patients remains without a satisfactory serological response after the baseline and adjuvant SARS-CoV-2 vaccination schedule.

Methods: In this prospective, randomized study, we evaluated the efficacy and safety of one and two booster doses of mRNA vaccines (either mRNA-1273 or BNT162b2) in 125 COVID-19 naive, adult kidney transplant recipients who showed an insufficient humoral response after the baseline and adjuvant SARS-CoV-2 vaccination schedule.

Results: A positive humoral response was observed in 36 (62%) patients who received two booster doses and in 28 (44%) patients who received one booster dose (p=0.043). Moreover, median SARS-CoV-2 IgG levels were higher with two booster doses (p=0.009). The number of patients with positive virus neutralizing antibody levels was numerically higher in the two booster doses compared to the single booster dose, but without statistical significant (66% vs. 50%, p=0.084). There was no significant difference in the rate of positive seroconversion and antibody levels between mRNA-1273 and BNT162b2 vaccines.

Conclusions: A higher number of kidney transplant recipients achieved a positive antibody response after two booster doses compared to one booster dose.

Funding: Other NIH Support - Charles University Cooperatio Program; "Fighting Infectious diseases" (FIND) project; Faculty Hospital in Pilsen; BBMRI-CZ: Biobank network
FR-PO1108

SARS-CoV-2 Vaccination Reduces the Frequency of Acute Kidney Disease in COVID-19 Patients: A Prospective Multicenter Multinational Study

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COVID-19 Hospitalization after Reinfecction

FR-PO1111

Outcomes of Patients with CKD and ESRD Hospitalized with COVID-19: A Retrospective Cohort Study in Michigan

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1The University of Tennessee Health Science Center College of Medicine, Memphis, TN; 2Trinity Health, Livonia, MI.

Background: A large patient cohort, multivariate regression models, and inverse probability of treatment weights (IPTWs) to determine the effect of kidney disease on mortality in hospitalized COVID-19 patients.

Methods: 6,737 hospitalized, SARS-CoV-2 positive patients from the South East Michigan COVID Consortium dataset were analyzed for common dimensions of risk factors for increased mortality. Univariate, multivariate logistic regression, and IPTW propensity scoring models were used to reflect the effect of each variable on outcomes. IPTW models required patient population trimming to include patients only within the region of common support, thus less patients were analyzed in the fully adjusted (N=6,117) and IPTW (N=4131) models.

Results: Unadjusted models show significant increases in all outcomes in any level of renal disease. No association with increased mortality as a result of renal disease after adjusting for covariates. IPTW model finds that renal dysfunction infers longer duration of renal disease. No association with increased mortality as a result of renal disease after (N=6,117) and IPTW (N=4131) models.

Conclusions: Here, we show that renal disease in of itself does not directly lead to increased mortality in COVID-19 patients. Initial findings of increased mortality in CKD and ESRD patients may more likely be a result of chronic disease burden as shown by sequelae comorbidities seen in CKD and ESRD patients.

Association between CKD/ESRD and Binary CoVid-19 Outcomes

<table>
<thead>
<tr>
<th>Model</th>
<th>N</th>
<th>Overall p-value</th>
<th>CKD 1 vs No CKD</th>
<th>ESRD 1 vs No ESRD</th>
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</thead>
<tbody>
<tr>
<td>IRR 95% CI</td>
<td>p-value</td>
<td>IRR 95% CI</td>
<td>p-value</td>
<td>IRR 95% CI</td>
</tr>
<tr>
<td>In Hospital Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>6,737</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>IPTW</td>
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<td>0.59</td>
<td>1.00</td>
<td>0.00</td>
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<tr>
<td>In Hospital Death or Expected Death (Transfer to Hospital)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>6,737</td>
<td>0.00</td>
<td>1.00</td>
<td>0.00</td>
</tr>
<tr>
<td>IPTW</td>
<td>4,131</td>
<td>0.49</td>
<td>1.00</td>
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<tr>
<td>Admissions to ICU</td>
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<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>6,737</td>
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<td>Total Duration of Hospitalization (days)</td>
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<tr>
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<td>Highest SOFA score recorded across hospital stay</td>
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<td>IPTW</td>
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</tbody>
</table>

FR-PO1112

COVID-19 Omicron Infections in a Chinese Peritoneal Dialysis Center

Jin Chen, Guisen Li. Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital, Sichuan Clinic Research Center for Kidney Diseases, School of Medicine, University of Electronic Science and Technology of China, Chengdu, China.

Background: In December 2022, an outbreak of the COVID-19 Omicron variant occurred in China, resulting in widespread population transmission. Peritoneal dialysis (PD) and patients with COVID-19 infections were at higher risk. Traditional risk factors such as age, diabetes, low serum albumin, and catheter usage remained significant.

Methods: Demographic and clinical characteristics of 341 PD patients were recorded at admission. Both binary logistic regression analysis and Cox proportional hazard regression analysis were used to evaluate potential risk factors for infection and mortality.

Results: COVID-19 was confirmed in 260 (76.2%) patients. Among infected patients, 57 (16.7%) were hospitalized and 11 (4.2%) patients died. Old age (odds ratio [OR] 1.042, 95% CI 1.001-1.087, p=0.04), diabetes (OR 1.164-29.201, p=.03), baseline hyponatremia (OR 3.096, 95% CI 1.125-8.517, p=0.03), and baseline high-sensitivity C-reactive protein huCRP (OR 1.089, 95% CI 1.011-1.173, p=0.02) were associated with hospitalization. Patients with a higher Charlson comorbidity index score (OR 2.143, 95% CI 1.049-4.148, p=.03), weight loss (OR 9.168, 95% CI 1.604-52.399, p=.01), and baseline hyponatremia (OR 19.345, 95% CI 2.229-167.862, p=.007) were more likely to die compared to survivors.

Conclusions: Older PD patients with hyponatremia, in receipt of glucocorticoid therapy, and baseline hyponatremia had a higher risk of hospitalization. Charlson comorbidity index score, weight loss, and baseline hyponatremia were associated with mortality.

FR-PO1113

Encapsulating Peritoneal Sclerosis Related to SARS-CoV-2 Infection

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Introduction: Encapsulating peritoneal sclerosis (EPS) is an extremely rare complication of long-term PD, associated with high morbidity and mortality (50%). The reported incidence is 0.7 and 13.6 per 1,000 pts-year. PD duration is the key risk factor, higher dialysate glucose exposure, peritonitis rate, younger age, abdominal surgery, icodextrin (ICO), UF failure, and higher peritoneal solute transport rate as well. Diagnosis is based upon a combination CT findings and intermittent subacute bowel obstruction. Only a fibrous cocoon wrapped around the bowel is diagnostic.

Case Description: 41-year-old female, history of diabetes and hypertension. CKD 4 of unknown etiology since 2020, she began APD since 1 yr, 2.5% PD solution + ICO. 9 days before admission with a + Covid-19 test, 3 days before she had abdominal pain and clinical data of intestinal occlusion (IO). She was admitted with BP 60/40 mmHg, IV resuscitated and treated w/MTZ and CRO. PD count (PDC) showed 1,842 leu, concluding IO and peritonitis. An exploratory laparotomy (EL) was performed with removal and replacement of catheter. After 5 days a PDC showed refractory peritonitis, transferred to ICU and treated w/treatmentsescalated (VCM and CTZ). 7 days after EL, PD catheter was removed. She persisted with IO, a CT scan corroborate it; A new EL was done with finding of fibrous cocoon wrapped around the bowel and peritoneal biopsy with fibrosis and chronic inflammation.

Discussion: The patient has risk factors for EPS: PD w/ ICO, and 2.5% PD solution, however the main reported risk factor is time in PD, in her case it was considered low. Covid-19 infection has been associated with a possible effect of the virus on the peritoneal mesothelial cells (MCs). Although there is no in vivo direct evidence so far of MCs infection by the virus, despite this, MCs have been found to express SARS-CoV-2 specific receptors/co-receptors ACE2. In this case we consider a strong association between Covid-19 and EPS. To our knowledge there are not previous reported cases and this represents and area for future research.

FR-PO1114

Comparing Infectious Diagnoses in ESKD Before and After the COVID Era


Background: Undoubtedly, the 2020 worldwide COVID-19 pandemic had a major impact on healthcare. This study aims to compare infections among inpatients with end stage kidney disease (ESKD) before and after the onset of the pandemic in the USA.

Methods: All adult hospitalizations from the 2016-2020 National Inpatient Sample (NIS) database with a principal diagnosis of infection and a secondary diagnosis of ESKD were analyzed. We compared data between the pre-COVID era (2016-2019) with those from the COVID era (2020).

Results: 990,550 hospitalizations between 2016-2020 had both an infection and ESKD. Of those, 752,640 were from the pre-COVID era and 237,910 were from the COVID era (figure 1). Those from the COVID era had less females, higher inpatient charges, and higher adjusted in-hospital mortality (14.4% vs 10.2%; p<0.001) (figure 1). In 2020, COVID-19 became the second most frequent infection seen among the inpatients (figure 2). Various types of sepsis remained frequent in both groups, along with pneumonia, line infection, peritoneal dialysis catheter infection, and urinary tract infection.
The Effect of ESKD on COVID-19 In-Hospital Mortality

FR-PO1115

The Effect of ESKD on COVID-19 In-Hospital Mortality

Background: Significant morbidity resulted when the COVID-19 infection became a pandemic in the United States. This study aimed to study the effect of end stage kidney disease (ESKD) on mortality on those with COVID.

Methods: We performed a retrospective analysis of all adult hospitalizations with a principal diagnosis of COVID from the 2020 National Inpatient Sample (NIS) database. They were subdivided in those with and without ESKD. Variables with a p value ≤0.2 in the univariable screen were included in a multivariable analysis for in-hospital death.

Results: There were 27,668,666 adult hospitalizations in the 2020 NIS database. Of those, 1,011,340 had COVID without ESKD and 38,705 had COVID with ESKD (figure 1). Among COVID inpatients, univariable analysis showed an association for death for the following variables: age, CCI, male gender, White, African American, Hispanic, Native Americans, ESKD, Income Q1, and Income Q3. Multivariable analysis showed higher odds for death for the following variables: age (OR 1.04; p<0.001), CCI (OR 1.18; p<0.001), Male (OR 1.39; p<0.001), Hispanics (OR 1.09; p=0.019), Native American (OR 1.57; p<0.001), ESKD (OR 1.25; p<0.001), and Income Q1 (OR 1.12; p<0.001) (figure 2).

Conclusions: Age, CCI, male gender, Hispanic race, Native American ethnicity, ESKD, and a lower income were associated with higher odds of death among those hospitalized with COVID. This information can alert nephrologists of the negative effects of ESKD on COVID mortality. Further studies on COVID mortality must account for ESKD.

COVID-19’s Impact on Dialysis Waste: A Greek Dialysis Group’s Experience
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Background: The COVID-19 pandemic has increased the generation of biomedical waste and put enormous strain on waste collection thus damaging the environment. Our dialysis group operates 9 dialysis clinics in Greece treating approximately 1000 patients. We are continuously implementing national regulations-protocols and extra measures protecting patients from COVID-19. We investigated the effect of COVID-19 pandemic on the generation of hazardous and infectious waste amounts and waste production rate in our dialysis clinics.

Methods: We performed routine weighing of all dialysis clinics’ infectious and hazardous waste including: 1.Personal protective equipment(PPE): gloves, gowns, tapes, coveralls, goggles, masks, caps, shoe covers. 2. The SARS-CoV-2 rapid antigen test (RAT) components 3.dialyzer filters, circuits, connections. 4. Contaminated single-use material, drapes, gauzes, compresses, bandages, and single-use care kits. We compared all amounts of waste produced before the pandemic, year 2019, and during the pandemic, years 2020, 2021 and 2022: per waste category, as total categories’ aggregates, per dialysis session, per dialysis clinic and for all dialysis clinics.

Results: Aggregated hazardous and infectious waste increased during the pandemic in all our dialysis clinics. Indicatively: Total kilograms of waste discarded were 142561.04, 152866.92 and 166430.5 in the years 2019, 2020, 2021 and 2022 respectively. 2022 presented a 4% increase compared to 2019. Per dialysis session Kilograms of waste produced before the pandemic, year 2019, and during the pandemic, years 2020, 2021 and 2022: per waste category, as total categories’ aggregates, per dialysis session, per dialysis clinic and for all dialysis clinics.

Conclusions: Dialysis waste management is of paramount importance. In the years following the pandemic, our dialysis clinics’ waste generation increased, making efficient waste management even more critical. Our group’s dialysis clinics are currently implementing new, more efficient and environment friendly practices and we trust that their beneficial effects will be soon documented.
FR-PO1117

**Nationwide In-Hospital Morbidity and Mortality Analysis of COVID-19 Infection in Advanced CKD (aCKD), Dialysis Patients, and Kidney Transplant (KT) Recipients**

**Mingyue He, Avrum Gillespie. Temple University Hospital, Philadelphia, PA.**

**Background:** Individuals with kidney disease, including aCKD, end-stage kidney disease (ESKD), and KT have an increased risk for COVID-19 infection, hospitalization, and mortality compared to those without CKD (CKD-free). The comparative morbidity and mortality among hospitalized COVID-19 patients with aCKD, ESKD, KT, and CKD-free remain uncertain.

**Methods:** We queried the 2020 Nationwide Inpatient Sample (NIS) database for non-elective adult COVID-19 hospitalizations. Patients were classified into four kidney disease categories: aCKD (stage 3-5, non-dialysis), ESKD (dialysis), KT, and CKD-free. The primary outcome was in-hospital mortality; secondary outcomes included morbidity (septic shock, acute respiratory failure, acute respiratory distress syndrome (ARDS), mechanical ventilation, pressor requirement) and resource utilization (length of hospital stay (LOS), total charges). Outcomes were analyzed with either multivariable logistic or linear regression and adjusted for demographic and comorbidity confounders.

**Results:** A total of 1,018,915 adults hospitalized for COVID-19 in 2020 were included. Of these, 5.9% had aCKD, 3.9% had ESKD, 0.4% were KT recipients, and 85.0% had no pre-existing CKD. The all-cause in-hospital mortality was 9.7% for CKD-free, 20.9% for aCKD, 19.7% for ESKD, and 12.4% for KT. Results were shown in Figures.

**Conclusions:** Our study found hospitalized COVID-19 patients with aCKD and ESKD exhibited more morbidities and higher mortality than those without renal disease. Notably, mortality in KT patients was comparable to the CKD-free group. Thus, managing comorbidities and promoting vaccination is critical in aCKD and ESRD patients.

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**FR-PO1118**

**Circulating FGF23 Is Associated with AKI and Predicts Survival in COVID-19**

Gyatri Narayanan, Heather Burney, Elliott Arroyo, Arvin Halim, Yang Li, Xiaochnu Li, Syed J. Sher, Kenneth Lim. Indiana University School of Medicine, Indianapolis, IN.

**Background:** 20-40% of severely ill COVID-19 patients develop acute kidney injury (AKI). AKI is now considered to be a negative prognostic factor for survival in COVID-19 patients. FGF23 is a bone-derived phosphatonin that is elevated in AKI. To-date, no study has investigated the associations between FGF23 and AKI in the COVID-19 population. Herein, we performed a study evaluating FGF23 levels in a cohort of COVID-19 patients and its association with AKI status and survival.

**Methods:** We conducted a prospective cohort study in 111 patients hospitalized with COVID-19. Total FGF23 levels were measured using an ELISA assay (Quidel). AKI status and FGF23 levels were determined concurrently. The primary outcome was death and secondary endpoint was AKI status. The median follow-up to death was 22.6 months.

**Results:** Of the 111 patients, 77 had no AKI (eGFR≥90 [69.2,103.1] mL/min/1.73m²), 17 had AKI (eGFR<39.7 [28.7,57.8] mL/min/1.73m²), and 17 had end-stage kidney disease (ESKD, p<0.001). Patients did not significantly differ in sex (p=0.6) or age (p=0.9) but differed in BMI (p<0.02). Median FGF23 levels were higher in patients with COVID-19 [305.6 [134.6, 350.8] RU/mL] and ESKD (3,607.7 [440.5, 7,452.7] RU/mL) compared to those with no AKI (120.7 [64.3, 249.7] RU/mL), p<0.001. After adjusting for patient age, patients with high FGF23 showed increased odds of having AKI (p=0.004). Survival at 24 months was better among patients (71%) compared to AKI (65%) and ESKD (35%) patients (p<0.02). Finally, controlling for patient age and group-specific death hazards among non-AKI, AKI and ESKD groups, FGF23 was significantly associated with an increased risk of death (p<0.001).

**Conclusions:** Elevated FGF23 levels are associated with AKI and were predictive of death in a cohort of COVID-19 patients. These findings indicate that FGF-23 levels may help with risk stratification and management of AKI in patients with COVID-19.

**Funding:** Other NIH Support - National Institutes of Health, Clinical and Translational Sciences Award.
injury and antiviral-based countermeasures in COVID-19 infection. We hypothesized that cytokine storm induced kidney injury in COVID-19, MA10-infected mice were treated with anti-IL-6R mAb or Baricitinib. Unexpectedly, ACR and Ngal/Cr ratio tended to be increased in anti-IL-6R mAb group. Upon Baricitinibtreatment, ACR and Ngal/Cr ratio was significantly increased.

Conclusions: Blockade of IL-6-JAK signaling in the early phase of SARS-CoV-2 infection exaggerates kidney injury, providing a novel insight into the pathogenesis of COVID-19-related injury.

FR-PO1121

Ferroptosis of Kidney After SARS-CoV-2 Infection

Wooong Park,1 Yujin Jung,1 Hyeyongwan Kim,2 Jihyun Yoom,2 Sookyun Lee,2 Yujin Shin,2 Won Kim,1,2 Yeonbuk National University Medical School, Jeonju, Jeollabuk-do, Republic of Korea; 1Yeonbuk National University Hospital, Jeonju, Jeollabuk-do, Republic of Korea.

Background: Although kidney involvement have been evaluated for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, none have fully evaluated the ferroptosis in the kidney after SARS-CoV-2 infection. Here, we evaluate the ferroptosis in the renal injury in the transgenic mice expressing the human ACE2 receptor driven by the cytokeratin-18 gene promoter (K18-hACE2) after SARS-CoV-2 infection.

Methods: To investigate the effect of SARS-CoV-2 on renal ferroptosis, we administered 2.5 x 10^6 p.f.u. of SARS-CoV-2 via intranasal to K18-hACE2 mice. After 7 days of SARS-CoV-2 infection, kidney tissues were harvested. SARS-CoV-2 infection and ferroptosis were evaluated by immunohistochemistry. Next, ferroptosis-related markers, gluthatamine peroxidase 4 (Gpx4), prostaglandin-endoperoxide synthase 2 (Pgks2), Acyl-CoA synthetase long chain family member 4 (Acsl4), nuclear factor erythroid-2-related factor 1 (Nrf2), ferritin heavy chain 1 (Fth1) and nuclear receptor coactivator 4 (Ncoa4) were evaluated by quantitative PCR.

Results: SARS-CoV-2 infection significantly increase the expression of SARS-CoV-2 spike protein in the tubular epithelial cells of the renal cortex and medulla. Protein expression of Gpx4 was significantly decreased in the renal medulla. In the kidney of SARS-CoV-2-infected mice, the ferritin-related markers ferritin heavy chain 1 (Fth1) and transferrin receptor 1 (Tfr1) and lipid peroxidation marker, dihydroethidium (DHE) were also increased in histological experiments. Next, the mRNA levels of Prg5, Acsl4, Nrf2, Ho-1, Fth1 and Ncoa4 were increased in the kidneys of SARS-CoV-2-infected mice compared to non-infected mice.

Conclusions: All of our data suggest that SARS-CoV-2 infection shares many features of ferroptosis in the kidney and can be used to define the ferroptosis of kidney injury and antiviral-based countermeasures in COVID-19 infection.

Funding: Government Support - Non-U.S.

FR-PO1122

University of California (UC) Kidney COVID-19 Study AKI Cohort

Hiba Hamdan, Brian M. Piacotti, Blythe Durbin-Johnson, Juan P. Moreno-Ortiz, Brian Y. Young, Baback Roshanravan. UC Davis Health, Sacramento, CA.

Background: A wide range of rates of AKI associated with COVID-19 have been reported, often specific to select timeframes and associated SARS-CoV-2 variants of the pandemic. The aim of our study is to comprehensively describe the rates of AKI in people hospitalized with COVID-19 over the course of the first two years of the pandemic and identify risk factor for AKI in that population.

Methods: We conducted a retrospective cohort study of adults receiving care within the 5 major University of California (UC) Health Systems. The cohort included people who underwent PCR testing and were positive for SARS-CoV-2 between March 1, 2020, and December 31, 2021, and required hospitalization within 10 days of testing. The cohort was further restricted to those without ESKD, without documented pregnancy, and length of stay ≥1 day. To examine risk factors associated with AKI, we used a logistic model including age, gender, race, HTN, CKD, and in hospital sepsis and mechanical ventilation, and month of COVID-19 diagnosis.

Results: The cohort included 5451 people with COVID-19. Patients had an average age of 59 years, 59% were male and 45% were Hispanic. From March 2020 to December 2021, the rates of AKI ranged from 20-38% and varied over the course of the pandemic (Figure 1). The factors associated with the highest odds (OR,95% CI) of AKI were: Black race (2.2,1.0-1.5), mechanical ventilation (5.1,4.2-6.2), sepsis (2.9,2.4-3.6), HTN (1.7,1.4-2.1) and CKD (1.5,1.2-2.0).

Conclusions: In a large, multicenter cohort of people hospitalized with COVID-19, in one of the largest healthcare systems in California, AKI rates generally exceeded 25%. Black race, HTN, CKD, and in hospital sepsis and mechanical ventilation were associated with higher odds of AKI.

Funding: Other NIH Support - UC Davis School of Medicine

FR-PO1123

University of California (UC) Kidney COVID-19 Study Outpatient Cohort

Hiba Hamdan, Brian M. Piacotti, Blythe Durbin-Johnson, Brian Y. Young, Juan P. Moreno-Ortiz, Baback Roshanravan. UC Davis Health, Sacramento, CA.

Background: The long-term kidney effects of COVID-19 infection are unknown, especially among non-hospitalized patients where changes may be less noticeable. Among five major University of California (UC) Health Systems, we compared changes in kidney function between non-hospitalized COVID-19 patients to those without COVID-19.

Methods: We conducted a retrospective cohort study that included all adults who had SARS-CoV-2 PCR testing between 3/1/2020-12/31/2021 and were not hospitalized within 10 days of testing. Individuals were classified with or without COVID-19 based on index SARS-CoV-2 PCR. Inclusion required kidney function measurement within 12 months prior and at least one outpatient creatinine 30 days after index SARS-CoV-2 PCR. Follow up was until December 31, 2022. The cohort excluded patients with ESKD or pregnancy. We also excluded from controls any patients with a subsequent positive SARS-CoV-2 PCR test during the study period. Thus, none of the controls were ever COVID-19 positive. The primary outcome was the difference in the rate of change in eGFR at least 30-days after index SARS-CoV-2 PCR. Three linear mixed models were fitted, as detailed in the figure below.

Results: The cohort included 10915 and 152620 people with and without COVID-19. COVID-19 Patients were more likely to be Hispanic, have higher BMI and DM, and reside in areas with higher ADI (Area deprivation index). Results of the three linear mixed effects models are shown in figure below. Conclusions: In a cohort from the largest academic health system in California, in adjusted models we didn’t observe a statistically significant difference in the rate of eGFR loss in non-hospitalized COVID-19 patients compared to controls over an average follow up period of two years. This study has one of the longest follow up times of kidney function post SARS-CoV-2 infection.

Funding: Other NIH Support - UC Davis School of Medicine

FR-PO1124

Association Between Urine Sediment Examination and Adverse Outcomes in Hospitalized Patients with AKI and Severe COVID-19


Background: COVID-19 and Acute kidney injury (AKI) are associated with increased mortality and worse kidney outcomes. Although several factors including age, sex, and comorbidities are associated with increased morbimortality, to our
knowledge, no study has dwelled into the evaluation of urine sediment and prognosis in patients who developed AKI during COVID-19.

Methods: Retrospective cohort study that included clinical and biochemical data of 288 hospitalized patients with COVID-19 who developed AKI at any stage. Urinary and Cox regression analyses were used to evaluate the role of urine sediment and progression in AKI with Covid-19. The study was performed in a tertiary kidney center of the Kidney stage 3, mortality, and need for renal replacement therapy. The Perazella score was evaluated to number of cellular renal tubular epithelial cells (CRTEC) and granular casts.

Results: The mean age of the patients was 57 ± 14 years, 69% were women, the mean body mass index (BMI) was 26.5 kg/m2, and median time in hospital was 11 (6-19) days. Overall, 47.3% had diabetes and 33.8% hypertension. The rate of AKI was 27.9 ± 5.6 kg/m2, and median time in hospital was 11 (6-19) days. The risk of AKI was compared among the COVID-19 patients receiving different medications. Pharmacovigilance data obtained from the FAERS was analyzed. Specifically, patients aged 50-70 or over 70 years were twice as likely to report AKI, compared to the <50 age demographic. Male patients prescribed remdesivir had a two-fold higher likelihood of reporting AKI compared to females. Additionally, patients who took vancomycin alongside remdesivir exhibited a 3.87-fold increased likelihood of reporting AKI compared to patients treated with other medications.

Conclusions: COVID-19 patients treated with remdesivir exhibited a higher risk of reporting AKI as an adverse event than patients prescribed other approved treatments for COVID-19 infection. This increased occurrence of AKI may be attributed to the activity of MAPK/JNK signaling pathway.

Funding: NIDDK Support, Private Foundation Support

FR-P01128

Association of Body Mass Index with Multiple Organ Failure in Hospitalized Adults with COVID-19

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Background: Patients with severe coronavirus disease 2019 (COVID-19) experience an excessive cytokine release syndrome, which promotes an increased risk of acute organ dysfunction and death. The aim of our study was to examine whether excessive adipose tissue mass measured by body mass index (BMI), is associated with higher (systemic markers of inflammation and higher risk of severe acute organ failure or in-hospital death among hospitalized patients with COVID-19.

Methods: 1370 hospitalized adults (18 years or older) with COVID-19 during the first wave of the pandemic in Massachusetts (March 1, 2020, to July 31, 2020) met inclusion criteria. Our primary outcome was the composite of severe acute kidney injury (AKI), as defined by acute dialysis requirement, severe acute lung injury (ALI), as defined by use of high-flow nasal canula, non-invasive ventilation, or mechanical ventilation, or in-hospital death. Secondary endpoints included need for mechanical ventilation and the association of BMI with serum peak CRP level, a systemic marker of inflammation.

Results: After adjustment for age, gender, race, Charlson Comorbidity Index (CCI), baseline eGFR, and the NIH clinical spectrum of SARS-CoV-2 infection, the highest BMI stratum (≥ 40 kg/m2 compared to the BMI < 25 kg/m2 reference group) was associated with higher odds for the composite of severe AKI, severe ALI, or in-hospital death (adjusted odds ratio [OR] ≥ 1.69; 95% CI 1.03, 2.78), and the composite of severe ALI or in-hospital death (OR ≥ 1.69; 95% CI 1.03, 2.77). As a continuous variable, BMI (per 5-kg/m2 increase) remained independently associated with these outcomes. Interestingly, this association was no longer significant after adjustment for peak CRP level.
Conclusions: Among hospitalized adult with COVID-19, higher BMI associates with higher risk of severe organ failure or death, which dissipates after adjustment for CRP level. This supports the hypothesis that inflammation is a downstream mediator of the adipose tissue on acute organ dysfunction, possibly through dysregulated immune responses. More research is needed to understand this association in COVID-19.

Funding: Other NIH Support - National Institutes of Health, Grant No. U1L TR000703 and U1L TR001064

FR-POI129

Prolonged Myoglobinuric AKI in Young Female in the Era of the COVID-19 Pandemic

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Introduction: We present a 26-year-old female with no pertinent medical history who presented to the nephrologist with persistently elevated creatinine (Cr) and urinalysis significant for microscopical hematuria without red blood cells.

Case Description: The patient reported being ill 2 months prior to presentation with symptoms of fatigue, myalgias, pharyngitis and general malaise. During her illness, she ran a marathon, treated her myalgias with NSAIDs and discontinued spironolactone for acne vulgaris. On assessment, she described ongoing symptoms of fatigue, myalgias and decreased appetite. Lab work indicated Cr of 2.15 mg/dL (baseline <1 mg/dL), mild metabolic acidosis, urinalysis and urine chemistry indicated 1+ myoglobinuria (88.26 ng/mL, normal <21 ng/mL) and creatine phosphokinase 44 IU/L. Further studies revealed normal ANA, complements, ANCA, myositis panel and other autoimmune workup. She was diagnosed with myoglobinuric acute kidney injury (AKI) in the setting of recent viral illness, remote NSAIDs and spironolactone. However, the extent and permanence of her AKI was not completely understood. COVID antibody screen was positive for anti nucleocapsid antibody and antispike glycoprotein antibody titer >250 units/mL. She was closely monitored with biweekly labs, encouraged to drink electrolyte rich fluids, and treated with oral sodium bicarbonate. Her Cr peaked at 2.3 mg/dL and urine myoglobin at 278.9 ng/mL, however both normalized by the fourth month. We concluded the patient likely had COVID-19 infection in November and was experiencing “long COVID” renal disease.

Discussion: COVID-19 infection can directly injure kidneys through endothelial destruction, complement activation, coagulopathy and indirectly through multiorgan damage. Large-scale studies exploring COVID-19 and AKI focus on severely ill, unvaccinated, older patients, with multiple comorbidities. There are also a handful of small case reports that have examined COVID-19 induced rhabdomyolysis requiring hemodialysis. However, there remains limited understanding of why healthy, vaccinated, younger patients may develop persistent AKI and what this means for their future kidney function, even in cases where creatinine levels return to normal. This case demonstrates the importance of considering COVID-19 induced AKI even in patients who are not at high risk of developing severe infection related illness.

FR-POI130

Predictors of Mortality in COVID-19 Patients Diagnosed with AKI: A Case-Control Study

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Background: COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multi-systemic infection with various manifestations, including acute kidney injury (AKI). This study aimed to identify factors associated with mortality in COVID-19 patients diagnosed with AKI during hospitalization at Clinica de la Costa in Barranquilla, Colombia from 2020 to 2022.

Methods: A case-control study. COVID-19 patients with acute kidney injury (AKI) were enrolled. Cases included fatal outcomes, while controls survived. AKI was defined using The Kidney Disease: Improving Global Outcomes criteria. A range of independent variables, including sociodemographic characteristics, comorbidities, initial laboratory parameters, and clinical features, were examined. Inferential analysis was performed using Chi-square, t-test, and Mann-Whitney U tests (p < 0.05). Associations were further evaluated using logistic regression, and odds ratios (OR) with 95% confidence intervals were calculated.

Results: The study sample included 159 cases (deceased) and 74 controls (survivors). The average age in the deceased group was 66 ± 14 years, significantly higher than the average age of 59 ± 17 years in the control group (p = 0.005). No statistically significant differences were observed in terms of gender (p-value = 0.278) and municipality of residence (p-value = 0.078) between the study groups. The final adjusted model identified several significant risk factors for mortality, including admission to the intensive care unit (OR = 4.8; 95% CI 1.5-15.6), invasive mechanical ventilation (OR = 51.1; 95% CI 10.9-240.7), renal replacement therapy (OR = 11.7; 95% CI 1.1-123.0), and Acute Kidney Injury Network (AKIN) II classification (OR = 8.8; 95% CI 3.2-53.0).

Conclusions: It is crucial for healthcare providers to maintain heightened surveillance in COVID-19 patients with AKI who require ICU admission, IMV, and RRT, as these factors are associated with higher mortality rates.

Funding: Clinical Revenue Support

FR-POI131

Proteinuria and Clinical Outcomes in Hospitalized COVID-19 Patients: Bolivia Experience

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Background: Kidney involvement is frequent among patients with coronavirus disease 2019 (COVID-19), and occurrence of AKI is associated with higher mortality in this population. The objective of this study was to describe incidence of proteinuria and its influence on AKI in COVID-19 patients.

Methods: We conducted a single-center prospective study among patients who were admitted with COVID-19 in a tertiary care center in Bolivia. Urine dipstick was performed, and spot urine protein/creatinine ratio was quantified within 24 hours of admission. AKI at hospital admission was excluded from analysis. Subsequent development of AKI was diagnosed using KDIGO criteria over 7 days follow-up. Secondary outcome was initiation of renal replacement therapy and death.

Results: Among 57 patients, de novo proteinuria at admission was present in 44 patients (77.1%). Mean urine protein/creatinine ratio was 896±420 mg/g; with 4 patients (9%) presenting nephrotic range proteinuria. Patients with de novo proteinuria had higher leukocyte count (639±1580/mm3 vs. 521±870/mm3; p = 0.0127). De novo proteinuria was not different in patients with diabetes, hypertension or CKD. Of patients with de novo proteinuria, 34% (15/44) patients developed subsequent AKI. Majority of AKI cases (70%) were mild (stage 1 KDIGO). Urine protein-creatinine ratio ≥150 mg/g was associated with AKI (odds ratio (OR), 17.4; 95% CI, 0.97 to 31; p = 0.05). None of patients required kidney replacement therapy. Total proteinuria was associated with mortality in unadjusted and adjusted models.

Conclusions: We observed higher prevalence of proteinuria among patients admitted with COVID-19. Patient will proteinuria also had a higher risk of developing AKI and a poor prognosis for survival. Future studies should focus on proteinuria for risk stratification and prognosis.

FR-POI132

Liver and Kidney Cross-Talk in Korean COVID-19 Patients

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Background: Previous studies suggested that liver function tests (LFTs) could serve as a prognostic tool in assessing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. However there have been no published large-scale studies conducted for Koreans with similar topics.

Methods: This research was conducted using the data from two hospitals in Korea. Data from 4,367 adults out of 4,423 patients without missing values, end-stage renal disease, a history of kidney transplant, or use of immunosuppressants were analyzed. We used LFTs measured on the day of hospitalization for SARS-CoV-2 infection. The main outcomes of interest were two things: all-cause mortality and the incidence of acute kidney injury (AKI). Statistical analysis was performed with logistic regression.

Results: Analysis of data for 4,367 people (mean age 54.5±18.3 years, 53.4% female) suggests that high bilirubin is associated with high mortality (adjusted hazard ratio [aHR], 1.79; 95% confidence interval [CI], 1.29 to 2.49; P=0.001) and risk of AKI (aHR, 1.263; 95% CI, 1.005 to 1.588; P=0.045). Also low albumin level is associated with high mortality (aHR, 0.574; 95% CI, 0.378 to 0.873; P=0.001). However no significant impact of alanine transerase and alkaline phosphatase on mortality and the incidence of AKI is identified.
Conclusions: Abnormal LFTs, especially in aspartate transaminase, total bilirubin and albumin level, is relevant to higher mortality and risk of AKI in Koreans with COVID-19. Therefore LFTs should be performed early in hospitalization as a screening tool for risk stratification in Korean COVID-19 patients.

Significance of liver function on all-cause mortality

Significance of liver function on the incidence of AKI

FR-PO1133
Long-Term Renal Outcome and Mortality in Hospitalized Patients with COVID-19 Infection and AKI at UCLA
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Background: Acute kidney injury (AKI) is a common complication in patients with COVID-19 infection and has been associated with poor outcomes. At the ASN 2022 Kidney Week, we presented data from RECOVID study evaluating the need for renal replacement therapy (RRT) and early mortality among patients with COVID-19 infection and AKI in both vaccinated and unvaccinated populations. Here we present updated long term mortality follow-up data from RECOVID cohort.

Methods: In this retrospective, observational cohort study, we explored long term mortality data for the RECOVID cohort, which evaluated patients admitted for COVID-19 infection who developed an AKI at UCLA from March 2020. These patients were followed until February 2023.

Results: Among the 3527 hospitalized patients with COVID-19, 878 patients met criteria for inclusion in the study. Of the 878 patients with AKI 46.8% did not receive the COVID-19 vaccine and 53.2% were vaccinated. When evaluating long term mortality follow-up data from RECOVID cohort.

Conclusions: Vaccinated patients with COVID-19 infection and AKI had improved long-term survival and were less likely to be dialysis-dependent.

Table 1. Patient Characteristics and Outcomes

FR-PO1134
Patient Outcomes in De Novo Kidney Replacement Therapy Requiring AKI Following COVID-19 Infection
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Background: Among patients infected with COVID-19, AKI affects >20% of hospitalized patients and >50% of patients admitted to the ICU. While kidney function recovery in COVID-19 patients at discharge and for a short duration of follow up after discharge has been studied, little is known about longer-term outcomes and kidney function recovery in patients who go on to require dialysis during the acute hospitalization for COVID. The aim of the study was to look at the factors associated with dialysis requiring AKI, the impact on survival, the factors associated with continued need for dialysis in patients who start KRT during hospitalization for COVID-19 pneumonia and rate of kidney function recovery following the initiation of KRT.

Methods: A retrospective observational cohort study was conducted at the Mayo Clinic Hospital system in the United States. The study included hospitalized patients aged 18 years or older who were admitted between January 1, 2020, and December 31, 2022, and had a diagnosis of both SARS-CoV-2 infection and new onset Acute Kidney Injury (AKI) requiring Kidney Replacement Therapy (KRT). The primary outcome was mortality and the secondary outcomes included incidence of the composite outcome of death, requirement for KRT and kidney function decline of ≥25% from baseline at 60 days and 365 days (MAKE60 and MAKE365).

Results: A total of 145 patients required Kidney Replacement Therapy (KRT). Among them, 64 patients (44.1%) survived to discharge and 21 patients (14.5%) remained dependent on dialysis at discharge. At 60 days, major adverse kidney event (MAKE60) was 17.2%. Among the patients discharged on dialysis, the MAKE 365 incidence was 52.4%.

Conclusions: COVID-19-associated AKI was associated with high mortality, was associated with worse long-term post-AKI kidney function recovery and MAKE outcomes.
FR-PO1135

Association of Renal Function with Mortality Among Hospitalized Patients Treated with Remdesivir for COVID-19
Maria Lourdes Gonzalez Suarez, Kristin C. Mara, Christina Rivera, Supavit Chedsachai, Evan Draper, Raymund Razonable. Mayo Clinic Minnesota, Rochester, MN.

Background: Renal dysfunction is associated with poor outcomes in patients with coronavirus disease 2019 (COVID-19). In an effort to improve outcomes, intravenous remdesivir has been broadly used off label for the treatment of COVID-19 in patients with low estimated glomerular filtration rate (eGFR). Our study assessed the outcomes of patients with low eGFR after treatment with remdesivir for COVID-19.

Methods: We conducted an observational, retrospective, cohort study of adults hospitalized with COVID-19 treated with at least one dose of remdesivir between 11/6/2020, and 11/5/2021. Electronic medical records were reviewed to obtain patient characteristics, laboratory data, and outcomes. Primary endpoint was all-cause mortality by day 28. Multivariable logistic regression was used to evaluate association among groups.

Results: We studied 3024 patients hospitalized with COVID-19 and treated with remdesivir. Median age was 67 [IQR 55, 77] years; 42.7% were women, 88.6% were white. Median eGFR was 76.6 mL/min/1.73 m² [IQR 52.5, 95.2]; 67.2% of patients had eGFR ≥60, while 9% had eGFR <30. All-cause mortality by day 28 was 8.7%. All-cause mortality rates were significantly higher among patients with impaired renal function (Odds Ratio [OR] 1.94 for patients with eGFR 30-59; OR 1.94 for eGFR 15-29; OR 3.62 for eGFR <15 and OR 9.08 for patients on dialysis) compared to patients with eGFR ≥60 (all p<0.01) (Figure 1).

Conclusions: Lower eGFR is an independent risk factor for mortality in COVID-19 despite treatment with remdesivir. These observations suggest that, even with the availability of effective antiviral treatment, prevention of COVID-19 remains a major goal especially among those with impaired renal function.

Funding: Commercial Support - Gilead

Overall survival according to eGFR

FR-PO1136

Decision Tree Analysis to Study the Short- and Long-Term Renal Outcomes in Patients Hospitalized During the First Year of the COVID-19 Pandemic
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Background: COVID-19 has been associated with AKI in hospitalized patients and GFR decline after discharge. However, analysis of risk factors associated with renal outcomes has been limited to traditional machine learning models. Additionally, length of hospitalization (LOH) or days on the ventilator (DOV) have not been typically used for risk prediction.

Methods: In this retrospective single center study, we applied a Classification and Regression Trees algorithm (CART decision tree) to study renal outcomes in patients hospitalized in the United States during the COVID-19 pandemic in 2020 (pre-vaccination era). Outcomes: Moderate/severe AKI (Stage 2 & 3) in the hospital and GFR decline during a 24-month follow-up (until February 2023). To address the effect of confounding demographics in ICU vs. non-ICU and COVID-19 positive vs. negative patients, propensity score matching (PSM) was applied. Influential variables were selected based on feature importance in Random Forest plots.

Results: In our initial cohort of adult 6.933 patients (without baseline end-stage kidney disease), 10.4 % (719) were diagnosed with AKI-2/3. CART decision tree analysis on the primary cohort and the ICU and COVID-19 status PSM cohorts showed DOV, sepsis, age and vasopressor use as key factors for AKI-2/3 risk categorization. In the follow-up study hospital survivors (n = 1,747), those originally admitted to the ICU and those with COVID-19 had a greater mean GFR decline compared to control groups. CART analysis (Figure 1) showed LOH, age, AKI-2/3, body mass index, vasopressor use, and baseline CKD as the main features that risk categorized patients for rate of GFR decline.

Conclusions: To our knowledge, this is one of the first studies to report renal outcomes in patients with and without COVID-19 using CART decision tree analysis. Besides traditional risk factors, days in the hospital and on the ventilator were noted as key features that stratified patients’ risk for renal outcomes.
FR-PO1137

Long-Term Kidney Function of Hospitalized COVID-19 Survivors Who Did or Did Not Develop AKI


Background: COVID-19 increases acute kidney injury (AKI) risk; however, it is unclear its long-term effect in high CKD prevalence settings. Aim: To assess evolution, at least 6 months after discharge, of kidney function in hospitalized COVID-19 survivors who did or did not develop AKI.

Methods: Prospective cohort of confirmed COVID-19 patients (03/20-10/21). From inpatient registry, survivors were contacted; those who agreed to participate had a clinical interview and eGFR and albumin/creatinine ratio evaluation.

Results: Of 585 COVID-19 patients discharged alive, 121 (21%) developed AKI; 160 without AKI and 34 with AKI were included and evaluations performed at 20.0±0.3 months. Comparisons between groups are shown in Table 1 and Table 2. Overall mean time survival was 26.1±0.5 months; comparison according to AKI development is shown in Figure.

Conclusions: A fifth of surviving patients hospitalized for COVID-19 developed AKI, 73% of them recovered kidney function upon discharge. Patients with AKI had lower kidney function throughout the study and higher ACR at end of follow-up compared to those without AKI; however, the latter displayed slight eGFR decrease at the end of the study compared to baseline. Survival was significantly lower in patients with AKI and seemed to be worse in those with higher stages.

Table 1. Comparison of kidney function recovery and treatment according to KDIGO classification

<table>
<thead>
<tr>
<th>Variable</th>
<th>AKI 1 (n=16)</th>
<th>AKI 2 (n=34)</th>
<th>AKI 3 (n=1)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney function recovery</td>
<td>10 (62.5)</td>
<td>11 (32.4)</td>
<td>4 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Treatment %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conservative</td>
<td>14 (87.5)</td>
<td>12 (35.3)</td>
<td>4 (66.7)</td>
<td>0.51</td>
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<tr>
<td>Conventional</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1 (6.2)</td>
<td>1 (2.9)</td>
<td>1 (16.7)</td>
<td>0.25</td>
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<tr>
<td>Peritoneal dialysis</td>
<td>0</td>
<td>6</td>
<td>1 (16.7)</td>
<td></td>
</tr>
</tbody>
</table>

FR-PO1138

Identification of COVID-19 Disease and Impact on Kidney Function Using Urine Raman Spectroscopy and Chemometrics

Ryan S. Sengen,1 Mariana Gomez de la Esprielia,2 Jasmine Y. Jackson-Akers,2 Amr Sayed Issa,3 John L. Robertson,1 Tasaadq Fazili,1 2 Virginia Polytechnic Institute and State University College of Engineering, Blacksburg, VA; 2Carilion Clinic, Roanoke, VA.

Background: COVID19 can have a deleterious effect on renal function. Timely prediction of renal dysfunction is not achievable with available laboratory armamentarium, and scores currently used for severity of illness are highly provider dependent and subjective in nature.

Methods: We developed a Raman spectroscopic technology (Rametrix® molecular urinalysis) to detect COVID19 systemic/renal effects by analysis of patient urine. It is based on chemometric analysis of the Raman spectrum of urine and detects metabolomic differences. The technology is not designed to detect virus/viral components. We hypothesized that COVID19 disease would alter urine composition and that Rametrix® analysis could detect renal dysfunction via urine molecular ‘fingerprinting’. We applied Rametrix® analysis on 85 urine specimens from 64 patients hospitalized for COVID19 disease (Omicron variant prevalent). Patients were 30-92 years of age (median age 67), and ca. 50%/50% M/F. Collections were done at admission (n=66), discharge (n=7), and follow-up (n=12). Medical record and laboratory data were correlated with Rametrix® results; 66 patients had GFR values at both admission and discharge. Disease severity scores were collected repeatedly during hospitalization. Using chemometric analysis, we compared hospitalized patient COVID19 urine spectra with urine spectra from healthy controls (pre-COVID19), patients with CKD (pre-COVID), asymptomatic/mildly symptomatic outpatients (2020/mid-2021 variants), bladder cancer patients (pre-COVID19) and Lyme disease patients (pre-COVID19).

Results: Rametrix® molecular urinalysis distinguished COVID19-associated changes in urine composition with predictive metrics (accuracy, sensitivity, specificity, PPV, and NPV) ranging between 93-96.5%. A correlation between changes in urine Raman spectra and physician assessment of disease severity was also found through computational analysis. Spectra from patient urine collected at admission and stratified based on eGFR, demonstrated molecular ‘fingerprints’ predictive of future renal dysfunction in 91.7% of high-risk patients.

Conclusions: Raman molecular urinalysis can be a useful tool in detecting and predicting future renal dysfunction in patients hospitalized with COVID19 disease.

Funding: Clinical Revenue Support

FR-PO1139

Postdischarge All-Cause Mortality in COVID-19-Recovered Patients: The Impact of CKD


Background: In Brazil, the COVID-19 burden was substantial, and risk factors associated with higher in-hospital mortality rates have been extensively studied. However, information on short-term all-cause mortality and factors associated with death in patients who survived the hospitalization period of acute SARS-CoV-2 infection is less abundant. We analyzed the 6-mo post-hospitalization mortality rate and possible risk factors of COVID-19 patients admitted from Mar/20 to Dec/20 in a single center in Brazil.

Methods: Retrospective cohort study focused on a 6-mo follow-up. Exclusion criteria were: death during hospitalization, transferece to another hospital, and age under 18. We collected data from the charts of all hospitalized patients from Mar/20 to Dec/20 with positive RT-PCR test for SARS-CoV-2, a time when vaccination against the infection was not available and no variant other than the wild one had been identified in Brazil. The main outcome was death after hospitalization. Comorbidities and demographics were evaluated as risk factors.

Results: We studied 106 patients. The crude post-hospitalization death rate was 16.0%. The first 30 days of follow-up had the highest mortality rate. In a Cox regression model for post-hospitalization mortality, previous CKD (HR, 4.06, 95%CI 1.46 – 11.30) and longer hospital length of stay (HR 1.01, 95%CI 1.00 - 1.02) were the only factors statistically associated with death.

Conclusions: Substantial 6-mo all-cause mortality was observed. Within the 6-mo follow-up, a higher risk of death was observed for patients who had prior CKD and longer hospital length of stay. These findings highlight the importance of more intensive medical surveillance during this period.

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

Underline represents presenting author.
Laura Bioengineering: Modeling, Diagnosis, Therapy

A High-Throughput Kidney-on-a-Chip Platform for CKD Therapy

...characterization, we also comprehensively studied the CD responses to vasopressin and... and enhanced mRNA expression of genes related to... enabled simultaneous tracking of optical microscopy and... developed a physiologically relevant human kidney collecting (CD) duct model using human stem cell-derived cells on the Epithelial Microphysiological Analysis Platform (Epi-MAP). scRNA-Seq analysis identifies the ureteric bud organoids as highly enriched in inner medullary CD principal epithelial cells... We succeeded in establishing a model of cisplatin-induced kidney injury... Tubuloids expressed LTL and Megalin, indicating that they were highly differentiated structures composed of proximal tubular epithelial cells. Treatment of tubuloids with cisplatin increased γH2AX, a marker for DNA damage, in a dose-dependent manner... We in the process of epithelial-mesenchymal transition. Enhancement of the NF-κB and IL-1β, which alter an acute phase response, were expressed as well. Vimentin, an intermediate filament, was also upregulated by cisplatin treatment, suggesting that tubular epithelial cells were in the process of epithelial-mesenchymal transition. Enhancement of the NF-κB and IL-1β, which alter an acute phase response, was observed. These findings may recapitulate the events of post-acute kidney injury, which, alter an acute phase response, acquired mesenchymal-associated secretory phenotype (SASP) and induces inflammation and fibrosis.

Conclusions: We succeeded in establishing a model of cisplatin-induced kidney injury based on tubuloids using hRTECs. Tubuloids can be utilized to simulate the response of epithelial cells to toxins and therapeutic agents. This alternative way is potentially an excellent tool not only as cisplatin-induced kidney injury, but also as a pathological model for various renal diseases including chronic kidney disease.

Funding: Commercial Support - Bayer Yakuhin, Ltd., Private Foundation Support, Government Support - Non-U.S.不敢

SA-P0003
Tubuloids on Primary Human Renal Tubular Epithelial Cells (hRTECs) Recreational Clipping Study: Key Insights

Yuki Nishihara, Yutarou Mori, Makiko Mori, Shinutaro Mandai, Tamami Fujiki, Fumiaki Ando, Koichiro Susa, Takaayasu Mori, Eisie Sohara, Shinichi Uchida.

Department of Nephrology, Tokyo Medical and Dental University, Tokyo, Japan.

Background: Kidney organoids derived from human pluripotent stem cells has been an attracting pathophysiological model recapitulating a response of human kidney to drugs in recent years. Here, we have developed an alternative way to make more homogeneous epithelial-like structures called tubuloids based on primary human renal tubular epithelial cells (hRTECs) and tested their efficacy by administering cisplatin.

Methods: hRTECs were obtained from the non-tumor kidney tissue removed from patients with renal or ureteric malignancies. Renal cortex was diced and digested with collagenase. Tubules were seeded on plates with serum-free media containing epidermal growth factor. After passage, cells were cultured on ultra-low attachment plates for several days and transferred into media containing matrigel, epithelial growth factor, hepatocyte growth factor, fibroblast growth factor-2 and 5% fetal bovine serum. After tubuloids were completed, cisplatin was administered at a concentration of 0.2 – 20.0 µg/ml. Tubuloids expressed LTL and Megalin, indicating that they were highly differentiated structures composed of proximal tubular epithelial cells. Treatment of tubuloids with cisplatin increased γH2AX, a marker for DNA damage, in a dose-dependent manner. KIM-1, a marker of kidney injury, and cleaved caspase-3, a marker for apoptotic signals were expressed as well. Vimentin, an intermediate filament, was also upregulated by cisplatin treatment, suggesting that tubular epithelial cells were in the process of epithelial-mesenchymal transition. Enhancement of the NF-κB and IL-1β was also observed. These findings may recapitulate the events of post-acute kidney injury, which alter an acute phase response, acquired mesenchymal-associated secretory phenotype (SASP) and induces inflammation and fibrosis.

Conclusions: We in the process of epithelial-mesenchymal transition. Enhancement of the NF-κB and IL-1β was also observed. These findings may recapitulate the events of post-acute kidney injury, which, alter an acute phase response, acquired mesenchymal-associated secretory phenotype (SASP) and induces inflammation and fibrosis.

Funding: NIDDK Support, Other NIH Support - NCATS Support

SA-P0004
In the Same Vein: Developing a Novel In Vitro Flow Model for Endothelium Using 3D-Printed, Patient-Specific Arteriovenous Fistulas

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Background: Endothelial cell dysfunction is a feature of several medical conditions including chronic kidney disease (CKD). The global prevalence of advanced CKD (Stage 3-5) is approximately 8%, affecting an estimated 850 million people worldwide. For patients with end stage kidney disease treated with hemodialysis, easy vascular access is best achieved using a surgically-created arteriovenous fistula (AVF). Why some AVFs fail to mature while others develop high blood flow is unclear. Standard cell culture conditions do not provide adequate insight into the response of endothelial cells in this process, but the flat surface neglects the complex physiology of disturbed blood flow through intricate vessel geometries. The use of animal models is limited by the ethical implications of the required interventions, the necessary surgical skill, an inability to simulate relevant comorbidities, changes in vessel size, genetic diversity, and limited commercially available reagents. The aim of this study was to use 3D-printing to create patient-specific models of arteriovenous fistulas for use in vascular research.
SA-PO005

Using Organ-on-a-Chip Co-Culture Technology to Explore the Pathophysiology of Tubulopathies: A Paradigm Shift in Kidney Disease Research

Background: Tubulopathies are a group of renal disorders that significantly impact patient morbidity and mortality, with limited current treatment options. The complex pathophysiology of these diseases hampers our understanding, resulting in a pressing need for advanced, physiologically relevant models. This research harnesses Organ-On-a-Chip (OOaC) technology to simulate human tubular physiology, thus elucidating the pathogenesis of tubulopathies and potentially facilitating development of novel therapeutic strategies.

Methods: Urine-derived renal tubular epithelial cells (uRTEC) and blood outgrowth endothelial cells (BOEC) were isolated from individual healthy volunteers and patients from tubular clinic by methods previously described (Ormiston et al., 2015; Ikeda et al., 2020). uRTEC and BOEC cells were applied adjacently in a three-layer microfluidic chip platform OrganOttePlate following manufacturer’s protocol with modifications on the constitution of the extracellular matrix gel.

Results: Patient uRTEC performed on the endothelial cell line with continuous monitoring of disease progression, ultimately bringing personalised medicine to tubular diseases.

Conclusions: These preliminary data demonstrate that patient-derived uRTEC and BOEC were able to form tubule/blood-vessel-like structures in the OrganOttePlate. Given these samples are primary cells from patients, we propose this OOaC model will dynamically reflect the pathogenesis of tubulopathies and potentially facilitate development of novel therapeutic strategies.

SA-PO006

Proteomic Profiling of a Novel Immortalised Human Distal Convoluted Tubule Cell Line

Background: Tubulopathies are renal disorders with complex and inadequately understood pathophysiology, creating an urgent need for improved in vitro models to facilitate research. The development of a novel immortalised human distal convoluted tubule cell (hDCT) line represents a breakthrough in this field, offering a promising model for investigating the pathogenesis of tubular diseases. This research focuses on the proteomic characterisation of this cell line, a critical step towards understanding its utility for research into distal tubulopathies.

Methods: Four immortalised hDCT cell lines, primarily isolated from healthy volunteer’s urine, were gifted from Dr Kusaba and were cultured as previously described. For comparison, we have used NCI cells obtained from the ATCC. The constitution of the extracellular matrix gel was modified in an attempt to recreate the peri-tubular extracellular matrix.

Results: Western blot analysis was performed for DCT-specific marker NCC (SLC12A3) and DCT-specific channel proteins. In addition, the expression of drug metabolism enzymes, such as CYP3A4 and CYP2C19, was investigated.

Conclusions: Our 3D model overcomes limitations of current cell culture techniques whilst maintaining the 3D geometry only seen in humans and animal models. This will allow rapid investigation of endothelial cell signalling in true AVF geometries.

SA-PO007

Quantifying Composition Changes in Serum Biomarkers of Vascular Calcification in CKD
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Background: Vascular calcification (VC) is a strong predictor of cardiovascular morbidity and mortality for chronic kidney disease (CKD). Cardiovascular disease (CVD) is the leading cause of death for patients with CKD worldwide. Despite its importance in CVD/CKD, there are no tools to noninvasively diagnose VC, monitor progression, or prognosticate outcomes. Calciprotein particles (CPPs) are circulating biological nanoparticles composed of minerals, lipids, and proteins, and represent a novel biomarker of CVD. When CKD disrupts serum mineral and protein balance, CPPs mature into pathogenic secondary CPPs, which initiate tissue calcification. Here, we present the development of a new technology to assess VC risk: Ramen Trapping Analysis (RTA), a quantitative label-free optical technique, is used to quantify composition of healthy and uremic patient-derived serum.

Methods: Serum collected from healthy and uremic patients was processed to isolate CPPs and initiator components. Size exclusion was used to separate soluble CPP constituents and incubation in FBS supplemented with Ca and PO4 was used to generate mature CPPs. The gel-filtration method using OsteoSense reporter was used to quantify CPP levels, and dynamic light scattering (DLS) and transmission electron microscopy (TEM) to assess particle size and morphology. RTA of CPPs was acquired during maturation (24 hr) and after incubation (72 hr). Particle spectra were analyzed to investigate compositional differences between disease groups and time points.

Results: Analysis validated the formation of secondary CPPs. DLS/TEM confirmed particle maturation, and the OsteoSense assay indicated increased CPP levels between uremic vs healthy samples. RTA obtained particle spectra from CPPs comprising Ca-Po4 mineral, lipid, and protein signatures. A spectral model of chemical constituents was developed, and signatures were extracted for further statistical analysis.

Conclusions: RTA is capable of noninvasive label-free chemical characterization of CPPs derived from patient serum and provides novel information regarding dynamic changes in the composition and heterogeneity of these biomarkers. Precise evaluation of CPPs may provide clues into screening for patients who can differentiate innate mineralization propensity and prognosticate patient risk for VC.

Funding: NIDDK Support
SA-PO009

Development of Kidney-Targeted Nanoparticles for Delivery of Gene Therapies

Methods: Here, we investigated the potential to adapt this MNP platform to specifically deliver various RNA-based gene therapies to the renal proximal tubules. We formulated MNPs loaded with either reporter or gene-specific siRNA, mRNA, or CRISPR gRNA/Cas9 that conformed to the 300-400 nm diameter size range which demonstrates tubular localization. We then conducted in vitro studies using renal proximal tubular epithelial cells, as well as in vivo studies with healthy mice, to confirm their function and renal-specific delivery.

Results: Our results demonstrated successful modification of polymeric MNPs such that they maintained kidney targeting while encapsulating RNA therapeutics. mCherry mRNA-loaded MNPs exhibit rapid and bright protein translation in vitro with no cytotoxicity. GFP-targeted CRISPR gRNA-Cas9 MNPs turned off expression of GFP in a stably-transfected cell line. In vivo, we found that kidney-targeted MNPs specifically target the kidneys and achieve gene-specific knockdown.

Conclusions: In ongoing studies, we are using this modified MNP design to deliver gene therapies that modulate inflammation and oxidative stress in salt-sensitive hypertension models, with the potential to target the kidneys and improve treatment of kidney disease.

Funding: Other NIH Support - CA132378

SA-PO011

Development of a Glomerulus-on-a-Chip Model: An Innovative Model to Study Paracrine Pathways to Unravel Glomerular Disorders

Methods: The custom-made glomerulus-on-a-chip model was designed using soft lithography. The chip consisted of two parallel microfluidic channels separated by a semi-permeable polycarbonate membrane. JPS C derived podocytes and conditionally immortalized GenC and podocytes were differentiated in the chip. Shear stress induced by laminar flow was applied on endothelial cells. Cellular morphology and glyocalyx was visualized by fluorescent staining. The barrier integrity of the model was determined by measuring the transport rate of labelled dextran from top to bottom channel. The effect of cross talk on the transcription profile of GenC and podocytes was investigated via RNA-sequencing.

Results: GenC and podocytes were successfully cultured on opposite sides of the membrane in our glomerulus-on-a-chip. Barrier integrity of the chip was significantly improved when GenC were co-cultured with podocytes compared to monocultures. Co-culture of glomerular podocyte foot process surface area and increased glyocalyx thickness. RNA-sequencing analysis revealed the regulation of cellular pathways involved in cellular differentiation and cellular adhesion as a result of the interaction between GenC and podocytes.

Conclusions: We present a novel custom-made glomerulus-on-a-chip and demonstrated that co-culture in the device affects the morphology and transcriptional phenotype of GenC and podocytes. Moreover, we showed that co-culture improves barrier function as a relevant functional readout for clinical translation. This model can be used in future studies to investigate specific glomerular paracrine pathways and unravel the role of barrier cross talk in glomerular (patho)physiology.

SA-PO012

Isolation and Purification of Mesangial Cells for Bioengineered Kidneys

Background: With over 85,000 patients waiting for a kidney transplant, bioengineered kidneys (BEKs) offer a way to address this large clinical need. BEKs are created from isolated native tissue types from one or more donor kidneys. The isolation of mesangial cells has been shown to be useful for determining the primary BEK filtration function. However, the mechanism to maintain the glomerular filtration barrier (GFB) integrity. However, in vitro studies directly investigating the effect of this cross talk are scarce because of the lack of suitable models. Therefore, we developed a custom-made glomerulus-on-a-chip model recapitulating the GBF, in which we investigated the effects of co-culture of GenC and podocytes on barrier function and cellular phenotype.

Methods: Using enzymatic digestion, whole glomeruli were isolated from human kidneys and then plated on tissue culture flasks for 14 days. Mesangials were purified from the outgrowths using CD140b/PDGFRα positive magnetic bead sorting. Purification of the bound mesangial cell population was confirmed using flow cytometry. Post sort, mesangials were expanded, then cryopreserved at passage 2. Cryopreserved MNs were thawed and expanded to passage 5, where the mesangials were seeded into a BEK along with another native glomerular cell type.

Results: The bound mesangial population isolated from 6 kidney donors had 89.2% ± 13.1% CD140b positive cells. To assess the potential of isolated mesangials for cryo-banking and expansion, mesangials were cryopreserved, and expanded in 2D up through passage 5. The mesangials remained viable through 2D culture (95.3% ± 2.9% at passage 5, n=7), and were seeded and cultured in 3D in a BEK (n=7) along with other glomerular cell types (podocytes). This BEK demonstrated improved protein and RBC filtration in comparison to BEKs seeded only with podocytes and parietal epithelial cells, after 60 minutes of whole porcine blood perfusion.

Conclusions: Mesangial cells are a necessary cell type known for their structural support as well as their contractile properties to aid in ultrafiltration. This study demonstrates a process in which the mesangial population can be isolated from human donor kidneys, purified, cryo-banked, and expanded for making BEKs. Furthermore, when seeded into a BEK, the mesangials demonstrated improved BEK filtration function. Cryo-banked mesangial cells, as well as other cell types, may be accepted for transplantation on demand, thus helping to reduce the number of patients waiting for a kidney transplant.

Funding: Commercial Support - Miraform Medical Inc.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO013
Case Series of Novel PTEC Isolations from Human Kidney Biopsies: Optimized Protocols and Systematic Characterisation
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Background: Human kidneys provide water, electrolyte, and acid-base homeostasis while enabling endo- and exogenous compound metabolism and excretion. Various causes, such as medications (especially in polypharmacy), can quickly disrupt this delicate balance, and currently used methods for nephrotoxicity assays limit the prediction of human response. Our work aimed to develop novel and optimised protocols for isolating proximal tubular epithelial cells (PTEC) from human kidney biopsy.

Methods: We performed nine diagnostic kidney biopsies (informed consent was obtained from the patients) with parts of tissue used to isolate and characterise PTEC. We used two protocols, using five and four biopsy specimens, respectively. The first employed enzymatic dissociation with 0.25% trypsin/EDTA and culture with Advanced DMEM supplemented with 5% fetal bovine serum. In comparison, the second used 0.2% collagenase type 1 and was cultured in selective serum-free culture media (Advanced DMEM/F12 with added insulin, transferrin, epidermal growth factor, and hydrocortisone). Light microscopy was used for morphologic characterisation, while several markers characteristic of PTEC were chosen for phenotypic characterisation.

Results: Following the protocols resulted in isolating cells that formed first colonies after seven days (range 1-13 days) and three days (range 1-5 days), respectively. Based on light microscopy, we evidenced a cobblestone appearance and reached confluence after approximately three weeks following the first protocol and ten days following the second protocol. Population doubling time (PDT) for the best isolate in the first and the second protocol was 29.7 hours and 23.6 hours, respectively. The isolated cells were positive among others for sodium-glucose cotransporter 2 (SGLT2), multidrug-resistant protein 4 (MRP4), organic anionic transporter 1 and 3 (OAT1 and OAT3), organic cation transporter 2 (OCT2), p-glycoprotein (p-gp), multidrug and toxin extrusion protein 1 (MATE1), and N-cadherin.

Conclusions: In this study, we developed two protocols for isolating and cultivating primary human PTEC from biopsy samples. To the best of our knowledge, we have performed the most extensive systematic characterisation following the isolation of PTEC from the diagnostic kidney biopsy reported.

SA-PO014
Investigating the Use of the Biodex Microsampling Device for Longitudinal Biomarker Studies in Glomerulonephritis (GN) and Renal Transplantation
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Background: Human kidneys provide water, electrolyte, and acid-base homeostasis while enabling endo- and exogenous compound metabolism and excretion. Various causes, such as medications (especially in polypharmacy), can quickly disrupt this delicate balance, and currently used methods for nephrotoxicity assays limit the prediction of human response. Our work aimed to develop novel and optimised protocols for isolating proximal tubular epithelial cells (PTEC) from human kidney biopsy.

Methods: We performed nine diagnostic kidney biopsies (informed consent was obtained from the patients) with parts of tissue used to isolate and characterise PTEC. We used two protocols, using five and four biopsy specimens, respectively. The first employed enzymatic dissociation with 0.25% trypsin/EDTA and culture with Advanced DMEM supplemented with 5% fetal bovine serum. In comparison, the second used 0.2% collagenase type 1 and was cultured in selective serum-free culture media (Advanced DMEM/F12 with added insulin, transferrin, epidermal growth factor, and hydrocortisone). Light microscopy was used for morphologic characterisation, while several markers characteristic of PTEC were chosen for phenotypic characterisation.

Results: Following the protocols resulted in isolating cells that formed first colonies after seven days (range 1-13 days) and three days (range 1-5 days), respectively. Based on light microscopy, we evidenced a cobblestone appearance and reached confluence after approximately three weeks following the first protocol and ten days following the second protocol. Population doubling time (PDT) for the best isolate in the first and the second protocol was 29.7 hours and 23.6 hours, respectively. The isolated cells were positive among others for sodium-glucose cotransporter 2 (SGLT2), multidrug-resistant protein 4 (MRP4), organic anionic transporter 1 and 3 (OAT1 and OAT3), organic cation transporter 2 (OCT2), p-glycoprotein (p-gp), multidrug and toxin extrusion protein 1 (MATE1), and N-cadherin.

Conclusions: In this study, we developed two protocols for isolating and cultivating primary human PTEC from biopsy samples. To the best of our knowledge, we have performed the most extensive systematic characterisation following the isolation of PTEC from the diagnostic kidney biopsy reported.

SA-PO015
Rapid Loss of Proximal-Tubule-Specific Gene Expression in Primary Culture Associates with HNF4a Downregulation
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Background: Cell culture models are used widely to study the functions of proximal tubule epithelial cells on the implicit assumption that in vitro cell behavior represents in vivo cell function. The advent of tools for transcriptome-wide analysis in culture models has revealed that immortalized cell lines poorly mimic the native proximal tubule. While the dedifferentiation of proximal tubules induced by cell culture has long been appreciated, the dynamics of genome-wide transcription changes accompanying this process have not been described in detail yet are critical to interpret findings in bioengineered and standard cell culture models.

Methods: We isolated proximal tubules from 6-week-old female C57B6 mice by enzymatic and mechanical dissociation followed by gradient centrifugation yielding > 90% proximal tubules. We cultured cells on standard non-porous tissue culture plastic in a standard incubator (37 °C, 5% CO2) in DMEM/F-12 with standard glucose (3.8 g/L) supplemented with low serum (0.5%) and epithelial growth factor (EGF) as representative conditions among the myriad of reported techniques. At various timepoints, RNA was harvested and subjected to bulk RNA sequencing. Cells also were characterized by immunofluorescence staining.

Results: Proximal-tubule-specific genes with more than 15 transcripts per million detected decreased from 77% to 18% after only 4 d. This fraction did not increase with culture duration despite the formation of morphologically mature epithelial structures and loss of typical cuboidal cell architecture. Apical ZO-1 staining and basolateral sodium potassium ATPase identified by confocal microscopy. Gene set enrichment against the Molecular Signatures Database Hallmark gene sets indicated cultured cells permanently downregulated genes associated with oxidative and fatty acid metabolism within the first 24 h of culture. The transcriptional networks inferred by these changes using C3EA3 point to a central role of decreased HNF4a activity, which itself is silenced by 1 week of culture.

Conclusions: Our results indicate that cultured proximal tubules irreversibly silence most proximal tubule specific genes within just a few days of culture. These findings highlight the need for optimized culture conditions from the moment of isolation.

Funding: NIDDK Support

SA-PO016
AMP-Activated Protein Kinase (AMPK) and TGF-β Alter Cell Size and Morphology in Renal Tubule Epithelial Cells
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Background: Epithelial barrier function is regulated by tight junction protein complexes (TJ) between adjacent cell membranes. TJ may develop non-linear ruffled or spiked architectures which in turn alter cell morphology. Here we observe that AMP-activated protein kinase (AMPK) and Transforming Growth Factor-β (TGF-β) alter renal tubule epithelial cell (RTEC) morphology and induce a ruffled appearance when administered together.

Methods: Primary human RTEC were obtained from Innovative Biotherapies (Ann Arbor, MI). Cells were maintained in DMEM/F12 and seeded onto polycarbonate cell culture inserts at 100,000 cells/cm². After two weeks, cells were apically supplemented with AMPK activator Metformin (200uM, MET), TGF-β receptor 1 inhibitor SB431542 (10uM, SB), or both. After four weeks, cells were stained with DAPI and ZO-1, and imaged using conventional methods. CellProfiler (Broad Institute) was used to threshold and segment nuclei and cell perimeters. Form factor (FF) was calculated as 4*π*area/ perimeter². Compactness index (CI) was calculated as the mean² distance between the objects pixels from the centroid divided by area. Statistical significance was assessed by performing 2-way ANOVA using Prism 9 (GraphPad).

Results: In comparison to controls, all treatments increased cell perimeter and cell area. MET increased cell perimeter and cell area, in comparison to SB and combination treatments. All treatments significantly reduced FF and increased CI, respectively.

Conclusions: All treatments increase cell perimeter and area, suggesting cell swelling. All treatments reduce FF, suggesting reduced circularity. All treatments increase CI, which suggests increased irregularity of shape, such as increased cell interdigitation or plasma membrane ruffling.

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SA-PO017
Smad4 Knockout Increases NHE3 Expression in Renal Tubule Epithelial Cells In Vitro
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Background: Sodium-hydrogen antiporter 3 (NHE3) is a critical indicator of terminal renal proximal tubule epithelial cell (RPTEC) differentiation and accounts for 80% of tubular water reabsorption in vivo. In vitro, RPTEC have reduced NHE3 expression, which limits their functional fidelity. Transforming Growth Factor-β (TGF-β) is a pleiotropic cell signaling pathway, involved in the regulation of epithelial cell fate and plasticity. Canonical TGF-β signaling is mediated by the Smad proteins, Smad2/3/4. Here we observe that knockout of Smad4 increases NHE3 transcription in vitro.

Results: HEK293 (ATCC, Manassas, VA) were plated at a density of 3x10^4 in 35mm plates to achieve 60% confluence the following day. Cells were co-transfected with CRISPR sgRNA with PiggyBac (Pb) hygromycin resistance and eGFP vectors and the mT/Phyrevactive Pb transposase at a 3:1 ratio using Lipofectamine LTX Plus (Thermo Fisher). For control transfection, cells were transfected with a scramble sequence. 48 hours post-transfection, cells were supplemented with 200µg/mL hygromycin for one week. Cells were passaged once then harvested for RT-PCR analysis.

Methods: HEK293 (ATCC, Manassas, VA) were plated at a density of 5x10^4 in 35mm plates to achieve 60% confluence the following day. Cells were co-transfected with CRISPR sgRNA with PiggyBac (Pb) hygromycin resistance and eGFP vectors and the mT/Phyrevactive Pb transposase at a 3:1 ratio using Lipofectamine LTX Plus (Thermo Fisher). For control transfection, cells were transfected with a scramble sequence. 48 hours post-transfection, cells were supplemented with 200µg/mL hygromycin for one week. Cells were passaged once then harvested for RT-PCR analysis.

Conclusion(s): Smad4 modulates NHE3 expression in renal tubule epithelial cells.

SA-PO018
Advancing Urine-Based Cell Studies: Introducing the Cell Catcher Device

Background: Urine-derived cells have gained prominence as a valuable tool for biomedical research and clinical applications due to their non-invasive and repeatable acquisition from patients, in contrast to invasive biopsies. However, the full potential of urine-derived cells remains untapped, due to lack of standardised protocols and reliance on lab-based centrifugation within 4 hours. This study aims to address these limitations by evaluating a novel filtration-based Cell Catcher device, and comparing its efficiency to centrifugation.

Methods: We obtained urine from 18 adults attending a tubulopathy clinic and directly compared the effectiveness of viable cell isolation using either Cell Catcher or centrifugation by using paired analysis.

Results: The results demonstrate that the Cell Catcher device significantly improves the chances of obtaining viable cells, with a 28% increase compared to centrifugation. Furthermore, the device enables the yield of primary renal cell types capable of attachment and proliferation, with a twofold increase compared to conventional methods. The cultured cells showed heterogeneity in terms of cell morphology and expression of renal markers. In all samples, we detected expression of WT1 and ENPEP suggestive of podocyte and proximal tubule cells. Some samples were also positive for NPHP1, AQP3, UMOD or UPK3A.

Conclusion(s): This innovation in urine processing methods has the potential to revolutionize urine-based cell studies and unlock the vast potential of urine as a non-invasive source of patient-specific cells. Further refinements and investigations are warranted to explore the device’s compatibility with different cell types and its potential applications in nephrology, regenerative medicine, and urological cancers.

Funding: Other NIH Support - Kidney Research UK, Commercial Support - Encelo Laboratories Limited

SA-PO019
A Microfluidic Approach for Cardiovascular Risk Stratification in CKD and ESKD Patients
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Background: Cardiovascular (CV) complications are responsible for over 50% of the overall morbidity and mortality in CKD and ESKD patients. Surprisingly, conventional cardiovascular risk factors such as hyperlipidemia and obesity are not as predictive of CV complications in the CKD/ESKD population as compared to the general population and statins in particular do not reduce CV events in hemodialysis patients. This so-called “reverse epidemiology” is thought to reflect a primacy of uremia induced vascular dysfunction in the pathogenesis of CV complications in this unique patient population. In order to develop novel, real world and holistic markers of uremia induced inflammation, oxidative stress and endothelial dysfunction, we herein report a 3D microfluidic device to quantify the negative effects of uremic serum on endothelial cells.

Methods: HUVECs were seeded in cylindrical channels in collagen I hydrogels to form microvessels (Fig. 1). After 48 h, perfusion media was exchanged from cell culture media to 100% human serum for 24 hours. To mimic the uremic environment, we added pathophysiological levels of indoxyl sulfate (IS) to serum from healthy donors (Fig 1 A-B).

Results: Microvessels perfused with serum from healthy donors exhibited distinct, pericellular VE-cadherin staining, while microvessels perfused with serum containing IS displayed diffuse VE-cadherin indicating immature or dysfunctional adherens junction integrity (Fig 1A). Consistent with these observations, microvessels perfused with serum containing IS exhibited marked increase in solute permeability compared to microvessels perfused with healthy serum (Fig 1B).

Conclusions: These results demonstrate a humanized microfluidic device that can be used to assess endothelial dysfunction in response to uremic toxins. We demonstrate high sensitivity of the assay, as IS at concentrations similar to those for CKD-3 patients resulted in significant cytoskeletal and permeability defects, suggesting that this platform could be used to screen for CV risk in CKD/ESKD patients.

SA-PO020
Pulsed Ultrasound of the Splenic Nerve Increases the Splenic Resistive Index in Humans
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Background: Splenic pulsed ultrasound (pUS) attenuates ischemia-reperfusion injury-induced systemic inflammation and AKI in mice by activate the cholinergic anti-inflammatory reflex pathway (CAP). We aimed to translate the preclinical discoveries to human inflammation and identify clinical parameters for evaluating the efficacy of pUS. Given the dense spleen innervation by sympathetic neurons (SNs) and noradrenergic NE release by sympathetic nerve terminals following CAP activation, we hypothesized that NE release post-pUS increases vascular resistance and, hence, the resistive index (RI).

Methods: We analyzed data from an ongoing human pilot study that tests whether pUS within FDA-approved limits of diagnostic medical sonography attenuates inflammation and alters immune cell composition (clinicaltrials.gov; NCT05685108). Healthy adults were exposed to pUS targeting the spleenic nerve with varying ultrasound intensities as defined by burst mechanical index (MI). Spectral Doppler ultrasonography was performed before, immediately after, and 24 h after pUS to determine any functional effects.

Results: 23 pUS procedures were performed in 12 subjects (median age, 28 [IQR, 26 to 36] years; median BMI 24 [22 to 27] kg/m2; 50% male). We observed a significant increase in splenic RI (+0.05 [0.01 to 0.08]; P=0.001) and decrease in splenic volume (-8.4 [-23.1 to -1.1] cm3; P=0.008) immediately after pUS, but not in renal RI or renal volume. The splenic RI increase was accompanied by an increase in the ratio of systolic-to-diastolic flow velocity, and seemed to depend on the magnitude of applied MI (Figure). 24 h post-pUS, the observed splenic changes were no longer detectable (data not shown).

Conclusions: Our preliminary results in humans demonstrate that pUS transiently increases the splenic RI. This novel physiological effect of pUS provides proof of concept that pUS activates SNs. The increase in vascular resistance may serve as a functional clinical measure of pUS and may contribute to the anti-inflammatory effect of CAP activation.

Funding: Other NIH Support - Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (R01 DK105133 to Mark D. Okusa).
SA-PO021
Fluid Shifts in Septic Shock During Early Hospitalization: A Bioelectrical Impedance Analysis (BIA) Study
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Background: In the early management of septic shock, aggressive fluid resuscitation is crucial but carries the risk of fluid overload, potentially increasing mortality rates. However, our understanding of fluid distribution and dynamics in the body during this phase is limited. To address this, bioelectrical impedance analysis (BIA) has emerged as an effective tool for monitoring fluid status and guiding treatment decisions in the ICU.

Methods: An observational study was conducted in a university hospital ICU from Feb 2020 to Jul 2021 to assess fluid status in adult septic shock patients. Enrolled patients required mechanical ventilation for respiratory failure. Assessments using the InBody S10, a multifrequency BIA device, were performed at three time points: within 24 hrs of admission; and on days 3 and 7 of ICU stay. Parameters evaluated included extracellular water (ECW) ratio, ECW, intracellular water, and total body water. Fluid status changes were calculated by comparing subsequent measurements to the baseline (day 1). Survival data at 60 days were collected, with 11 survivors and 8 non-survivors.

Results: The study found that most ICU patients had persistent overhydration. Survivors showed a progressive decrease in fluid status, while non-survivors had a temporary increase on day 3, followed by a decrease on day 7, but still elevated compared to the baseline. These fluid fluctuations were mainly driven by changes in ECW, particularly in the legs and trunk. The relative change in fluid status highlighted the predominant involvement of renal units in sepsis management, demonstrating its practicality for personalized measurements and informed treatment decisions.

Conclusions: Assessing individual changes was crucial due to patient variability. The findings offer insights into fluid shifts and the prognostic implications of BIA parameters in sepsis management, demonstrating its practicality for personalized measurements and informed treatment decisions.

SA-PO022
A 3D Organ-on-Chip Model of the Collecting Duct for the Study of Electrolyte Disorders

Background: Kidney basement membrane components play a crucial role in the function of different segments of the nephron. For example hensin is an ECM protein that promotes transition between α and β intercalated cells, stimulating different mechanisms of action in the collecting duct (CD). Current models using organ-on-chip systems mainly promote transition between M0-CCD and M1-CCD cells, stimulating different mechanisms in vivo.

Methods: M1-CCD cells from collecting duct were cultured on the top channel of a multi-channel bioreactor (Fig. 1a). Different combinations of collagen I, collagen IV and laminin I were used as ECM coatings. We successfully developed and characterised a 3D in vitro model of the collecting duct using organ-on-chip technology. Further steps include the incorporation of patient urine-derived epithelial and blood-derived endothelial cells to create a more accurate and personalised platform for disease modelling and drug testing.

Funding: Other NIH Support - NIH NIGMS IMMD (#R25GM056847-23), Private Foundation Support

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

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Results: (1) Exos numbers were comparable in Expri and Control groups. ExpriExos were more numerous than Controls. ExpriExos’ cargo contained both significantly increased immune modulatory miRNAs (IDO-1, CCL8, CXCL9, CXCL11, PD-L1) and 4 anti-inflammatory, angiogenic and anti-apoptotic miRNAs (MIR-548-3p; MIR-548N; MIR-
148-3p; MIR-877-3p). (2) In vitro, Exos therapy with both unexposed and INFg-treated MSCs reduced SCR short and long term vs. control. Only Exos from the INFg group significantly reduced both SCR and uProtein/Creatinine at 3 mos.

Conclusions: Programmed of MSCs with INFg results in the release of Exos that deliver significantly greater renoprotective activities in the compromised microvasculature of severe AKI. We posit, these data have significant clinical promise as rescue therapy in AKI.

Funding: Commercial Support - SymbioCellTech

SA-PO025

Application Myo-Inositol Oxygenase Fluorescent Renal Proximal Tubular-Specific Mitochondrial AKT1 Transgenic Mice in Kidney Disease Research

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Background: Renal tubular AKT1 is activated and translocated into mitochondria upon renal injuries. To determine whether tubulointerstitial AKT1 (tub-AKT) plays a protective role, we generated a novel transgenic mouse strain harboring inducible mitochondria-targeting constitutively active AKT1 (mca-AKT) driven by the renal proximal tubule-specific promoter.

Methods: The manufacturing process used a bacterial artificial chromosome clone containing mouse Miox as the transgene backbone and inserted the IRES-CreERT2-polYa and promoter CAGGS-foxP4-GFP-polyA-foxP-MTS-AKT1(308T-D; 437S-D)-3XFLAG-polyA cassettes into the exon 5 and 3' downstream of Miox, respectively, using Red/ET DNA recombination technology. The CreERT2 is tamoxifen-inducible Cre recombinase, the GFP is a green fluorescent protein, and the MTS is the mitochondria-targeting sequence. The modified transgenic construct was injected into mouse pronuclei and transferred into a surrogate mother to generate the transgenic mice.

Results: The GFP was expressed ubiquitously and observed by epifluorescence in transgenic mice carrying the transgene. The expression of mca-AKT protein was only detected in the kidneys of tamoxifen (TAM)-injected KMioCtAKT but not in corn oil-KMioCtAKT mice or TAM-wtlydype (WT) mice. The mca-AKT was exclusively expressed in kidneys but not in other organs in TAM-KMioCtAKT. Moreover, we confirmed mca-AKT co-localized with mitochondria in the renal tubules with tissue staining. To measure the mitochondrial respiratory capacity, we used the Seahorse XF Analyzer and found significant differences in basal respiration, spare respiration, and ATP-dependent respiration (p<0.05) between TAM-KMioCtAKT and corn oil-KMioCtAKT.

Conclusions: These findings suggest that mitochondrial AKT1 is a renal tubular bioenergy regulator. We will continue to explore whether it plays a protective role in renal tubules. These findings shed new light on the application in nephrology research. They may be used to screen for new drugs and develop new strategies for preventing and treating kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO026

Optimizing Free Radical Scavenger-Loaded Kidney-Targeted Polymeric Nanoparticles for Increased Therapeutic Efficacy in CKD

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Background: Therapeutic development for renal diseases has been hampered by a lack of poor pharmacological properties by many investigational drugs. To alleviate this bottleneck, our prior studies discovered a polymeric mesoscale nanoparticle (MNP) system for the kidney of targeting the kidneys, specifically the renal proximal tubules. Here, we sought to define MNP formulation characteristics such that the system is robust to delivery of a small molecule cargo while maintaining the appropriate surface chemistry and size necessary for renal targeting.

Methods: We used a quantitative statistical modelling approach based on the Design of Experiments (DoE) to define which drug and particle formulation characteristics allow for MNP renal targeting. We formulated MNPs with the FDA-approved ROS scavenger edaravone and a biocompatible, FDA-approved polymer made of poly(lacto-co-glycolic acid) coated with polyethylene glycol (PLGA-PEG).

Results: We found that MNP formulation parameters control the ability to target the renal proximal tubules and modifications allow for robust production of MNPs with varying therapeutic cargos. Specifically, polymer concentration and solvent ratios allow mesoscale formation and optimization of drug cargo loading for therapeutic drug delivery to the kidney.

Conclusions: Ongoing studies are aimed at using these formulation parameters to incorporate increased therapeutic cargo and their ability to ameliorate hypertensive chronic kidney disease.

Funding: Other NIH Support - CA132378

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

728
SA-PO028
Facility-Level Variation in Care of Veterans with Urinary Stone Disease
Sh fabricated Rashid Shahzad,1 Calyani Ganesan,1,2 Chunch Thomas,2 Maria E. Montez-Rath,1,2 Simon John Christop Soerensen,1 Glenn Czertow,1 Alan C. Pao,1,2 John Leppert,1,2 Stanford University School of Medicine, Stanford, CA; 1,2VA Palo Alto Health Care System, Palo Alto, CA.

Background: Urologic care after kidney stone procedure presents an opportunity to implement stone prevention measures, but the frequency of urologic follow up and stone specific therapy across VA and non-VA care is unknown. We studied variation in urologic visits and stone prevention measures within 6 months after a urologic stone procedure.

Methods: We used data from the Veterans Health Administration (VHA) to identify patients from 97 facilities who had a stone procedure between 2016 and 2018. We constructed multilevel regression models to estimate Median Odds Ratio (MOR) for facility-level variation in urology follow up visits and stone prevention measures. The base model was a random intercept for facility. The 2nd model was adjusted for patient covariates (age, sex, race, driving distance to nearest VA, comorbidities). The 3rd model was adjusted for patient and facility characteristics (geographic region, complexity). We used MOR to quantify facility-level variation and variance partition coefficient (VPC) to quantify the sources of unexplained variation.

Results: Our cohort included 24,057 Veterans who were predominantly white (78.7%) and male (93.8%), with a mean age of 63.8 years. Within 6 months of stone procedure, 93.8% had urology follow-up, 7.4% completed 24-hour urine testing, 7.8% had serum PTH measurement, and 26.2% received stone-related medications. The fully adjusted VPC was 0.19, 0.33, 0.11 and 0.03 respectively.

Conclusions: Sizable variation exists in stone disease care across VHA facilities. Variation due to between-facility differences was higher for 24-hour urine testing (7.4-fold) in rates of 24-hour urine testing, 1.4-fold in obtaining serum PTH measurement, and 2.0-fold in rates of urology follow-up, 1.4-fold in obtaining 24-hour urine testing, 1.4-fold in obtaining PTH levels, and 1.2-fold in stone-related medication prescriptions. There is a need for standardization of urinary stone disease care across facilities. More work is needed to establish clear guidelines for stone prevention and the factors underlying variation in stone prevention care in the VHA and civilian healthcare systems.

Funding: Veterans Affairs Support

SA-PO029
Risk of ESKD and Death Among Homeless Veterans with Incident CKD
Alain K. Kovalom1, Robert Nee,2 Wei Yu,2 Devasmita Choudhury,3 Fei Heng,2 Alfred K. Cheung,4 Keith C. Norris,5 Monique E. Cho,6 GuoYan.7
1Centers for Disease Control and Prevention, Atlanta, GA; 2Walter Reed National Military Medical Center, Bethesda, MD; 3University of Virginia, Charlottesville, VA; 4Salem VA Medical Center, Salem, VA; 5University of North Florida, Jacksonville, FL; 6VA Salt Lake City Health Care System, Salt Lake City, UT; 7University of Utah Health, Salt Lake City, UT; 8University of California Los Angeles, Los Angeles, CA.

Background: Chronic kidney disease (CKD) requires comprehensive management to limit disease progression, a particular challenge among the homeless. We evaluated the risk of end-stage kidney disease (ESKD), defined by transplant or dialysis requirement, and death among homeless veterans with incident CKD in the US Veterans Health Administration (VHA).

Methods: Incident CKD was defined as the first time estimated glomerular filtration rate (eGFR) decreased to <60 mL/min/1.73 m² for ≥3 months. We excluded veterans with <6 months of VHA care before diagnosis to diagnosis with pre-existing ESKD. Homelessness was defined using VHA specific codes and/or ICD-9 and ICD-10 diagnosis codes for homelessness recorded at 1 time during the 2 years prior to incident CKD. Cox proportional hazards models examined the association between homelessness status and risk for ESKD and death.

Results: An incident CKD cohort of 836,361 veterans were identified from 2005-2017, with follow-up through 2018. A total of 46,561 veterans (6%) were identified as homeless. In a model adjusted for age, sex, race, incident CKD year and eGFR, homelessness was significantly associated with a 6% increased risk of ESKD and a 46% increased risk of death. Further adjustment for variables that may be both a cause and consequence of homelessness, such as race, mass index, comorbidity burden (use of renin-angiotensin-aldosterone system antagonists and statins, behavioral factors) attenuated findings for both outcomes. Therefore, the abovementioned factors may in part explain the observed associations between homelessness and ESKD and death.

Conclusions: The hazard for ESKD or death is significantly higher among homeless veterans compared to those not experiencing homelessness, and the increased risk is partly driven by modifiable factors. These findings emphasize the importance of housing and comprehensive health care in addressing the difficulties in CKD management among homeless veterans.

Funding: Other NIH Support - WV, AKC, KN and GV are partially funded by NIH R01DK112008., Veterans Affairs Support, Other U.S. Government Support

SA-PO030
Implementing a Successful Tele-Nephrology Program for Rural Veterans
Ramon Bonégo,1,2 Katharine Tuozzo,1,3 Ian R. Rifkin,1,2 Aimee Kroll-Dresosiers,3,4 Susan T. Crowley,3,4 Kristin Mattock,3,4 David T. Moore.3,5 On Behalf of the TeleNephrology Enterprise Wide Initiative, Veterans Health Administration, Boston, MA; 2Boston University, Boston, MA; 3University of Massachusetts Chan Medical School, Worcester, MA; 4Yale School of Medicine, New Haven, CT.

Background: Rural Veterans experience increased morbidity and mortality as a result of chronic kidney disease (CKD) and refractory hypertension. Nephrologists usually practice in urban, acute-care facilities and decreased access to specialist care likely contributes to poorer outcomes in rural Veterans.

Methods: We established a Tele-Nephrology Hub & Spoke Network (TNN) to provide care to rural facilities. Hub nephrologists reviewed the medical record and provided video-based visits to spoke sites in Maine, New Hampshire, Indiana, Oklahoma, Montana, and Colorado. Where possible, hub staff trained a local advanced practice provider (APP) to triage consultations and manage emergencies. To understand barriers and facilitators to TNN implementation, we conducted a structured interview with clinic administrators at five spoke sites. We used the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework to develop our interview guide. Interviews were conducted using Microsoft Teams and qualitative data was analyzed using open thematic analysis. Results are presented according to each major RE-AIM dimension.

Results: Reach: Rural and highly rural Veterans were seen at all spoke sites. Veterans were given the option of seeing a local and/or tele-provider. Adoption: Adoption was more successful when facilities had a local APP. Local APPs were quickly able to triage consultations and address emergencies independently. Where APP were not available, more reliance was placed on hub providers. Implementation: The TNN was successfully implemented at each facility, with >50% of consults being addressed through telegenephrology. Maintenance: A telegenephrology champion organized the program. Across most interviews, the telegenephrology champion was mentioned as a key reason for program success. We anticipated finding that sites had challenges with technology or that Veterans were uncomfortable with remote care but neither of these issues emerged during interviews. We found that the Covid-19 pandemic served as an excellent introduction to telehealth and so there was high enthusiasm for the TNN. Conclusions: In conclusion, establishing a TNN improved access to specialist care for rural veterans. A telegenephrology champion and local APPs with renal training facilitate program adoption and expansion.

Funding: Veterans Affairs Support

SA-PO031
Interaction of Race and Treatment with GLP1-RA, SGLT2i, and Insulin on Mortality in Veterans with Type 2 Diabetes Mellitus (T2DM) and CKD
Stephen Monte-Rath,1,2 Simon John Christoph Soerensen,1 Glenn Czertow,1 Alan C. Pao,1,2 John Leppert,1,2 Stanford University School of Medicine, Stanford, CA; 1,2VA Palo Alto Health Care System, Palo Alto, CA.

Racial disparities in the use of anti-glycemic medications have been reported but it is unclear whether there is an interaction between diabetic medications and race on mortality.

Methods: In an active comparator, new user design study of veterans (N = 3,016,500) with T2DM and CKD (85% with eGFR < 60), we examined the interaction between diabetic medications (GLP1-RA, SGLT2i, and Insulin) and race on mortality.

Results: Mean age was 71 years, mean baseline eGFR 49.5 ml/min/1.73 m². Compared to White veterans, Black veterans were less likely to be prescribed GLP1-RA's (OR 0.69, CI 0.63-0.77) and were similarly prescribed SGLT2i's (OR 1.05, CI 0.99-1.12). There were 4,660 deaths over 80,043 patient-years in the active cohort. Compared to GLP1RA, insulin glargine was associated with increased mortality in both Blacks and Whites (Figure).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO032
Factors Influencing SGLT2i Utilization in an Inner-City Public Hospital
Luis C. Despradel,1,2 Nanq San Hti Lar Seng,1,2 Belinda Jin,1,2 New York City Health and Hospitals Jacobi, Bronx, NY; †Albert Einstein College of Medicine, Bronx, NY.

Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i’s) remained underutilized in chronic kidney disease (CKD) patients despite their renoprotective benefits. We present the factors associated with SGLT2i prescription in a public hospital in New York City.

Methods: Cross-sectional analysis of adult primary care patients at Jacobi Medical Center, Bronx, NY was done from Jan 2022 to Dec 2022. The sample included patients with CKD and Type 2 Diabetes Mellitus (T2DM). Exclusion criteria were no medication list and eGFR<20 mL/min/1.73 m². Descriptive statistics and logistic regression analysis were performed using STATA 18 (StataCorp).

Results: Among 2307 eligible patients, SGLT2i prescription rate was 14%. After controlling for gender, age, and subspecialty follow-up, no significant association was found between the prescription of SGLT2i and the patient’s race, language, or coexisting comorbidities/complications. Please see Table 1 for the odds ratios of different significant variables.

Conclusions: Women were found to be prescribed less SGLT2i than men, perhaps due to side effects that affect women not identified in this study. Patients without insurance or with public insurance were more likely to be prescribed. As the drug can be dispensed in our hospital pharmacy for the uninsured as opposed to the need for an onerous prior authorization process for those with insurance; public insurances usually do not require prior authorization. Subspecialized services and hospital physicians increased the likelihood of SGLT2i prescription, perhaps reflecting the higher level of evidence-based application in a teaching hospital. By understanding these factors, we can strategize to enhance the utilization of this class of medications.

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Table 1. Logistic Regression SGLT2i Prescription

SA-PO034
Individual vs. Neighborhood-Level Social Determinants of Health and ESKD Mortality
Daisel Kang,1,2 Will Simmons,1,2 Arindam Roychoudhury,1,2 Kwan Kim,1,2 Jeffrey I. Silberzweig,1,2 Deirdre L. Sawinski,1,2 Sri Lekha TummalaPalli,1,2 Weill Cornell Medicine, New York, NY; 2Rogosin Institute, New York, NY.

Background: Social determinants of health (SDoH) have a substantial impact on disease morbidity and mortality. Neighborhood-level SDOH indices are increasingly being used for clinical risk prediction and resource allocation to improve health equity. However, whether neighborhood-level SDoH are independently associated with mortality among incident end-stage kidney disease (ESKD) patients is unknown.

Methods: We identified patients with incident ESKD admitted to the Rogosin Institute, a New York City-based non-profit dialysis organization, and excluded patients with missing Social Vulnerability Index (SVI) and acute kidney injury requiring dialysis. We used Cox regression to create four nested prediction models for mortality. Model 1 adjusted for age, sex, and race and ethnicity. Model 2 additionally adjusted for primary cause of ESKD and 31 Elixhauser comorbidities. Model 3 additionally adjusted for individual SDOH (marital status and employment). Model 4 additionally adjusted for neighborhood-level SVI, which incorporates Census variables of socioeconomic status, household composition and disability, minority status and language, and housing type and transportation.

Results: Of 3,585 patients with incident ESKD, the median age was 62 (IQR 50 – 73). A total of 56% were male, 24% Hispanic, 15% White, 15% Hispanic, and 14% were Asian. The mortality prediction model containing age, sex, and race and ethnicity had a Harrell’s C-statistic of 0.702. Adding cause of ESKD and comorbidities improved prediction performance (Harrell’s C 0.7585, likelihood ratio...
Background: There is a global epidemic of chronic kidney disease (CKD) and people of ethnic minority groups and those living with socioeconomic deprivation are disproportionately affected. Peer educators (PEs) are members of target demographic groups and provide culturally congruent education and support. HIDDEN-CKD explored the feasibility of using PE led kidney health screening events in South East London to increase the reach, equity and acceptability of routine healthcare interventions to identify early disease in African and Caribbean communities.

Methods: Stage 1: Public engagement to co-develop culturally appropriate CKD materials
Stage 2: PE recruitment and accredited training; engagement with local faith and non-faith community leaders
Stage 3: Events were held in African and Caribbean faith and non-faith based community settings; following an educational session people were invited to consent to the study and demographic and medical details, blood pressure, body mass index and urinary albumin creatinine ratio (uACR), (measured by smartphone analysis) were collected. Culturally tailored information and peer support were available throughout and after testing. Stage 4: All participants individually followed up by phone and supported to seek medical attention where appropriate.

Results: We have trained 30 PEs, who have performed 305 uACR semi-quantitative tests, and invited 66 participants to date. The majority of participants were black African or black Caribbean (n=228, 75%, n=29, 10% respectively), female (n = 163, 53%) and had no known medical history (n=128, 49%). 164 (54%) tests were ACR >3mg/mmol and 24 (8%) >30mg/mmol.

Conclusions: People from African and Caribbean communities appear to be willing to participate in PE led community CKD screening, and high rates of albuminuria are detected. Further qualitative and longitudinal work is underway to assess acceptability and to confirm CKD diagnosis. This approach may provide a new opportunity to reduce health inequalities.

SA-PO306
Social Deprivation Index and Kidney Failure Replacement Therapy (KFRT) Risk Among 2.5 Million Patients

Deidra E. Agyekum,1 Kathryn Griffths,1 Rachel Z. Musomba,2 Neerja K. Jain,3 Denis O. Onyango,4 Kate Bramham.1 HIDDEN Working Group.1 King’s College London, London, United Kingdom; 2Africa Advocacy Foundation, London, United Kingdom; 3Kidney Research UK, Peterborough, United Kingdom.

Background: A plethora of studies have investigated the association between neighborhood social deprivation (SDI) and kidney failure replacement therapy (KFRT) risk, but most of the studies have been restricted to multi-ethnic, national samples with measured risk factors. We aimed to determine the unequally distribution of SDI by race/ethnicity and to confirm CKD diagnosis. This approach may provide a new opportunity to reduce health inequalities.

Methods:
Stage 1: Public engagement to co-develop culturally appropriate CKD materials
Stage 2: PE recruitment and accredited training; engagement with local faith and non-faith community leaders
Stage 3: Events were held in African and Caribbean faith and non-faith based community settings; following an educational session people were invited to consent to the study and demographic and medical details, blood pressure, body mass index and urinary albumin creatinine ratio (uACR), (measured by smartphone analysis) were collected. Culturally tailored information and peer support were available throughout and after testing. Stage 4: All participants individually followed up by phone and supported to seek medical attention where appropriate.

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Conclusions: People from African and Caribbean communities appear to be willing to participate in PE led community CKD screening, and high rates of albuminuria are detected. Further qualitative and longitudinal work is underway to assess acceptability and to confirm CKD diagnosis. This approach may provide a new opportunity to reduce health inequalities.

SA-PO035
Health Inequalities in Kidney Disease: Meeting the Urgent Need to Identify Early Disease in High-Risk Communities (HIDDEN-CKD): A Feasibility Study

Roseline Ballew,1,5 Kunihiro Matsushita,2,4 Josef Mills,2,4 Morgan Fricker,1 David J. Gunderman,1 Kassap Y. Konduy,1 Sharon M. Moe,1 Akram Almakki.1,2 Indiana University School of Medicine - West Lafayette, West Lafayette, IN; 3Indiana University School of Medicine, Indianapolis, IN; 4Indiana University Health Arnett Inc, Lafayette, IN

Background: Neighborhood-level SDI does not improve mortality prediction in a diverse cohort of incident ESKD patients in New York City, independent of demographics, comorbidities, and individual-level SDI. Neighborhood-level SDI indices may have limited utility to predict clinical outcomes in the ESKD population.

Methods:
Stage 1: Public engagement to co-develop culturally appropriate CKD materials
Stage 2: PE recruitment and accredited training; engagement with local faith and non-faith community leaders
Stage 3: Events were held in African and Caribbean faith and non-faith based community settings; following an educational session people were invited to consent to the study and demographic and medical details, blood pressure, body mass index and urinary albumin creatinine ratio (uACR), (measured by smartphone analysis) were collected. Culturally tailored information and peer support were available throughout and after testing. Stage 4: All participants individually followed up by phone and supported to seek medical attention where appropriate.

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Conclusions: People from African and Caribbean communities appear to be willing to participate in PE led community CKD screening, and high rates of albuminuria are detected. Further qualitative and longitudinal work is underway to assess acceptability and to confirm CKD diagnosis. This approach may provide a new opportunity to reduce health inequalities.

SA-PO037
Population Impact of Social Determinants of Health on Premature Death Among US Adults with CKD

Joshua D. Bundy,1 Ling Tian,1 Alexander D. Kimbrough,1 Katherine T. Mills,1 Amanda H. Anderson,1 Hua He,1 Katherine Theall,1 Jing Chen,2,3 Jing He.1,2,3 Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; 4Tulane University School of Medicine, New Orleans, LA.

Background: Social determinants of health (SDOH) are important underlying components of population health and are associated with adverse outcomes among patients with chronic kidney disease (CKD). However, the US population-level impact of SDOH on premature death among adults with CKD is unknown.

Methods: A nationally representative sample of individuals aged 20-74 from the US National Health and Nutrition Examination Survey (NHANES) 1999-2018 were included. We restricted those with CKD defined as estimated glomerular filtration rate <60 ml/min/1.73 m² and/or urinary albumin-creatinine ratio ≥30 mg/g. Self-reported SDOH were collected in each survey cycle (Figure). Deaths were ascertained from linkage to the National Death Index through 2019. Multivariable Cox proportional hazards regression and average population attributable fractions were used to investigate the contributions of SDOH to population-level premature all-cause mortality. All analyses accounted for the complex survey design.

Results: A total of 8422 individuals aged 20-74 years with CKD were included (11.0% weighted population prevalence). Mean survey-weighted age was 52.6 years and 55.3% were women. During a mean 8.6-year follow-up, 1252 deaths were recorded. After adjustment for age, sex, and race/ethnicity, all SDOH were significantly and independently associated with higher all-cause mortality and accounted for substantial portions of the US population mortality burden (Figure). Furthermore, dose-response associations were observed between the cumulative number of unfavorable SDOH and premature death, with having six or more unfavorable SDOH increasing mortality 6-fold.

Conclusions: SDOH were strongly and independently associated with premature death among US adults with CKD, and accounted for 50% of premature deaths in this population. Innovative structural policy interventions are urgently needed to prevent adverse events associated with SDOH among patients with CKD.
have been reported for Black patients following implementation of the new CKD-EPI 2021 formula. However, the impact of the new equation on care and referral disparities is not well understood.

**Methods:** We conducted a retrospective cohort study of all adult patients referred to Indiana University Health outpatient nephrology clinics during a two-year period surrounding the change in eGFR formula. To analyze the impact of the new formula, we performed a multivariate linear regression with eGFR as the dependent variable, and sex, self-reported race, age, timeframe, BMI, and an interaction term between race and timeframe as covariates.

**Results:** 912 patients met our criteria for analysis. Multivariate linear regression revealed that mean eGFR was statistically influenced by sex, race, age, and implementation of the new formula. Mean eGFR increased by 5.9 mL/min/1.73m² (95% CI: 0.3, 11.4) for all patients after implementation of the new formula. However, the analysis revealed no evidence that the racial disparity in mean eGFR at the time of the first visit with nephrology was significantly influenced by the formula change (-3.7, 95% CI: -10.1, 2.7). Mean eGFR at the first visit was 6.7 mL/min/1.73m² (95% CI: 2.4, 10.9) lower for Black patients compared to non-Black patients across the entire study period.

**Conclusions:** A general trend of increased mean eGFR across all patients after the equation change indicates earlier overall referrals to nephrology. Despite this improvement, our analysis did not reveal a significant change in the existing disparity in timely referral to nephrology observed between Black and non-Black patients. Black patients still had a lower mean eGFR at the initial visit to nephrology when compared to non-Black patients after implementation of the new eGFR formula, suggesting a persistent delay in referral to nephrology for Black patients.

SA-PO039
Combating CKD: Kidney Health Screenings Through the Kidney Disease Screening and Awareness Program at the University of Virginia
Marissa Yee, Tushar Chopra. University of Virginia, Charlottesville, VA.

**Background:** The Kidney Disease Screening and Awareness Program (KDSAP) was initially founded with the goal to increase awareness about chronic kidney disease (CKD) in the community through education and free kidney health screenings. The KDSAP chapter at the University of Virginia (UVA) was founded in 2021 to bring these initiatives to members of the Charlottesville area.

**Methods:** The Diversity, Equity, Inclusion, and Community Health Grant funds KDSAP at UVA through the UVA Department of Medicine. In the spring of 2023, KDSAP at UVA hosted its first kidney health screening at Mt Zion First African Baptist Church. The screening is run by volunteers, organized by undergraduate students, and supported by medical students, residents, fellows, and physicians. Participants proceeded through 8 stations within 30 minutes: registration, form filling, urinalysis, BMI, blood glucose, blood pressure, physician consultation, and exit survey. We performed a descriptive analysis amongst screened members/self-reported racial representation. Descriptive data is reported as numbers (n). The reported race/ethnicity was: White/Non-Hispanic White, Black, Asian, Hispanic or Latin/o, and not reported.

**Results:** 34 community members were screened during the inaugural KDSAP at UVA kidney health screening. 15 participants were referred to follow-up with nephrology due to abnormal results from: urinalysis, blood pressure, or blood glucose. With regards to racial representation amongst folks screened are outlined in the table.

**Conclusions:** KDSAP at UVA is the first organization to be led by undergraduate students in collaboration with the UVA Department of Medicine for kidney health-related community outreach to underserved populations. We screened 58.8% African americans, 26% Asians, 2% hispanic or Latin/o, 8% white population. Continued efforts to host more kidney health screenings in different locations in Charlottesville, targeting at-risk communities, will forge a future of increased kidney disease awareness and early detection.

SA-PO040
A Trauma-Informed Approach to Address Systemic Racism in Outpatient Clinics

**Background:** The primary objective of this project is to mitigate perceptions of racism noted among Black Veterans with kidney disease at the Crescenz VA Medical Center (Philadelphia). Understanding that racism can be traumatic, we hypothesized that a trauma-informed care intervention to address systemic racism would reduce perceptions of racism, improve trust in our healthcare system, and lead to improvements in overall health (e.g., reduction in no-show visits).

**Methods:** Informed by the Center for Health Care Strategies, we developed a multi-level intervention: provider training, environmental scan (health equity walkthrough), developing a patient advisory board, and creating a referral pathway for racial trauma. We provided two 60-minute workshops to clinicians. We provided a framework to define interpersonal discrimination from structural racism and tools to help center Black Veterans and their experience with systemic racism. The training provided guidance to create an inclusive environment during clinical encounters. Clinicians were surveyed to evaluate the acceptability and feasibility of the surveys. We conducted a “walkthrough” of the Renal Clinic to assess how the clinic infrastructure could be redesigned to be more inclusive for all Veterans. A health equity researcher, led the walkthrough and invited Veterans and clinicians to conduct their own walkthroughs of the clinic. Findings were compiled to generate action items to improve the clinic infrastructure.

**Results:** Eight clinicians (42%) attended the 2 workshops conducted in November 2022. The clinicians included 5 advanced practice providers and staff, 2 MDs, and 1 social worker. Five participants completed the surveys, all of whom ranked the workshop quality as “high” (on a scale from “very low” to “very high”) and noted they would recommend the training to others. Participants “completely agreed” that the workshop was appropriate to education, experience, and skill level. All “agreed” or “completely agreed” to use the information and skills provided by the workshop during clinical encounters with their patients.

**Conclusions:** Our pilot demonstrates that 1) it is feasible and acceptable to deliver trauma-informed care training to clinicians to help address perceptions of systemic racism in clinics and 2) health equity walkthroughs can generate action items to expand inclusivity in healthcare settings.

**Funding:** Veterans Affairs Support

SA-PO041
Advancing Excellence in Diversity, Equity, and Inclusion: A Concept Map for Development of a DEI Chief Fellowship in Nephrology

**Background:** Despite decades of attempts to recruit and retain a diverse physician workforce that better represents the patients we serve, inequities in medicine persist. In keeping with the 2021 Executive Order to advance racial equity, the University of Pennsylvania’s Renal-Electrolyte & Hypertension Division developed the DEI Chief Fellowship program to provide training and a leadership role to fellows interested in advancing excellence in DEI. This abstract describes a concept map of the core components of the DEI chief fellowship.

**Methods:** Through stakeholder feedback and a review of the AAMC DEI competencies, we developed a concept map outlining the core trainings and objectives of the DEI fellowship.

**Results:** See attached image

**Conclusions:** The DEI Chief Fellowship is a structured year-long position designed to help trainees become leaders in responsibly advancing excellence in DEI through 1) furthering the inclusion of those underrepresented in medicine, 2) identifying and reducing healthcare disparities, 3) expanding equity into quality improvement and research, and ultimately 4) to improve patient outcomes. It encompasses work-in-progress sessions, leadership experience (e.g., leading community engagement projects, facilitating fellowship recruitment), and core lectures (e.g., addressing implicit biases and microaggressions, incorporating health equity into learning health system). The Renal DEI Chief Fellowship position helped establish similar DEI tracks in Endocrinology and Pulmonary/Critical Care Division within the University of Pennsylvania. We hope Nephrology Divisions across the country will use this concept map to build a pipeline of leaders who graduate fellowship with a strong foundation of excellence in DEI.
SA-PO042

Beck Depression Index-II Scores and Survival in a Multi-Center Prospective Hemodialysis Cohort


University of California Irvine School of Medicine, Irvine, CA; Harbor-UCLA Medical Center, Torrance, CA.

Background: Population-based studies have uncovered a high burden of depression among advanced CKD patients, including those receiving dialysis. We examined the relationship between self-reported depression and mortality among a diverse multi-center prospective cohort of HD patients.

Methods: We evaluated 956 HD patients from the prospective NIH MADRAD Study recruited across 18 dialysis clinics across Southern California who underwent protocolized Beck Depression Index-II (BDI-II) surveys over 2011-2021. Using multivariable Cox models adjusted for expanded case-mix covariates, we examined associations of time-dependent BDI-II score categorized as tertiles with all-cause mortality risk. We then examined differential BDI-II score – mortality associations across race/ethnicity using interaction tests.

Results: The mean±SD age of the cohort was 55±14 years, among whom 45% were female; 29% were Black; and 55% were Hispanic. In analyses of time-dependent BDI-II score, the highest (worse) Tertile 3 was associated with higher death risk (ref: Tertile 1): HR (95%CI) 1.40 (1.08, 1.81) (Fig A). Subgroup analyses showed that point estimates for the highest Tertile 3 of BDI-II scores was associated with higher mortality in Black vs. Non-Black patients (HRs [95%CIs] 1.30 [0.81, 2.08] and 1.18 [0.87, 1.61]) and in Hispanic vs. Non-Hispanic patients (HRs [95%CIs] 1.18 [0.83, 1.68] and 1.25 [0.86, 1.82]), with non-significant p-interaction values suggesting equivalent risk across race/ethnicity (Fig B).

Conclusions: In a multicenter prospective HD cohort, higher (worse) BDI-II scores were associated with worse survival in all racial/ethnic groups. Further studies are needed to identify multi-modal strategies that effectively treat depression in diverse HD populations.

Funding: NIDDK Support

SA-PO043

Association of Food Insecurity and Treatment Nonadherence or Hospitalization Among Adults on Hemodialysis


Johns Hopkins University School of Nursing, Baltimore, MD; Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; The Johns Hopkins University School of Medicine, Baltimore, MD.

Background: Food insecurity is associated with hospitalization among children on hemodialysis, but existing research has not tested associations among adults.

Methods: We conducted a prospective cohort study to test associations between food insecurity and missed treatments or hospitalizations. We enrolled a convenience sample of adults (/>18 years) on hemodialysis (/>3 months) from 17 facilities in Maryland, Washington, D.C., or Virginia from February through November 2021. Participants completed demographics and the US Adult Food Security Survey Module at baseline and remained in the study for 6 months. We collected missed treatment counts and hospital admission and discharge dates (all-cause fluid or electrolyte-related) from facility records. We created negative binomial regression and Cox models to test associations between food insecurity and missed treatments or hospitalizations, respectively. We repeated hospitalization analyses stratifying by age (<55 or >=55 years) to account for confounding.

Results: We analyzed data from 288 out of 322 participants (89%) who completed surveys. Mean age was 60 years (range 27 – 86 years). 58% of the sample were male, 73% self-identified race as Black. At baseline, 61 participants (21%) reported food insecurity. During follow-up, 138 participants (48%) missed at least one hemodialysis treatment (range 0 – 29 treatments) and 91 participants (32%) were hospitalized (range 0 – 5 hospitalizations). Twenty participants (7%) were hospitalized due to fluid overload or hyperkalemia. Participants reporting food insecurity missed more dialysis treatments (Table 1). Food insecurity was not associated with all-cause hospitalization, but the association differed by age group (food insecurity x age group interaction term p = 0.14). In bivariate analyses, food insecurity increased relative hazard of fluid or electrolyte-related hospitalization.

Conclusions: This is the first report of associations between food insecurity and outcomes among adults on hemodialysis. Food insecurity was associated with missed treatments and fluid or electrolyte-related hospitalizations.

Funding: Other NIH Support - National Institute of Nursing Research

SA-PO044

Multilevel Challenges Faced in Renal Replacement Therapy of Morbid Obesity

Lina Frauenfeld, Sheena Pramod. University of Florida College of Medicine, Gainesville, FL.

Introduction: We discuss the challenges faced in treatment options in a morbidly obese patient with advanced CKD. Methods: Dialysis modalities have significantly improved over the years with several options. Home dialysis increases patient autonomy, portability and compliance, but remains low due to multiple challenges.

Case Description: 57 year old male is referred to with advanced CKD. PMHx includes morbid obesity, gastric bypass in 2003, anemia and proteinuria. Previously, patient weighed 700 lbs, before gastric bypass, and went down to 300 lbs. He is 598 lbs at the time of evaluation. Since 2018, he has been bedridden due to back issues and has not been able to leave his home until his visit in a modified stretcher. Labs reveal: Serum Creatinine of 4.1 mg/dl, EGFR (CKD-EPI) of 16 mL/min/1.73m2, microalbumin/ Creatinine ratio 938 mg/g creatinine and urine protein creatinine ratio 2,272 mg/g creatinine suggestive of secondary FSGS. On follow up visit, he reports mild uremic symptoms, resulting in a discussion regarding his RRT options. In-center HD was not an option given his physical condition and inability to sit in HD chair or weight bear. Home HD was considered, but 6 week home training was not feasible due to patient's current living situation which included no working, bariatric stretcher unable to fit through doorways, and out of pocket costs of transportation for training. We considered PD as a last option. He would need a pre-ster nal PD catheter placed given his large pannus. Surgeon though agreeable to place pre-ster nal PD catheter, if cleared by anesthesia, sadly, his bariatric stretcher was too large to fit the local dialysis home units, prohibiting his training and an option to perform PD training at home was limited. The only future alternative is him presenting to emergency room for inpatient hemodialysis knowing that he may not receive OP placement. He was referred for home palliative care simultaneously.

Discussion: This case highlights the challenges faced by our morbidly obese population which are growing in numbers despite the advancements that have been made in home hemodialysis. Dialysis and insurance companies should incentivize and support unique presentation of hemodialysis training at patient’s homes, alleviating some of the hurdles faced in improving the shift to home therapy. The ability to train younger patients such as ours in their own homes may alter their clinical trajectory.
Sex, Gender, and Quality of Life in Hemodialysis

Victoria J. Riehl-Tom, Jennifer M. MacRae, Sandi M. Dumanski, Meghan J. Elliott, Neesh I. Panu, Kara Schick-Makaroff, Kelsea Drall, Colleen M. Norris, Hassam Behloul, Sofia B. Ahmed. University of Calgary, Calgary, AB, Canada; McGill University, Montreal, QC, Canada; University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; University of Alberta Faculty of Nursing, Edmonton, AB, Canada.

Background: Women with kidney failure treated with hemodialysis (HD) report lower quality of life (QoL) compared to men. Decreasing HD frequency is a potential strategy to improve QoL but may result in undertreatment of females compared to males due to biological differences in body water distribution.

Methods: Individuals initiating HD in Alberta, Canada were recruited. Sex assigned at birth (SAAB) and gender identity were self-reported and gender score, a measure of social expectations and norms typically associated to a given gender, was calculated using the GENESIS-PRAXY scale. The primary outcomes were the change in Kidney Disease Quality of Life 36 physical (PCS) and mental component scores (MCS) at 3 months, validated markers of mortality, stratified by HD dose (3 vs 2 sessions/week). The associations between SAAB, gender score and change in PCS and MCS by HD dose were measured using non-parametric test and multiple linear regression, respectively.

Results: There were 33 participants on 3x/wk HD (14 female, 19 male) and 27 on 2x/wk (12 female, 15 male). PCS increased with 3x/wk (p=0.030) but not 2x/wk (p=0.521) in females, but no differences were observed in MCS. No changes were observed in PCS or MCS in males, irrespective of HD dose. Gender score was positively associated with change in PCS of 2x/wk HD (p=0.049) but not 3x/wk HD (p=0.102). While gender score was not associated with change in PCS, HD dose modified the relationship (p=0.035).

Conclusions: Higher HD dose was associated with improved physical health in females, but lower HD dose was associated with improved mental health in participants with roles traditionally ascribed to women.

Race and Ethnicity Do Not Influence the Performance of Fistula Failure Machine Learning Model

Suman K. Lama, Joanna Willetts, Caitlin Monaghan, Sheetal Chaudhuri, John W. Larkin, Franklin W. Maddux, Nwamaka D. Eneanya, Michael A. Kraus, Murat Sot, Len A. Usuyat. Fresenius Medical Care Holdings Inc, Waltham, MA; Azura Vascular Care, Malvern, PA.

Background: Risk stratification models are important decision support aids in medicine yet can inadvertently introduce bias if social factors, such as race and ethnicity, are included in models that predict biological outcomes. (Obermeyer et al., Science 2019). The inclusion of social factors in model development may not have a significant impact on model performance. In the development of a model to predict an arteriovenous fistula (AVF) failure event in a hemodialysis (HD) patient, we investigated the effect of inclusion/exclusion of race and ethnicity as predictor variables on model performance.

Methods: AVF failure was defined by the change from active to unusable status within 30 days. We built two machine learning (ML) algorithms (XGBoost) using HD patient data from Jan to Dec 2018 at large integrated kidney disease healthcare provider. Models were trained using demographics, treatment, laboratory, comorbidity, clinical notes, hospitalization data. Model A included race and ethnicity and Model B did not. Both models considered approximately 2,400 predictor variables. Dataset was randomly split into 60% training, 20% validation, 20% testing data. Unseen testing data was used to evaluate the model’s performance.

Results: Models were developed using data on approximately 67,000 patients (approximately 14,000 patients had events). Model A & B showed an area under the curve (AUC) of 0.76 vs 0.75, sensitivity of 0.53 vs 0.63, and specificity of 0.84 vs 0.84 respectively (Figure 1).

Conclusions: ML model performance was not affected by race or ethnicity data, suggesting they should be excluded from models of biological outcomes to minimize biases that could disproportionally classify risk and lead to disparities in care. Patient factors that may affect biology are critical to consider and validate during model development, and should span beyond race and ethnicity.

Sociodemographic Characteristics of Hemodialysis Patients Prescribed Sucroferric Oxxyhydroxide and Other Phosphate Binders

Meijiao Zhou, Joanna Willetts, Linda Ficociello, Nwamaka D. Eneanya, Len A. Usuyat. Fresenius Medical Care Global Medical Office, Waltham, MA.

Background: Promoting health equity in the treatment of hemodialysis (HD) patients (pts) includes ensuring ready access to effective medications, regardless of an individual’s sociodemographic characteristics (SDC). One such medication is sucroferric oxyhydroxide (SO), a brand-name phosphate binder (PB) that has demonstrated effectiveness in managing serum phosphorus with a lower pill burden. However, the cost of brand-name medication may limit its availability to certain pt populations. To address this issue, Velphoro Access Solution (VAS) was created as a program to explore available resources that make SO more accessible and affordable through the benefit investigation (BI) process. In 2022, >56,000 BIs were submitted to VAS for Fresenius Kidney Care (FKC) pts. This study examines the SDC of HD pts prescribed SO and other PBs, to identify disparities in SO access that may exist.

Methods: Adult HD pts from FKC with active prescription (Rx) of PBs (SO, ferric citrate, lanthanum carbonate, sevelamer, and calcium acetate) during 7/1/2022-12/31/2022 were included. Pts were divided into 2 groups: SO Rx (n=30,513) and other PB Rx (n=121,357). We described SDC such as age, gender, race, ethnicity, and insurance status.

Results: 20% of pts were prescribed SO. The average age of pts with SO Rx was 60, 4 years younger than those with other PB Rx. There was a 4% higher proportion of male (56% vs 52%), African American (40% vs 36%) and 4% lower White (54% vs 58%) pts among those prescribed SO. The ethnic composition was similar in SO group and other PB group (Hispanic 18% vs 19%). A higher % of pts with commercial insurance (17% vs 14%) and Medicaid (47% vs 44%) but with lower Medicare (34% vs 38%) were observed in those with SO compared to pts with other PB Rx.

Conclusions: In our analysis of FKC HD pts, we found a higher % of pts prescribed SO who were younger, male, African American, and insured by Medicaid or commercial coverage. Programs such as VAS may improve access and affordability of medications that are crucial for dialysis care.

Funding: Commercial Support - Fresenius Medical Care
SA-PO049

Applying Sequence Analysis Techniques to Describe ESKD Patients’ Treatment Histories

Jonathan Daw,1 Léa Pessin,1 Avrum Gillespie,2 Catherine Butler,3
1Pennsylvania State University Department of Sociology & Criminology, University Park, PA; 2Lewis Katz School of Medicine at Temple University, Philadelphia, PA; 3University of Washington School of Medicine, Seattle, WA.

Background: Although outcomes for particular treatments for ESKD have been studied, characterizing full treatment sequences (including timing, order, and duration) for different racial/ethnic groups may offer deeper insights into patient experiences and outcomes.

Methods: We study 10-year treatment sequences of the 2009 incident ESKD cohort age 18-44 in the USRDS. The state plot characterizes the distribution of treatments over time; the index plot traces individual patients’ treatment sequences with one line per unique sequence.

Results: State plot: White and Asian groups exhibit higher rates of hemodialysis (especially CAPD and CCPD for Asians) and transplant. Index plot: More sequences for non-White patients involve uninterrupted hemodialysis than for White patients. More sequences for Black patients involve early loss to follow-up. White patients have more preemptive LDKTs than other groups. Significant shares of sequences for White, Hispanic, and Asian patients begin with CCPD/CCAD before transitioning to other treatments, but this is a smaller share of sequences for Black patients.

Conclusions: Sequence analysis techniques hold potential to more fully describe ESKD patient treatment histories and offer a new insight into racial/ethnic disparities.

Funding: NIDDK Support

SA-PO050

Switchers from Medicare Fee-for-Service Program to Medicare Advantage Early 2021 Among ESKD Patients

Jiannong Liu,1 James B. Wetmore,1,2 David T. Gilbertson,1 Eric D. Weinhandl,1 Kirsten L. Johansen.1,2 Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN; 2University of Minnesota Twin Cities, Minneapolis, MN; 1Satellite Healthcare, San Jose, CA.

Background: Before 2021, Medicare beneficiaries with end-stage kidney disease (ESKD) were not permitted to switch from traditional Medicare (Medicare fee-for-service, MFFS) to Medicare Advantage (MA). However, starting in January 2021, beneficiaries were eligible to switch to MA, thanks to the 21st Century Cures Act. Using the United States Renal Data System, we examined differences between beneficiaries who continued with MFFS and those who switched to MA.

Methods: Adults (aged≥18 years) on dialysis or with a kidney transplant (ktx), with MFFS as primary payor, as of December 2020 were assessed for their Medicare coverage in January 2021.

Results: In total, 412,769 patients (pts) were included; 315,015 receiving dialysis and 97,754 with a ktx. Among dialysis pts, 11.5% switched from MFFS to MA (9.6% among home dialysis pts, 11.8% among in-center dialysis pts); 5.4% among Ktx pts. Those who switched were younger (median age for dialysis pts, switcher vs non-switcher: 61.3 vs 65.6 years; for those with a ktx, 62.4 vs 63.6). Pts who switched were also more likely to be non-Hispanic (NP)-Black or Hispanic (dialysis pts, NP-Black: 47.9% vs 32.7%; Hispanic, 17.8% vs 15.3%; ktx recipients, NP-Black: 37.3% vs 21.6%, Hispanic, 15.8% vs14.1%); and more likely to have dual Medicare and Medicaid coverage (dialysis, 51.7% vs 43.8%; ktx, 35.7% vs 29.1%). Those who switched were also more likely to have diabetes or hypertension as their cause of ESKD (Table).

Conclusions: In 2021, more than one tenth of pts with ESKD switched from MFFS to MA; switching was associated with age, race/ethnicity, and Medicaid enrollment. This shift alters the generalizability of the MFFS population with ESKD, and heightens the need for monitoring of outcomes among patients enrolled in MA.

Funding: NIDDK Support

735

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO051

Characteristics of Migrant and Non-Migrant ESRD Patients in Nepal
Shailendra Sharma, Yoko Inagaki, Rishi K. Kaffe, Sweta Kostrala, Nasavya Khadka, Pouya K.C., Kristina M. Jakobsson, Jason R. Glaser, Catharina Wesseling, Dinesh Neupane, Sparrow Health System, Lansing, MI; Johns Hopkins University, Baltimore, MD; National Kidney Center, Kathmandu, Nepal; Nepal Development Society, Pokhara, Nepal; Goteborgs universitet Sahlgrenska Akademin, Goteborg, Sweden; La Isla Foundation, Ada, MI.

Background: Thousands of young Nepali migrant workers have died and many developed ESRD while working abroad. Although the etiology of kidney disease is yet to be established, exposure to recurrent heat stress is identified as a potential risk factor.

Methods: Cross-sectional study was conducted in 2 dialysis centers. Patients 18-80 yrs of age getting incenter hemodialysis were sampled. Questionnaire with migration and occupational history was administered.

Results: A total of 354 patients were included (mean age 46.5 ± 13.9 yrs; 36% female). 31% were returnee migrant workers (88% male; 83% worked in the Gulf States, Malaysia, & India). The median duration of work abroad was 14 yrs (IQR 9-18) & >50% returned due to health problems. 50% of returnee migrant workers were <40 yrs old, compared to 30% of non-returnee migrant workers (P<0.001). A lower prevalence of diabetes (12% vs 24%; P=0.009) & immunologic diseases (5% vs 14%; P=0.022) were observed among returning migrants. Returnee migrants experienced extreme workloads (36%), no breaks (37%), & exhaustion (68%). Among those who reported heat exposure at work, 70% were exposed daily.

Conclusions: The findings provide meaningful information on potential risk factors for CKDnT. These results underscore the importance of conducting further studies to better understand & address the specific risks & challenges they face.

Funding: Private Foundation Support

SA-PO052

Assessment of Dialysis Operations in Conflict-Affected Areas: Insights from Survey Results from Northwest Syria
Sami Alasfar, Hani S. Alashawi, Lina Murad, Gilbert M. Burnham, Mayo Clinic Arizona, Scottsdale, AZ; Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; Metropolitan Access Center, Brentwood, MD; The Health Cluster, Gaziantep, Turkey.

Background: In areas affected by armed conflict, the operations of hemodialysis (HD) are hindered by the lack of required infrastructure. Despite the growing prevalence of kidney disease, humanitarian agencies have given little attention to HD in such situations. Northwest (NW) Syria is an example of such a conflict-affected region where approximately 800 patients rely on HD provided by non-governmental agencies (NGOs).

Methods: We conducted a survey consisting of 346 questions to assess HD operations in NW Syria. Onsite visits were made to interview HD facilities managers and technicians, and the data was collected during these visits. The survey covered various areas related to HD operations, including current infection and prevention and control practices, medical protocols, built environment, health care worker competencies, equipment maintenance, dialysis unit management and leadership, and record keeping.

Results: Answers to selected questions of the survey are in tables 1&2.

Conclusions: In regions affected by armed conflict, the operations of hemodialysis (HD) are hindered by the lack of required infrastructure. Despite the growing prevalence of kidney disease, humanitarian agencies have given little attention to HD in such situations. Northwest (NW) Syria is an example of such a conflict-affected region where approximately 800 patients rely on HD provided by non-governmental agencies (NGOs).

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Results: Answers to selected questions of the survey are in tables 1&2.

Conclusions: In regions affected by armed conflict, there are significant deviations from the standards of HD operations, highlighting the need for an action plan that involves NGOs responsible for administering HD, in order to implement and maintain minimal standards for HD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Primary Caregiver Burden in a Mexican Hemodialysis Facility: Prevalence and Risk Factors

Background: Caregiver burden is a subjective interpretation of resources, abilities and impact of caregiving process. A validated Zarit survey has been recommended among caregivers in patients with HD.

Methods: Primary HD caregivers from a single facility in Mexico responded a validated Zarit survey. Incident patient and caregivers (< 3 months) were excluded. Social and demographic caregiver data also included. Descriptive, linear regression and coeff. correlation analysis was done.

Results: 86 primary caregivers answered: Most females with a mean age of 47. Housewives 43% was the main occupation. Couples take care of patients in 42%. Median monthly income 220 dlls. We identified burden in 54%: slight 32% and severe 68%. Female sex and unemployees predicts higher scores. A non-significative negative correlation was found between income and score.

Conclusions: Caregiver burden is prevalent. Economic difficulties exacerbate complexity and caregiver burden. Results should be added to public health burden of ESRD in Mexico.

Caregiver factors and Zarit Score - Linear regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coef</th>
<th>CI 95%</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Female sex</td>
<td>1.04</td>
<td>(1.61 - 2.52)</td>
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<tr>
<td>Unemployed</td>
<td>0.63</td>
<td>(0.44 - 4.54)</td>
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<td>Caregiver age</td>
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<td>(0.81 - 0.04)</td>
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<tr>
<td>Monthly income</td>
<td>0.001</td>
<td>(0.003 - 0.001)</td>
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</table>

Adjusted by caregiver age, illness, sleeping hours, life spent caring, patient-caregiver relation, meals a day, social security.
SA-PO054
Increasing Home Dialysis Among Spanish-Speaking Mexican American Patients: Challenges and Opportunities
Karen-Marie Eaton,1 Steven M. Brunelli,1 Danelle Radney,1 Unini Odama,2 Francesca Tentori.1 1Davita Clinical Research, Minneapolis, MN; 2DaVita Inc, Denver, CO.

Background: Home dialysis offers patients another treatment option for kidney failure. Since home dialysis use is lower in Mexican American patients, in this study we sought to understand experiences and uncover influencing factors and barriers that patients and care partners face.

Methods: A total of 28 participants (Mexican American patients at a dialysis provider, both in-center and home, and their care partners) were recruited to join in-person focus groups held in December 2022. Focus groups were audio and video recorded and transcribed verbatim. Groups were held in Spanish language, translated in real time by a certified interpreter, and transcribed in English. Responses were analyzed using inductive thematic analysis.

Results: Patients reported that physicians did not make a clear connection between poor management of underlying health conditions and kidney failure; this led to difficulty accepting a kidney failure diagnosis and need for dialysis. Patients and caregivers want improved education in English and Spanish to help make the initial modality decision. Physican guidance was cited as the most important factor in the initial modality decision for Mexican American patients and care partners. Trust in physician recommendation is largely unquestioned, influenced by factors such as respect for physician authority, limited literacy, and language barriers. While most patients and care partners acknowledge the benefits of home dialysis, significant barriers include the fear of being solely responsible for a complex procedure and loss of social interaction and/or support from other dialysis patients and center staff. Unsurprisingly, care partners are a critical part of the decision to choose home dialysis. Faith plays a significant role for many respondents; many speak about their experience of disease in faith-based terms, such as trusting God.

Conclusions: Opportunities exist to build on the strong patient preference for physician led health information, and to focus on decreasing literacy and language barriers in the Mexican American population.

SA-PO055
Disparities in Home Dialysis for Latinx People with Kidney Disease: A National Qualitative Study of Dialysis Social Workers
Katherine M. Rizzolo,1,2 Lilia Cervantes,2 Boston Medical Center, Boston, MA; 1University of Colorado Anschutz Medical Campus, Aurora, CO.

Background: Latinx people have a 2.1 fold higher incidence rate of kidney failure compared to non-Latinx White individuals, yet are less likely to use home dialysis. This discrepancy has not been completely explained by medical, socioeconomic, or demographic variables. Improving access to home dialysis for Latinx social workers from ten different states, with a median age range of 30-40 (35%), 100% female, 14 (70%) identified as White and 5 (25%) of participants spoke Spanish. Participants described five themes affecting home dialysis decision making, and home dialysis uptake and maintenance. Interviews were audio-recorded, transcribed verbatim, de-identified and transcripts were analyzed independently by two members utilizing thematic analysis.

Results: We interviewed 20 dialysis social workers from ten different states, with a median age range of 30-40 (35%), 100% female, 14 (70%) identified as White and 5 (25%) of participants spoke Spanish. Participants described five themes affecting home dialysis decision making, and home dialysis uptake and maintenance. Interviews were audio-recorded, transcribed verbatim, de-identified and transcripts were analyzed independently by two members utilizing thematic analysis.

Methods: We conducted a qualitative study with adult (age >18) dialysis social workers in the US with experience working with Latinx populations. The semi-structured interview guide included open ended questions exploring dialysis modality education, dialysis decision making, and home dialysis uptake and maintenance. Interviews were audio-recorded, transcribed verbatim, de-identified and transcripts were analyzed independently by two members utilizing thematic analysis.

Results: We interviewed 20 dialysis social workers from ten different states, with a median age range of 30-40 (35%), 100% female, 14 (70%) identified as White and 5 (25%) of participants spoke Spanish. Participants described five themes affecting home dialysis decision making, and home dialysis uptake and maintenance. Interviews were audio-recorded, transcribed verbatim, de-identified and transcripts were analyzed independently by two members utilizing thematic analysis.

Conclusions: Our study illustrates early language and culture concordant education is critical for home modality uptake amongst Latinx people with kidney disease. Involving the social worker early in the home dialysis is critical for evaluating for important issues that may affect home dialysis treatment.

Funding: NIDDK Support

SA-PO056
Racial and Socioeconomic Differences in Success on Home Dialysis
Catherine A. Moore,1 Catherine W. Liu,1 Justin C. Weissberg,1 Tramahn Phan,1 David Skrill,1 Sai Subhodhini Reddy,1 Veronica G. Yu,1 Eliot Sachsenmeier,1 Hongmei Yang,1 Scott E. Liebman.1 University of Rochester Medical Center, Rochester, NY; 2Swedish Cherry Hill, Seattle, WA; 3New York University, New York, NY.

Background: Home dialysis offers several advantages to patients and health care systems, including improved patient-centered outcomes, lower cost, and equity if not better clinical outcomes. Despite this, utilization of home dialysis remains low. Although home dialysis is not always the ideal modality for patients with End Stage Renal Disease (ESRD), most dialysis patients are viable candidates for this modality. Variance in home dialysis utilization falls along both racial and socioeconomic lines, with lower home dialysis utilization by racial and ethnic minorities and higher rates among black individuals of transfer to in-center dialysis. Provider fear of adverse outcomes and home dialysis failure remains a barrier to home therapy referral. We investigated whether markers of sociodemographic stress would predict success on home therapy.

Methods: We performed a retrospective cohort study of adult incident ESRD patients from January 1 2015 through December 31 2021 admitted to providers within the University of Rochester division of nephrology (N= 898, including 794 in-center hemodialysis, 39 home-hemodialysis and 65 Peritoneal dialysis) with observation period ending December 31, 2021. Using cox proportional hazards model, we compared race to social deprivation index (derived through Census Tract) as predictors for home dialysis failure (defined by conversion to in-center dialysis or death).

Results: Black and African American patients were more heavily represented amongst subjects starting in-center HD (31% vs 16.3%). There was no significant difference between mean social deprivation index (SDI) or Charlson co-morbidity index (CCI) scores in subjects starting in-center compared to at home. Over the observation period, 128 subjects performed home dialysis for a mean of 45 months. None of the variables evaluated were predictors of success on home therapy (age, sex, race, SDI or CCI).

Conclusions: Despite similar markers of medical co-morbidity and sociodemographic stress, fewer non-white patients started dialysis on a home modality compared to in-center. Race and social deprivation are not race predicted on home therapy. This highlights a disparity in the initial referral process to home therapy which is not supported by commonly cited predictors of adverse outcome.

SA-PO057
Disparities in Home Dialysis Utilization Among Dual Eligible Medicare Fee-for-Service (FFS) Beneficiaries
Emily Belowich, Jack Fagan, Shalini Parekh, Mark J. Gooding, Avalere Health, Washington, DC.

Background: Since the 2019 Advancing American Kidney Health (AAKH) initiative, the federal government has focused on enhancing prevention and treatment of kidney disease, including introducing new incentives for home dialysis use for patients who require renal replacement therapy. Access to optimal kidney care services influences greater mortality and morbidity rates. We hypothesized that patients with lower socioeconomic status may have lower use of home dialysis due to the nature of what is required to access this dialysis modality (e.g., health literacy, caregiver support, proper home infrastructure).

Methods: We used 100% Medicare Fee-For-Service (FFS) claims data to identify patients with End Stage Renal Disease (ESRD) who received renal replacement therapy (peritoneal dialysis and hemodialysis) excluding beneficiaries who have received a kidney transplant between January 1 2019 to June 2022. We stratified beneficiaries by Medicaid dual eligibility status.

Results: Between Q1 2019 – Q2 2022, the rate of home dialysis utilization grew from 12.3% to 15.9% across all Medicare FFS beneficiaries. In Q2 2022, 12.0% of 113,226 dual-eligible beneficiaries utilized home dialysis compared to 19.7% of 115,497 non-dual eligible beneficiaries utilizing home dialysis (p<0.01). This difference in utilization
was consistent across the period of analysis; the rate of non-dual eligibles utilizing home dialysis was 7.7 percentage points higher than dual eligible beneficiaries in Q1 2019 and 7.4 percentage points higher in Q1 2022.

Conclusions: The AAKH initiative – compounded by the COVID-19 pandemic – served as a catalyst to advancing home dialysis. However, these findings indicate that access to care is still greatly influenced by socioeconomic status, even with policy changes that intentionally aim to close disparity gaps. Future research and policy should seek to identify how disparities in socioeconomic status and associated challenges can be addressed to allow for equitable access to all treatment modalities for ESRD.

Rates of Unique Medicare FFS Patients with a Home Dialysis Service in the Given Quarter

SA-PO058

Social Determinants of Health and AKI During Hospitalization

Tomonori Takeuchi,1 Lama Ghazi,1 Elizabeth H. Baker,1 Gabriela R. Oates,1 Lucia D. Juarez,2 Ariam F. Nassel,1 Akm F. Rahman,1 Edward D. Siew,2 Orlando M. Gutierrez,1 Javier A. Neyra,1 The University of Alabama at Birmingham, Birmingham, AL; 2Vanderbilt University, Nashville, TN.

Background: AKI is highly prevalent in hospitalized patients. Social determinants of health (SDOH) have been understudied as AKI risk factors. Our goal was to determine whether SDOH impacts AKI risk and AKI recovery during hospitalization.

Methods: Retrospective cohort study of patients aged ≥18 years without end-stage kidney disease admitted to the hospital from 10/2014 to 9/2017. Outcome measures were (1) Incident AKI defined by the KDIGO SCR-criteria and (2) AKI recovery defined as last SCR before discharge <25% or <0.3 mg/dl from baseline and not receiving dialysis within 72 h of discharge in patients who survived the hospitalization. We linked geocoded patient addresses at the index hospitalization to the corresponding U.S. Census tracts and block groups and the following SDOH measures: (1) neighborhood socioeconomic status measured with Area Deprivation Index (ADI) scores, (2) food access measured with Low Income Area/Low Income Area (LILA) scores, (3) rurality measured with Rural Urban Commuting Area (RUMA) scores, and (4) residential segregation measured with dissimilarity and isolation scores. Multivariable logistic regression was used to quantify the association between SDOH measures, each independently, and AKI development and recovery.

Results: Out of 26,769 patients, 6,976 (26%) developed AKI during hospitalization. Compared to those who did not develop AKI, patients who developed AKI were older (60 [47,71] vs 57 [47,68] years), more likely to be male (55 vs 50%), and more likely to be Black (38 vs 33%). Patients who lived in the highest tertile for ADI (most disadvantaged) were more likely to develop AKI during hospitalization even after adjustment (Table). In the fully adjusted model, Patients who lived in the highest tertile of ADI and in a LILA tract were less likely to have AKI recovery at the time of discharge (OR 0.85 [0.72,0.99]) and OR 0.86 [0.74,0.99]). Rurality and residential segregation were not associated with incident AKI or AKI recovery.

Conclusions: Patients in the highest tertile of neighborhood disadvantage were more likely to develop AKI and less likely to recover.

Funding: NIDDK Support

SA-PO060

Food Security in Jamaicans with CKD Following the COVID-19 Pandemic: A Pilot Observational Study


Background: Limited data exists on food security amongst persons with chronic kidney disease (CKD) in the Caribbean, especially since the onset of the COVID-19 pandemic. We describe the prevalence of food-insecurity in persons living with CKD from a single centre in Jamaica.

Methods: A cross-sectional survey was conducted between December 1,2022 and March 31, 2023 among 18 and 74 year old patients attending the University Hospital of the West Indies renal clinic prior to the onset of the pandemic (March 2020) and who were not on dialysis. Informed consent was obtained from patients who agreed to share their contact information with the study team prior to enrolment. A telephone administered questionnaire that included details on demographics, food security and health care utilization was administered by trained interviewers. Data on cause of CKD, creatinine values at each clinic visit, and hospital and emergency room visits were abstracted from hospital records. Self-reported food insecurity was based on responses to a standard Centers for Disease Control questionnaire. Means and standard deviations were used to describe continuous variables, whilst proportions were used to describe categorical data.

Results: 43 participants [51±4±1.8 (mean ±SD) years, 72% female] were included. The majority (52%) had CKD Stage 3 disease, with 11% with CKD Stage 4 and 2% with CKD Stage 5. CKD was attributed to diabetes/hypertension in 30% of persons, lupus in 25%, and sickle cell disease in 28%. The majority (84%) had at least high school education and 35% were either retired or unemployed. Food insecurity was reported by 42 (95% CI: 38-45%) of participants before the pandemic and 55%(60-68%) during the pandemic. Less than half (46%) of patients had one or more hospitalizations or emergency room visit during the covid pandemic. There was no difference in mean age between food secure and insecure(52.1 versus 48.2 years, p=0.238) but a higher proportion of women reported food insecurity (61 versus 27%, p=0.05) during the pandemic. There was no statistically significant association between hospitalization or emergency room visits and food insecurity (p=0.169).

Conclusions: There was no difference in mean age between food secure and insecure participants. Women were more likely to report food insecurity during the COVID-19 pandemic.

Funding: Government Support - Non-U.S.
to Care Questionnaire” to assess healthcare access. Parents or patients older than 18 completed the survey in their preferred language and had no barriers to care, and a score < 75 equates a failed score due to high barriers. We also collected sociodemographic data and the Area Deprivation Index (ADI), a metric of socioeconomic disadvantage that incorporates 17 socioeconomic measures. The national ADI score ranges from 1 (most advantaged) to 100 (most disadvantaged). We created linear regression models to describe the association between barriers and ADI scores and tested for interactions based on language.

Results: In 109 surveys (49% Spanish, 51% English), we identified high skills and pragmatic barriers to care in the English-speaking system. The English-speaking system had a higher mean ADI score of 74 (±26) and 75 (±21), respectively. The mean ADI score was 55 (±20). Spanish-speaking families had higher skills barriers (p=0.001); no difference in pragmatic barriers (p=0.40) and mean ADI score (p=0.38). A higher ADI score correlated with higher total barriers (p=0.006) and significant interaction effect by language (p=0.04).

Conclusions: Hispanic youth in Chicago face significant barriers to accessing nephrology care. Spanish-speaking patients with higher socioeconomic disadvantages struggle to navigate the healthcare system. Findings indicate the need for a diverse and multicultural team to support Spanish-speaking families. Prospective studies are necessary to advocate for programs and policy changes to address these barriers and reduce racial and ethnic disparities in pediatric nephrology care.

SA-PO062

Impact of Social Determinants of Health on the Prevalence of CKD in Jalisco, Mexico

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Background: Social determinants of health have been linked with disparities on the incidence and prevalence of CKD. In Mexico, CKD has become an important public health problem; current guidelines recommend routine CKD testing in patients at increased risk. We report the impact of social determinants of health on the prevalence of chronic kidney disease in Jalisco.

Methods: Between 2006-2019 we screened at risk for the presence of CKD using mobile units that traveled to rural and urban communities of Jalisco. Trained personnel collected demographic and clinical data and obtained blood and urine for serum chemistry and dipstick urinalysis. Individuals who were aware they had kidney disease were not assessed; all others were eligible to participate. GFR was estimated with the EPI-CKD formula; CKD was defined as an eGFR < 60 ml/min/1.73m².

Results: Between 2016-2019, 63,918 individuals were evaluated. Findings in individuals with CKD and without it were compared. CKD was more prevalent among individuals without schooling (p<0.001), homelessness (p=0.003), unemployed (p<0.001) and lacking health care insurance (p=0.001) (Table 1). By multivariate analysis, illiteracy (OR 1.10, 95% CI 1.01-1.21, p=0.04) and lack of health care insurance (OR 1.12, 95% CI 1.04-1.19, p=0.001) independently increased the risk of CKD.

Conclusions: Social determinants of health were associated with a greater prevalence of CKD in our population. Our findings suggest that interventions addressing the social determinant factors are needed in individuals with CKD.

Table 1 - Demographic characteristics of the participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>eGFR &gt; 60 ml/min/1.73m²</th>
<th>eGFR &lt; 60 ml/min/1.73m²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69.9 ± 11.4</td>
<td>67.9 ± 11.5</td>
<td>-0.01</td>
</tr>
<tr>
<td>Female gender</td>
<td>4,550 (43.9%)</td>
<td>38,914 (38.8%)</td>
<td>-0.01</td>
</tr>
<tr>
<td>DM</td>
<td>1,158 (11.8%)</td>
<td>12,252 (12.4%)</td>
<td>-0.01</td>
</tr>
<tr>
<td>IHD</td>
<td>3,466 (33.5%)</td>
<td>11,645 (11.5%)</td>
<td>-0.01</td>
</tr>
<tr>
<td>eGFR (median (IQR75/25))</td>
<td>48.9 (11.2)</td>
<td>120.0 (60.5)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Elastase</td>
<td>728 (13.8%)</td>
<td>7,884 (49.8%)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Hematuria</td>
<td>105 (1.8%)</td>
<td>757 (1.9%)</td>
<td>-0.05</td>
</tr>
<tr>
<td>Unemployed</td>
<td>3,075 (52.4%)</td>
<td>10,669 (63.6%)</td>
<td>-0.01</td>
</tr>
<tr>
<td>Uninsured</td>
<td>1,060 (28.7%)</td>
<td>12,060 (22.6%)</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

SA-PO063

Mesoamerican Nephropathy: Opening New Horizons

Carmen L. Caujapé,1,2 Amanda A. Ahmed,1,3 The University of Kansas Medical Center, Kansas City, KS; 2Hospital Monte Esparta, Managua, Nicaragua; 3Duke University, Durham, NC.

Introduction: Mesoamerican nephropathy is a chronic kidney disease of significant importance in Central America. It mainly affects young men in the agricultural field from the Pacific Coast of Nicaragua, and a prevalence of up to 42% has been described in this population. The precise etiology of Mesoamerican Nephropathy (MeN) still remains a mystery.

Case Description: A 37-year-old male from an urban area, who works in construction, with no personal history of hypertension, diabetes, or autoimmune diseases, presents with edema and fatigue. Creatinine levels of 16.5 mg/dL and BUN of 78 mg/dL were observed. Physical examination revealed normal blood pressure and hypereflective. Significant laboratory findings included urea 10.6, potassium 3.1 mmol/l, sodium: 134 mmol/l, proteinuria showing proteinuria lower than 0.7 g/dl, and urate crystals. Imaging findings were consistent with CKD. Considering his place of origin and occupation, which expose him to thermal stress and repetitive episodes of dehydration, and in the absence of other causes that could explain the CKD, the first differential to be considered is MeN. Histopathological findings are not feasible for diagnostic confirmation. According to case definitions, this patient can be classified as a probable case of MeN. The patient initiated renal replacement therapy with hemodialysis in a 3-session-per-week schedule, resulting in significant improvement of the clinical condition.

Discussion: The high risk of CKD in agricultural workers in warm areas of Central America has been previously described. However, a high prevalence (12.1%) has also been reported in other occupation with high temperature exposure. MeN diagnosis still remains a challenge due to the lack of access to histopathological diagnosis confirmation. This case highlights the importance of having a knowledge of geographical locations as possible risk factors for the occurrence of MeN. Priority and urgent actions to contain the advancement of this disease should be focused on early diagnosis and prevention in high-risk areas and occupations. It is important to expand the study of MeN to other occupations that share exposure to high temperatures. The economic and health impact of MeN should be mitigated with diagnostic and treatment strategies, as well as expanded research funding for other occupations.

SA-PO064

Geographic Disparities in the Rate of Major Adverse Kidney Events Among Patients with CKD in Alberta


Background: Individuals in rural communities in Alberta disproportionately experience adverse health outcomes. Characterizing temporal trends in the incidence of major adverse kidney events (MAKE) by geographic characteristics could identify inequities in the management of CKD that can guide policy action.

Methods: We quantified the annual incidence of MAKE in Alberta from 2003-2019, overall and by geographic characteristics of patients’ residential zip codes, using routine healthcare data available in the Alberta Kidney Disease Network (AKDN) database. CKD status for cohort eligibility was ascertained based on eGFR and defined as ≥ 2 eGFR values <60 ml/min/1.73m².

Results: Temporal trends in the rate of make were estimated using linear regression.

Results: Among 262,392 patients (median age 75 years; 56% female), the overall incidence rate of MAKE decreased from 7.5% between 2003 and 2004 to 6.5% between 2018 and 2019 (p<0.001) and the corresponding rate of change in the annual incidence of MAKE was −0.08 (95% confidence interval -0.10 to -0.06). There was an excess incidence rate of MAKE in rural vs urban locations between 2003 and 2004 (8.7% vs 7.4%); however, this excess rate was attenuated between 2018 and 2019 (6.7% vs 6.5%). Likewise, the excess rate of MAKE in rural communities >100 km from the nearest nephrology center in 2003 and 2004 (9.3% vs 6.8%) was substantially reduced between 2018 and 2019 (6.5% vs 6.4%).

Conclusions: Disparities in incidence MAKE by geographic characteristics of patients in Alberta have improved over the last 2 decades. Future studies exploring factors (e.g., CKD care indicators, population mix) that might have contributed to these noticeable improvements are needed for development of policy interventions to optimize CKD outcomes equitably for all patients.

Funding: Government Support - Non-U.S.

SA-PO065

Searching for Significance in Oceania: A Voyage of Recurrent FSGS in a Patient from the Marshall Islands with Variants of Uncertain Significance

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Introduction: The success of next generation exome sequence analysis has dependency on clinical and pathologic phenotypic correlation. There is a gap in knowledge of genetic variants in glomerulopathy unique to those referred to the Pacific Basin’s single adult organ transplantation program. The effects of the U.S. Nuclear Weapons Testing Program (USNWTP) in the Bikini Atoll between 1946-1958 with aggregate detonation of 7.20 Hiroshima atomic bombs” 4 are unknown for the relocated inhabitants. We present a case of recurrent FSGS with unusual mesangial IgM predominant deposits and associated variants of uncertain significance.

Case Description: The patient is a 21 year old female from the Marshall Islands with history of deceased donor renal transplant 3 years prior who presents with proteinuria. Renal biopsy showed no evidence of rejection but segmental sclerosis with foamy cells in a membranoproliferative pattern along with diffuse mesangial C4d positivity with electron dense deposits (Figure 1). Review of history showed she was diagnosed with FSGS on biopsy in the Philippines at age 16 then relocated to Honolulu, Hawaii where she was evaluated by pediatric nephrology. Results from KidneySeq v3.0 (Figure 2) revealed heterozygous variants of uncertain significance. Two were in XPO5 variants of which is associated with autosomal recessive FSGS, one in NPHS2 (podocin), and a variant in CUBN, a receptor on intestinal mucosa with high affinity binding to APOAI/HDL and intrinsic factor-vitamin B12.
Discussion: We demonstrate the possibility of a recurrent glomerulopathy due to circulating factor rather than donor related disease. VUS analysis must be made alongside biopsy phenotype correlation for greatest benefit. Patients most in need of equity in health and technology must also be included in gene variant databases.

SA-PO066 Climate Change and Sustainability in Kidney Care in Canada: A Knowledge, Attitudes, and Practices (KAP) Survey by the Canadian Society of Nephrology's Sustainable Nephrology Action Planning Committee

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Background: Climate change impacts kidney health while threatening the stability of kidney care delivery systems, while health care itself has a significant environmental impact. Knowledge and attitude of Canadian kidney care providers toward climate change is unknown, and there are limited published data on environmental sustainability measures in kidney care in Canada. This study aimed to (1) assess knowledge and attitude about climate change among Canadian kidney care providers; (2) establish the current state of kidney care sustainability activities in Canada.

Methods: An electronic KAP survey, created by the Canadian Society of Nephrology – Sustainable Nephrology Action Planning (CSN-SNAP) committee, was distributed to kidney care providers across Canada. A total of 386 individuals completed the survey, while an additional 130 incomplete answers were provided. Most respondents (79%) identified as women and 26%, 31% and 26% were aged 30-39, 40-49 and 50-59 years, respectively. Consultant nephrologists and kidney nurses comprised 23% and 44% of respondents, respectively. Most respondents were either extremely (25%), very (46%) or moderately (23%) concerned about climate change; and similarly extremely (23%), very (39%) or moderately (28%) concerned about the amount of waste generated in their kidney care program. Respondents deemed reducing the carbon footprint important in both their personal lives (23% important 35%; fairly 17%), and in the kidney care services they provide (very 34%; important 37%; fairly 18%). The sustainable strategies most frequently incorporated into kidney care were reduction of office consumables and equipment, water saving taps, waste management (mostly bins, including recycling), clinical care consumables’ use prioritized by expiry dates, virtual care options to minimize unnecessary transportation, and medication stewardship strategies.

Conclusions: Most Canadian kidney care providers are highly concerned about climate change and think it is important to reduce the environmental impact in both their personal lives, as well as in the kidney care services they provide. Few sustainable strategies are incorporated into kidney care services across the country.

SA-PO067 Assessment of Equity, Inclusiveness, and Quality of Life for French-Speaking Male and Female Nephrologists: A Survey by the FEMKY Group

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Background: Recent surveys report a high rate of burnout for nephrologists. The quality of life at work and in personal life as well as the perception of gender discrimination at work are insufficiently defined.

Methods: The FEMKY group (FEMmes KYndey) conducted a cross-sectional descriptive observational study by sending an online survey to French-speaking nephrologists members of the Francophone Society of Nephrology, Dialysis and Transplantation (SFNDT) and of the young nephrologists club in France (CJN), from November 2022 to January 2023. We assessed 6 domains: demographic characteristics, working conditions, quality of life at work and in personal life, gender discrimination and history of workplace harassment.

Results: 257 female and 128 male nephrologists responded. 76% of women and 66% of men were under 45 years old and 53% and 51% respectively worked in a university hospital. Quality of life at work was similar for both genders but significantly lower for women at the personal level (p=0.03). Feeling of fatigue (p=0.01) and dissatisfaction with leisure time were significantly higher in women (p<0.001). The opinions of the two genders were significantly different regarding whether the fact of being a woman closes doors at work (p=0.02), that women are less trusted (p<0.001), and that pregnancies and children education are an obstacle for a woman career (p=0.001). Harassment and humiliation at work were described by 37% and 46% of women and 26% and 36% of men (p=0.06 respectively).

Conclusions: The quality of life at work was similar between the two genders despite a more important and concerning rate of feeling of discrimination, harassment, and humiliation at work for women and a lower quality of personal life.

SA-PO068 Fellow Attitudes and Perceptions of Health Equity Care and Training in Nephrology

Areeba Jawed, Jennifer L. Bragg-Gresham, Michael Heung, Laura H. Mariani, Panduranga S. Rao, Julie A. Wright Nunes. University of Michigan Michigan Medicine, Ann Arbor, MI.

Background: Little is known about the current state of Health Equity care and training within Nephrology Fellowship. We developed a survey to assess fellow attitudes about caring for diverse and underserved patient populations and perceptions on fellow training to prepare them to do so.

Methods: Via a survey administered to all U.S nephrology trainees through the ASN in-service training exam (ITE) Spring 2022 we assessed fellow attitudes and perceptions. The survey included 13 questions: 5 demographics and 8 assessing attitude in caring for underserved patients and perceptions of how well training prepared them to do so.

Results: Of the 816 trainees taking the ITE survey, 706 provided informed consent to use their responses, and 689 responses were analyzed due to missing data, for a response rate of 84.4%. The survey reliability factor was 0.7-0.8. Respondents were on average 34 years old, 57% Male, and 11% Hispanic. Predominant races were White (34.2%) and South Asian (27.7%) and most were international (26.3%) or US (24.3%) medical graduates, with 72.3% reporting working with underserved populations often/always. In multivariate analysis Hispanic and African American fellows and graduates of US medical schools were more likely to have worked with underserved patients and show concern for disparities within nephrology. Women and fellows who were further out in training scored lower when it came to confidence and perceptions regarding adequate training to reduce health care disparities.

Conclusions: Although fellows stressed the importance of caring for underserved patients a high proportion did not feel fellowship prepared them adequately for this. Effort needs to be made to better equip trainees with the skills they need to care for all patients, with opportunity to address needs in women.
Trends in Race/Ethnicity of ASN Kidney Week Faculty (Speakers, Moderators, and Program Chairs): 2018-2022

Methods: We conducted a retrospective analysis of trends in race/ethnicity of U.S. KW faculty 2018–2022. Self-reported race/ethnicity for KW faculty (speakers, moderators, and program chairs) was obtained from ASN’s database. We performed a descriptive analysis amongst KW faculty cohort racial proportions over time. Descriptive data is reported as relative percentage frequency. The reported race/ethnicity was: White/Non-Hispanic White, Black, Asian, Hispanic or Latin(o), American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and Mixed. We also added a category of others/unknowns who did not report race.

Results: 23% (mean =12,132) of ASN members and 16% (mean =508) of faculty did not self-report race/ethnicity during KW 2018–2022. White (33-35%) was the most common self-reported race among ASN members, followed by Asian (24%). Blacks were 4.3-4.6%, and Hispanics or Latin(o) were 5.4-6% among ASN members. Over the five years, white faculty declined from 54.5% to 48.3%. At the same time, we found improving trends of Blacks in KW faculty representation from 2.7 to 5.4%. Hispanic or Latin(o) representation remains stable at 5.4-6% among KW faculty.

Conclusions: We found that Asian, Black and Hispanics KW faculty were underrepresented as KW faculty. However, these findings may also be reflection of their lower representation as ASN members. Prioritizing DEI to close this gap is key to fostering the innovation and creativity needed to advance kidney health.

SA-PO071

Assessing Ambient Heat Exposure and AKI Using Alternate Case Definitions

Background: Ambient heat exposure is an established risk factor for the development of acute kidney injury (AKI). However, prior work using International Classification of Disease (ICD)-coded data has important limitations in evaluating heat-AKI. We hypothesized that Kidney Disease: Improving Global Outcomes (KDIGO)-based AKI definitions would improve the accuracy of heat-AKI effect estimates compared to ICD-coded data by improving AKI case sensitivity.

Methods: We conducted a case–crossover study comparing AKI-related emergency department (ED) visits with same-day maximum temperatures in Atlanta, Georgia during 6 consecutive warm seasons. We created 7 case definitions for AKI using ICD-coded data and KDIGO-derived equations. KDIGO definitions compared an individual’s serum creatinine measurements to surrogate values for baseline renal function.

Results: We analyzed 338,682 total ED visits between 2014 and 2019. Cases of AKI ranged from 5,868 to 64,269 across the 7 definitions. Higher temperatures were associated with AKI-related ED visits in all 7 definitions (Figure 1). When we stratified individuals by the presence of an ICD-coded AKI diagnosis, we detected a persistent heat-AKI effect among individuals without a coded AKI diagnosis under the “CKD-EPI 75” (OR 1.06, 95% CI 1.02-1.12) and “CKD-EPI 90” (OR 1.07, 95% CI 1.03-1.11) definitions.

Conclusions: Our results support KDIGO-based definitions as an improved tool to evaluate the heat-AKI relationship. This method may enable researchers to capture additional AKI cases otherwise missed by code-classified data, for whom a significant heat-AKI effect exists.

Trends in Race/Ethnicity of KW Faculty

Validation of ISN 0by25 Acute Kidney Injury Risk Score for Low- and Low Middle-Income Countries

Background: Incidence of Acute Kidney Injury (AKI) is increasing in low-resource countries and is associated with morbidity and mortality. Early identification of patients at increased risk for AKI is the first step to implement preventive and treatment strategies. Multiple risk scores to predict AKI have been developed in higher-income countries and are specific for particular risk settings. Here, we validated new symptoms-based ISN 0by25 AKI risk score that can be easily implementable in resource-constrained environments.

SA-PO069

Diversity and Equity: Other Research

Validation of ISN 0by25 Acute Kidney Injury Risk Score for Low- and Low Middle-Income Countries

Background: AKI is a significant adverse outcome. Multiple risk scores to predict AKI have been developed in high-resource countries and are specific for particular risk settings. Here, we validated a new symptoms-based ISN 0by25 AKI risk score that can be easily implementable in resource-constrained environments.

Methods: Forty-seven hospitalized patients from Clinica “Los Olivos” in Cochabamba, Bolivia were enrolled in this ongoing study. Data for predictor variables was extracted from patient’s medical charts at the time of admission. The ISN 0by25 AKI risk score was calculated at admission and patients with a risk score of ≥3 points were included. Patient information was recorded from the time of diagnosis and renal function (serum creatinine[scr]) was followed up daily up to 7 days. AKI was defined using KDIGO sCr criteria.

Results: A total of 29 patients (61.7%) developed AKI and 77% were female. The main risk factors for AKI were age ≥65 years (64%), DM (60%) and congestive heart failure (49%). The 3 main causes of AKI were nephrotoxins exposure (93.6%), dehydration (87.2%), and hypotension (38.2%). Positive and negative predictive values for the optimal cutoff value of 6 points in the cohort were 87.5% and 65.2% respectively with an odds ratio (OR) of 13.1 (95% CI 3.0-57.8; p=0.0007). The risk score has a good performance in predicting AKI with a ROC-AUC of 0.85 (95% CI 0.75 - 0.96; p = 0.0001). None of the patients who developed AKI required dialysis.

Conclusions: We validated the performance of the ISN 0by25 risk score in predicting hospital-acquired AKI, which showed good performance. This risk assessment tool could help clinicians stratify patients for primary prevention, surveillance and early therapeutic interventions to improve the care and outcomes of high-risk patients in low-resource settings.
Worldwide Incidence and Associated Mortality of AKI in Neonates: A Systematic Review and Meta-Analysis

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Background: There is limited literature on the global incidence of acute kidney injury (AKI) and associated mortality in neonates. We aim to systematically assess the worldwide incidence of AKI in neonates to increase awareness and inform policymakers.

Methods: We searched three databases (PubMed, Embase, Web of Sciences) from 2004 to December 2022 without language or geographical restrictions. Cohort and Cross-sectional studies reporting the incidence of AKI in neonates were included in this systematic review. Eligible studies had at least 10 participants and used AKIN, RIFLE, and KDIGO or their equivalent criteria to define AKI. Two authors independently extracted data about the study and patients’ characteristics and outcomes (incidence and AKI-associated mortality) and assessed the risk of bias. We used a random-effects meta-analysis to generate pooled estimates.

Results: From the initial 6990 records, we included 201 studies (9847 neonates) from 51 countries. The pooled incidence of any stage AKI was 34% (95% confidence interval: 31-37), and that of severe AKI was 15% (14-17). The incidence of AKI was lower in high-income 31% (27-35), low-middle-income 40% (32-48), and low-income 47% (46-47) countries. Pooled mortality was higher (OR 3.2; 95% CI 2.9-3.5) in neonates with AKI (29%; 95% CI 25-34) compared to those without AKI (8%; 95% CI 8-10). Mortality was lower in high-income 25% (20-30), low-middle-income 30% (20-42), and low-income 37% (20-56) countries.

Conclusions: AKI was observed in almost one-third of hospitalized neonates and is associated with increased mortality risk. Incidence and mortality associated with AKI were higher in low-middle-income countries than in high-income countries.

SA-PO074
A Case of Fulminant Leptospirosis
Sakshi Yadav, Hanni Menn-Joseph. Boston Medical Center, Boston, MA.

Introduction: Leptospirosis, the most prevalent zoonosis worldwide, is a disease that has historically had low reported cases in the United States. However, recent discussions have focused on the re-emergence of Leptospirosis in this region.

Case Description: We present the case of a 69-year-old Hispanic male who presented with acute onset abdominal pain, fever, and muscle cramps persisting for three days. The patient was found to have acute kidney injury (with a creatinine of 3.3 mg/dL) and promptly initiated on intravenous fluids and empiric antibiotics. Urinalysis revealed mild proteinuria and hematuria, with microscopic examination of the urine sediment showing a few red and white blood cells, few granular casts, and rare white blood cell casts cellular casts. A 24-hour urine protein collection yielded a result of 452 mg. Despite antibiotic therapy, the patient continued to experience daily fevers, excessive night sweats, and severe myalgias and continued to deteriorate with worsening nonoliguric kidney injury. Creatinine level peaked at 5mg/dL. He developed thrombocytopenia (platelet count nadir of 45) and hyperbilirubinemia (total bilirubin 6mg/dL with direct bilirubin 4mg/dL), despite otherwise normal liver function. The patient had markedly elevated inflammatory markers with an erythrocyte sedimentation rate (ESR) of 104 mm/hour, C-reactive protein (CRP) of 226 mg/dL, and a fibrinogen level of <800 mg/dL. Complement C3 and C4 levels, creatine kinase, were within the reference range, and serological/autoimmune workup was negative. Subsequent renal biopsy revealed predominant acute interstitial nephritis and some focal acute tubular injury. An infectious workup confirmed the presence of Leptosptira DNA. The patient was initiated on doxycycline therapy, leading to symptom resolution and improvement of multiorgan failure.

Discussion: Leptospirosis, previously regarded as a rural disease primarily affecting tropical regions, is now increasingly reported in urban areas and temperate climates. Factors such as weather changes, population growth, and habitat encroachment have heightened the risk of human exposure to Leptospirosis and its carriers. Therefore, in cases of fulminant multiorgan failure with presumed infectious etiology, clinicians should consider Leptospirosis as a potential cause. Timely initiation of treatment can prevent the progression of chronic kidney disease and, ultimately, end-stage kidney disease.

SA-PO075
Persistent AKI Following Orthotopic Liver Transplant: Prevalence, Risk Factors, and Long-Term Renal Outcomes

Background: This study investigated the pre- and postoperative factors associated with the development of persistent AKI (AKI >72 hours of duration) post-transplant and its impact on renal function during a 5-year follow-up.

Methods: Retrospective study that included all patients who underwent OLT from January 2008 to December 2018. Demographic data, data inherent to the surgical procedure and post-operative factors associated with AKI. Subsequently, we performed logistic analysis with variables to predict persistent AKI. Finally, we analyzed the renal trajectory between the two groups: those with persistent AKI and those without it.

Results: 305 patients were included, 23% developed persistent AKI post-OLT. Demographic characteristics, comorbidities, and perioperative variables are shown in Table 1. In the multivariate analysis, the significant variables are shown in Table 2. Mortality at hospital discharge was not different between the groups. In the analysis of the renal trajectories, the patients who presented persistent AKI had a lower eGFR with a median difference at 5 years of follow-up of 10ml/min/1.73m2.

Conclusions: In this present study, the factors associated with AKI development were: male gender, ascites drainage during surgery, diuretics <500ml in the first 24 hours post-OLT, use of antifungals, and antihypertensive >50 minutes. Long-term renal function in patients who developed persistent AKI deteriorated more compared to those who did not.
SA-PO076

AKI due to Acute Tubulo-Interstitial Nephritis and Diabetic Nephropathy in a Patient with Pulmonary Aspergillosis

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Case Description: A 45-year-old woman with diabetes mellitus, 8 years of evolution in poor control, asthma, and chronic smoking. Admitted with hyperglycemic crisis due to pneumonia: procalcitonin 0.3, Hb 16g/dl, WBC 16, albumin 3.74g/dl, SCr 0.79mg/dl, urea 25mg/dl, glucose 933mg/dl, HbA1c 14%. Patient presents cough, fever, hemoptysis, and dyspnea. A chest tomography with pulmonary infiltrates and cavitated nodules. Bronchoscopy reported Aspergillus. Management with liposomal amphotericin, presented acute kidney injury (Scr 5.3mg/dl). Renal biopsy reports: Acute tubulointerstitial nephritis (aTIN), Kimmelstiel-Wilson nodules. Management with pulsed methylprednisolone 250mg and IVIG. The drugs normally associated are NSAIDs, antibiotics, and proton pump. Both cases of AIN were associated with ciprofloxacin use. Among those with toxic ATI, 3 were due to vancomycin, 2 to ciprofloxacin, 1 to uric acid, 1 to contrast, 15 to cholemic tubulopathy, and 4 due to other drugs. Without consultation to nephrology). HRS-1 in 76 (32%), cardiorenal syndrome type 1 (CRS-1) in 6 (3%), abdominal compartment syndrome (ACS) in 2 (1%) and obstructive uropathy (OU) in 3 (1%). Parenchymal etiologies of AKI were noted in 137 (59%) of patients. Among parenchymal etiologies of AKI, ischemic ATI was the primary diagnosis in 78 (58%), toxic ATI in 26 (19%), ischemic/toxic ATI in 22 (16%), and AGN in 2 (1%). Among those with toxic ATI, 3 were due to vancomycin, 2 to ciprofloxacin, 1 to uric acid, 1 to contrast, 15 to cholemic tubulopathy, and 4 due to other drugs. Both cases of AKI were associated with ciprofloxacin use. Among those with AGN, 4 were biopsy-proven (3 IgA nephropathy, 1 immune complex-GN) and 3 were clinical diagnoses (2 IgA nephropathy, 1 SLE-GN).

Conclusions: Combinig toxic ATI (drug-induced, endogenous toxins), AGN, and non-traditional parenchymal causes of AKI accounted for 15% of the cases in this cohort of patients with ESLD and AKI. When added to CRS-1, ACS and OU, a total of 19% of the cases were not within the traditional 3-way split (PRA, HRS-1, ischemic ATI). We hypothesized that other parenchymal causes of AKI including toxic ATI, acute glomerulonephritis (AGN) and acute interstitial nephritis (AIN) may account for a small but not negligible proportion of cases of AKI in patients with ESLD.

Methods: We established prospective data collection in patients with ESLD with AKI stage ≥ 2 (AKIN) over 5-years who were seen by the nephrology consultation service. Demographic and clinical data were collected. Etiology of AKI was adjudicated based on history, clinical assessment, laboratory results, urine microscopy findings, and kidney biopsy data.

Results: We included 234 patients with AKI and ESLD. The median age was 57 (20-88), 37% were female, 76% were white, and 15% were black. CKD was a pre-existing comorbidity in 26%. PRA was the cause of AKI in 12 (5%) (low rate likely explained by resolution without consultation to nephrology). HRS-1 in 76 (32%), cardiorenal syndrome type 1 (CRS-1) in 6 (3%) abdominal compartment syndrome (ACS) in 2 (1%) and obstructive uropathy (OU) in 3 (1%). Parenchymal etiologies of AKI were noted in 137 (59%) of patients. Among parenchymal etiologies of AKI, ischemic ATI was the primary diagnosis in 78 (58%), toxic ATI in 26 (19%), ischemic/toxic ATI in 22 (16%), and AGN in 2 (1%). Among those with toxic ATI, 3 were due to vancomycin, 2 to ciprofloxacin, 1 to uric acid, 1 to contrast, 15 to cholemic tubulopathy, and 4 due to other drugs. Both cases of AKI were associated with ciprofloxacin use. Among those with AGN, 4 were biopsy-proven (3 IgA nephropathy, 1 immune complex-GN) and 3 were clinical diagnoses (2 IgA nephropathy, 1 SLE-GN).

Conclusions: Combinig toxic ATI (drug-induced, endogenous toxins), AGN, and non-traditional parenchymal causes of AKI accounted for 15% of the cases in this cohort of patients with ESLD and AKI. When added to CRS-1, ACS and OU, a total of 19% of the cases were not within the traditional 3-way split (PRA, HRS-1, ischemic ATI). Comprehensive diagnostic assessment is recommended in this clinical setting.

SA-PO077

Parenchymal and Nontraditional Etiologies of AKI in Patients with End-Stage Liver Disease

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Background: In the context of acute kidney injury (AKI) and end-stage liver disease (ESLD), AKI is frequently attributed to either hepatorenal syndrome type 1 (HRS-1), ischemic acute tubular injury (ATI), or pre-renal azotemia (PRA). We hypothesized that other parenchymal causes of AKI including toxic ATI, acute glomerulonephritis (AGN) and acute interstitial nephritis (AIN) may account for a small but not negligible proportion of cases of AKI in patients with ESLD.

Methods: We established prospective data collection in patients with ESLD with AKI stage ≥ 2 (AKIN) over 5-years who were seen by the nephrology consultation service. Demographic and clinical data were collected. Etiology of AKI was adjudicated based on history, clinical assessment, laboratory results, urine microscopy findings, and kidney biopsy data.

Results: We included 234 patients with AKI and ESLD. The median age was 57 (20-88), 37% were female, 76% were white, and 15% were black. CKD was a pre-existing comorbidity in 26%. PRA was the cause of AKI in 12 (5%) (low rate likely explained by resolution without consultation to nephrology). HRS-1 in 76 (32%), cardiorenal syndrome type 1 (CRS-1) in 6 (3%) abdominal compartment syndrome (ACS) in 2 (1%) and obstructive uropathy (OU) in 3 (1%). Parenchymal etiologies of AKI were noted in 137 (59%) of patients. Among parenchymal etiologies of AKI, ischemic ATI was the primary diagnosis in 78 (58%), toxic ATI in 26 (19%), ischemic/toxic ATI in 22 (16%), and AGN in 2 (1%). Among those with toxic ATI, 3 were due to vancomycin, 2 to ciprofloxacin, 1 to uric acid, 1 to contrast, 15 to cholemic tubulopathy, and 4 due to other drugs. Both cases of AKI were associated with ciprofloxacin use. Among those with AGN, 4 were biopsy-proven (3 IgA nephropathy, 1 immune complex-GN) and 3 were clinical diagnoses (2 IgA nephropathy, 1 SLE-GN).

Conclusions: Combinig toxic ATI (drug-induced, endogenous toxins), AGN, and non-traditional parenchymal causes of AKI accounted for 15% of the cases in this cohort of patients with ESLD and AKI. When added to CRS-1, ACS and OU, a total of 19% of the cases were not within the traditional 3-way split (PRA, HRS-1, ischemic ATI). Comprehensive diagnostic assessment is recommended in this clinical setting.
is immune reconstitution inflammatory syndrome (IRIS). AR can lead to a rapid decline in renal function, with serum creatinine within 1-2 weeks after ART initiation, and the reemergence of both memory and naïve CD4 T cells, which can sometimes lead to unmasking of opportunistic infections (OIs) by an exaggerated immune response. One of the earliest OIs unmasked after ART therapy is Mycobacterium avium Complex (MAC). MAC is present in the lungs of 35% of the patients, usually occurs 5cm, fevers, night sweats, fatigue, and significant weight loss. A biopsy of the enlarged left cervical lymph node 1 month after ART initiation revealed the presence of MAC infection. He was subsequently initiated on MAC therapy with azithromycin and ethambutol. Prior to the initiation of these antimicrobials, he was noted to have a CR 2.7 (baseline 0.8–1). His urine microscopy showed numerous RTE casts with abundant WBCs or WBC cast. Kidney biopsy was performed showing AIN with an infiltrate consisting of predominantly CD8+ T cells and histiocytes. He was then started on slow prednisone taper over months while continuing ART with eventually improving kidney function.

Discussion: MAC-associated IRIS is a rare cause of AKI in patients with HIV/AIDS. It presents after initiation of ART, making it sometimes difficult to differentiate from medication associated kidney injury. The injury pattern on kidney biopsy is AIN, which may not present after base urine on microscopy as in the case we described here.

SA-PO079

Late-Onset Shiga Toxin-Related Hemolytic Uremic Syndrome

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Introduction: HUS may occur after improvement of gastrointestinal tract symptoms, and we should carefully monitor for the onset of HUS, even if the patient has few symptoms.

Case Description: A 34-year-old male who had been started on Biktary after being diagnosed with advanced HIV (initial CD4 count 8, VL 119k). At the time of HIV diagnosis, he had signs and symptoms that included the following: left cervical lymphadenopathy with a predominant node measuring 5cm, fevers, night sweats, fatigue, and significant weight loss. A biopsy of the enlarged left cervical lymph node 1 month after ART initiation revealed the presence of MAC infection. He was subsequently initiated on MAC therapy with azithromycin and ethambutol. Prior to the initiation of these antimicrobials, he was noted to have a CR 2.7 (baseline 0.8–1). His urine microscopy showed numerous RTE casts with abundant WBCs or WBC cast. Kidney biopsy was performed showing AIN with an infiltrate consisting of predominantly CD8+ T cells and histiocytes. He was then started on slow prednisone taper over months while continuing ART with eventually improving kidney function.

Discussion: MAC-associated IRIS is a rare case of AKI in patients with HIV/AIDS. It presents after initiation of ART, making it sometimes difficult to differentiate from medication associated kidney injury. The injury pattern on kidney biopsy is AIN, which may not present after base urine on microscopy as in the case we described here.

SA-PO080

Associations Between Blood Pressure Variability and Renal Recovery and Mortality During Continuous Renal Replacement Therapy

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Background: Acute kidney injury (AKI) requiring dialysis is frequently occurred in critically ill patients, leading to chronic kidney disease progression and dialysis dependency. Blood pressure variability (BPV) has been known to contribute the development of AKI by impairing kidney perfusion. However, the association between short-term and long-term BPV and AKI recovery and mortality remains uncertain.

Methods: We enrolled the patients aged ≥18 years who underwent continuous renal replacement therapy (CRRT) due to AKI for ≥24 hours at Inha University Hospital from January 1, 2018 to December 31, 2020. Patients with end-stage kidney disease were excluded. We extracted 1-hour interval blood pressure records during CRRT and calculated several BPV parameters including standard deviation (SD), coefficient of variation (CV), average real variability (ARV), and variation independent of mean (VIM). Outcomes are in-hospital mortality and dialysis dependence at the time of discharge. Multivariable logistic regression and Cox proportional hazard analysis were performed.

Results: A total of 517 patients were included in the main analysis. Mean age was 69.7 years and male was 56.8%, and 52.2% were sepsis-associated AKI. Median duration of CRRT was 4 days. Multivariable logistic regression showed a significant association between four BPV parameters and dialysis dependence at discharge (SD, OR 1.94 [95% CI 1.07-3.50]; CV, OR 2.69 [95% CI 1.47-5.06]; VIM, OR 2.19 [95% CI 1.06-4.34]; ARV, OR 1.90 [95% CI 1.03-3.54]). These parameters also showed close associations with in-hospital mortality in cox-proportional hazard analysis (SD, HR 1.74 [95% CI 1.25-2.43]; CV, HR 2.17 [95% CI 1.55-3.03]; VIM, HR 1.77 [95% CI 1.27-2.47]; ARV, HR 1.65 [95% CI 1.17-2.32]).

Conclusions: BPV during CRRT was found to be an independent predictor of dialysis dependence at discharge and in-hospital mortality in AKI patients who underwent CRRT. Minimizing BPV during CRRT might be an important factor for recovery to dialysis independence and patient survival.

SA-PO081

Hope in Hardship: AKI in Haiti

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Background: AKI is a significant global issue, especially in low-resource areas with limited healthcare. Worldwide estimates suggest 13 million AKI occurrences/year with 1.7 million deaths, 85% in developing nations. In this study, we describe the presentation of AKI to a single healthcare center in Haiti and how collaboration can improve health care delivery for AKI.

Methods: The Hôpital Universitaire de Mirebalais (HUM), a 300 bed Partners in Health facility in rural Mirebalais has six residency programs. A partnership was formed between Beth Israel Deaconess Medical Center (BIDMC), Dartmouth Health and HUM focusing on educating internal medicine residents and staff through online presentations and short visits to Boston or Hanover for training in nephrology, urinalysis, HD, kidney biopsy, and bedside renal ultrasound. We planned that trainees would advance the ISN goal of eliminating preventable or treatable deaths from AKI by 2025.

Results: This program has enhanced the knowledge of medical residents and students in AKI management, electrolyte physiology, and HD, improving patient care and clinical outcomes at HUM. Between July 2021 to October 2022, 194 patients presented with AKI (11 cases/wk). Their mean age was 48 and main causes were heart failure (45%), glomerulopathy (26%), sepsis (12%) eclampsia (5%), other infectious diseases (e.g., leptospirosis, COVID-2, 2%), and volume depletion (2%). Due to lack of dialysis nurses, all HUM medical residents receive training in hemodialysis, and if the patient meets criteria for HD, a resident will initiate the procedure, performed without cost, as the majority of Haitians cannot afford dialysis. Of these 194 AKI patients, 19% had received HD of which 83% survived. The overall survival was 78%. Despite shortages of HD supplies and other medical equipment and inability to bring visiting professors to teach in Haiti due to multiple lockdowns and unrest, we have found alternative ways to receive shipments and to train our residents online. These residents become our future teachers, as with only 10 nephrologists for 11 million Haitians, the internists and general practitioners provide care for the large proportion of patients with AKI.

Conclusions: HUM, through education and training, in cooperation with BIDMC and Dartmouth, has provided care for patients with AKI, small victories that offer hope in managing hardship in Haiti.
Results: Of 144 participants, mean age 27 ±3.4 years, 62.2% were female and 45.5% Hemoglobin SS genotype. In a multivariable, black race, obesity (BMI ≥ 30 vs. < 30 kg/m²) and hospitalization were associated with inpatient SCr ≥ 2.0 mg/dL, using all inpatient SCr data available and the lowest value of the first three inpatient SCr. Study outcomes included (1) incidence and severity of AKI and (2) non-recovery from AKI: ESKD or kidney transplant who were admitted to the hospital from 10/2014 to 9/2017. Data were extracted from electronic health records of 3 large academic medical centers.

Background: Few studies showed higher incidence of AKI among Black patients compared to Whites but failed to adequately characterize this disparity. Further delineation on racial/ethnic risk of defined types of AKI could inform preventive interventions.

Methods: We describe a cohort of hospitalizations of pediatric and adult patients without prior kidney failure in Montefiore Health System, Bronx, NY, between October 1, 2014 to December 31, 2018. We defined community-acquired AKI (CA-AKI) as criteria met by KDIGO in first 48 hours of admission and hospital-acquired AKI (HAAKI) as a 48-hour window rise in creatinine defined by KDIGO occurring after 48 hours of admission and before discharge. We examined unadjusted logistic regression with HAAKI and CA-AKI as outcomes, race, as exposure, and sequentially adjusted variables accounting for comorbidities and in-hospital risk of mortality. We stratified multivariable adjusted models by in-hospital events according to: 1) severe illness: exacerbation of heart or liver failure, sepsis/shock, cardiac arrest and mechanical ventilation, 2) exposure to nephrotoxic agents: chemotherapy, diuretic use, diuretics and nephrotoxic chemotherapy, and 3) surgery: occurrence of cardiopulmonary, vascular, orthopedic or neurosurgery; to understand association of race with risk of HAAKI in each scenario.

Results: Of a total 286,383 hospitalizations, 42% were male, 11% were White, 29% were Black, and mean age was 48 years(SD:27). White patients [mean age 63 years(SD: 23)] were older than Black [51 years(SD:25)]. AKI occurred in 56,731 (20%) instances, of which 23,524 (41%) were HAAKI and 33,207 (59%) were HAAKI. Black patients were older than HAAKI [OR 1.21, (CI 1.17-1.27)] and lower risk for HAAKI [OR 0.92, (CI 0.89-0.96)]. Risk for HAAKI attenuated with addition of prior comorbidities, BMI and APR score, but remained significant [OR 1.13, CI (1.08-1.17)]. Black patients had higher odds of HAAKI than White patients when hospitalized with severe illness and underwent major surgery. There was no difference in HAAKI frequencies by agent exposure.

Conclusions: Black patients are at higher risk of HAAKI when hospitalizations involve severe illness or major surgery, and at lower risk of CA-AKI. Drivers of higher HAAKI risk among severely ill Black patients should be identified.

SA-PO085

Association of Black Race, Diabetes, and Obesity with AKI During Hospitalization in a Large Multicenter US Cohort

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Background: AKI is a common complication during hospitalization that is associated with morbidity and mortality. Whereas multiple studies have identified risk factors for the development of AKI in hospitalized patients, few have examined risk factors for the severity of AKI, including non-recovery of AKI.

Methods: Multicenter retrospective cohort study of patients a 18 years old without ESKD or kidney transplant who were admitted to the hospital from 10/2014 to 9/2017. Data were extracted from electronic health records of 3 large academic medical centers. Study outcomes included (1) incidence and severity of AKI and (2) non-recovery from AKI in those who survived the hospitalization. AKI was defined by KDIGO Scr-criteria, using the definition of hospitalization (the first three inpatient SCr) as the measurements as the baseline. Non-AKI recovery was defined in hospital survivors as persistent AKI stage a1 using the last SCR during the hospitalization or if the patient received dialysis within 72h of hospital discharge. We used multivariable logistic regression models to evaluate the association of black race, diabetes and obesity (BMI ≥ 30 vs. < 30 kg/m²) with the outcome, and of the each models was adjusted for 2 other of these main factors, and covariates such as study site, age, sex, baseline eGFR, and Elixhauser comorbidity score.
Hazard ratios for risk of progression to ESRD in CKD patients, Iodixanol emerges as a preferable choice to mitigate the risk of ESRD. Therefore, when considering contrast agents for these procedures, particularly in CKD patients, Iodixanol emerges as a preferable choice to mitigate the risk of ESRD.

**Table 2. Hazard ratios for risk of progression to ESRD**

**SA-PO087**

**Imaging Evidence of Contrast-Induced Nephropathy: A Case Report**

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**Introduction:** AKI after IV contrast media (CM) exposure has been reported since 1950. CKD and DM are two major risk factors associated with contrast-induced nephropathy (CIN). One of the mechanisms is that the hyperosmotic property of CM increases tubular fluid viscosity which leads to renal CM retention and eventually tubular and myocardial injuries. We report a case of CIN with a CT scan visualizing the prolonged CM renal retention.

**Case Description:** An 85-year-old man with HTN, DM II, CAD, and BPH was admitted for syncope with poor oral intake while taking furosemide. His initial serum BUN and serum creatinine (sCr) were 32mg/dL and 1.6mg/dL (baseline 1.3mg/dL). He received IV fluids (IVF) and furosemide was continued. sCr was 2.3mg/dL on day 2 when furosemide was stopped. sCr improved to 1.9mg/dL and he had CTA of chest to rule out pulmonary embolism with Onnpuqae 95 ml. His sCr rose to 3.5md/dL within 48 hours. After addition of Valsartan he became oliguric. Renal service recommended IVF, post void bladder scan and discontinuation of Valsartan, with differential diagnoses including CIN, pre-, and post-renal etiology. Urinary obstruction was ruled out. However his sCr continue to rise 3 days after IV contrast. A non-contrast CT of abdomen to evaluate lymphadenopathy revealed renal parenchyma significantly enhanced by contrast administered 5 days ago. His sCr worsened to 6.7mg/dL on day 10, with improved urine output and normal electrolytes. He had a cardiac arrest and passed away before planned RRT.

**Discussion:** We hypothesized that this patient developed CIN with risk factors of DM, AKI on CKD, dehydration, use of ARB and urinary retention, with CT scan 5 days after IV contrast still showing contrast in the renal parenchyma. This prolonged exposure to CM proved by imaging may have contributed to his severe renal injury. This case report provides imaging evidence and highlights the risk factors that are strongly associated with CIN.

**SA-PO088**

**Atorvastatin and Renoprotective Effects for Contrast-Induced Nephropathy Prevention (ARENA): A Pilot Feasibility Randomized Controlled Trial**

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**Background:** Contrast-induced acute kidney injury (CI-AKI) can complicate coronary angiography (CAG) that can lead to increased morbidity and mortality. Previous studies have shown the protective effects of high-dose statin pretreatment in various scenarios. However, the role of statins in preventing subclinical AKI is still under investigation.

**Methods:** We conducted a randomized controlled trial including 50 patients at stage G3-A, who were randomly assigned to receive either 80 mg of atorvastatin or placebo once daily for 2 days prior to undergoing CAG. The primary outcome was the change in urine NGAL concentration 6 hours after CAG compared to baseline. Secondary outcomes included the incidence of AKI based on serum creatinine criteria, changes in estimated glomerular filtration rate (eGFR) from baseline to 7 days after the procedure, and the occurrence of adverse events such as hepatitis and myositis. Additionally, an in-vitro study was conducted to explore the effect of radiocontrast on NGAL assay.

**Results:** The mean baseline eGFR was 53.4 ± 17.8 ml/min/1.73m², and 22 patients (44%) had not previously used statins. Percutaneous coronary intervention was performed in 19.1% of patients, and all participants received iso-osmolar contrast with a median volume of 37.5 ±30-80 ml. There were no significant differences observed in urine NGAL concentrations 6 hours after CAG between the atorvastatin and placebo groups (median [IQR] 4.4 [2.8-18.1] vs 6.6 [2.4-13.0], p = 0.9). The analysis also revealed no significant interaction with prior statin use, and no cases of CI-AKI were identified based on serum creatinine criteria. No adverse events were reported, and there were no significant increases in transaminase and creatine phosphokinase enzymes. The additional in-vitro study demonstrated no assay interference of radiocontrast in measuring urine NGAL.

**Conclusions:** The administration of high-dose atorvastatin as pretreatment of CAG was well tolerated in this study involving patients with early CKD and low-volume iso-osmolar contrast. However, the study did not demonstrate a renoprotective effect in this population, indicating a limited benefit for atorvastatin in this low-risk setting.

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

**SA-PO089**

**Spilling the Tea ON AKI**

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**Introduction:** Oxalate nephropathy (ON) is characterized by oxalate crystal deposition in the tubulointerstitium leading to acute kidney injury (AKI) and possible chronic kidney disease (CKD).1 We present two cases of ON from excessive black tea consumption with full recovery.

**Case Description:** Case 1: A 52-year-old diabetic male was admitted after two weeks of poor solid food intake complicated by three days of acute left-sided vision loss and creatinine 8.5 mg/dl (baseline 1.6 mg/dl). Urinalysis showed benign sediment without proteinuria. Renal ultrasound revealed no hydronephrosis. MRI orbit showed bilateral increased optic nerve enhancement. Renal biopsy demonstrated acute tubular injury with calcium oxalate deposits and underlying diabetic nephropathy (DN). He later reported consumption of 5.5 liters of black tea a day for several weeks. He had full recovery of his renal function 2 months later after complete cessation of black tea intake. He never regained left eye vision, which was likely due to acute oxalate vasculopathy. Case 2: A 70-year-old diabetic male was admitted for abnormal creatinine of 5.9 mg/dl (baseline 1.2 mg/dl) in the setting of one week of diarrhea. He denied toxic ingestion but had consumed large volumes of black tea for months to lose weight. He had a benign urinary sediment and enlarged kidneys on ultrasound (13 cm). Renal biopsy revealed ON changes associated with AKI.1 Avoidance of black tea led to full renal recovery within 4 months.

**Discussion:** Hyperoxaluria is defined as a urine oxalate level greater than 40-45 mg/ day.1 US diets contain approximately 150 mg/day of oxalate with intake over 1000 mg/day associated with toxicity.1 A recent 2020 study described 4.1% of biopsies in the New York City metropolitan area containing oxalate deposits, contributing to CKD progression in 3.6% of cases.1 Causes of hyperoxaluria include primary hyperoxaluria type 1 and 2, and secondary hyperoxaluria from nutritional deficiencies, increased intestinal absorption, impaired excretion, or excessive intake of oxalate-rich foods or precursors.1 Black tea contains 50-100 mg of oxalates per 100ml.1 Treatment of ON includes supportive care and calcium supplementation to bind intestinal oxalate. Over-ingestion of black tea is an underrecognized cause of acute ON. While acute ON can lead to residual CKD, our cases are notable for full renal recovery after timely cessation of the offending agent.
Outcomes of Intravenous Contrast Media on Patients with CKD: Systematic Review and Meta-Analysis

Ibrahim Tawhari, 1 King Khalid University of Medicine. King Khalid University, Abha, Saudi Arabia.

Background: Intravenous contrast media is frequently used in diagnostic and interventional procedures. Contrast-associated acute kidney injury (AKI) had been described as a complication associated with intravenous contrast media, which can lead to acute kidney injury and adverse clinical outcomes, especially in patients with underlying chronic kidney disease (CKD). However, this complication has been a subject of debate. The goal of this analysis is to evaluate the outcomes of intravenous contrast media use in patients with CKD.

Methods: A systematic search was conducted in PubMed, Scopus, ScienceDirect and Google Scholar for studies published from 2013 to March 2023. The reference lists of the included studies were also searched to retrieve possible additional studies.

Results: The meta-analysis included a total of 24 studies with a combined sample size of 278,908 participants. The pooled incidence of acute kidney injury in the OR was 0.85 (95% confidence interval [CI]: 0.75-0.95; P=0.005). In the association of dialysis and contrast media, had OR of 0.66 (95%CI: 0.26-1.69), p=0.39.

Conclusions: These findings suggest that contrast media use is not associated with a higher risk of acute kidney injury and dialysis needs in patients with chronic kidney diseases. Further research is needed to fully understand the potential risks of contrast media used in this patient population.

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SA-PO092
Preceding Veterans Aging Cohort Study Index Is Associated with AKI in Hospitalized People with HIV

Molly Fisher,1 David B. Hanna,2 Melissa Fazzari,1 Uriel R. Felsen,1 Christina M. Wyatt,2 Matthew K. Abramowitz,1 Michael J. Ross.1 Albert Einstein College of Medicine, Bronx, NY; 2Duke Medicine, Durham, NC.

Background: People with HIV (PWH) are at increased risk for acute kidney injury (AKI) and its sequelae. Numerous biomarkers have been shown to predict AKI but most are not routinely measured in practice. The Veterans Aging Cohort Study (VACS) index is a score based on age, CD4 count, HIV viral load, hemoglobin, eGFR, hepatitis C virus (HCV) antibody, platelets, and AST and ALT. The VACS index predicts a number of outcomes and is highly correlated with markers of inflammation, including TNF alpha and IL-6 which have been shown to be predictive of AKI. We therefore hypothesized that preadmission VACS index would be associated with AKI.

Methods: We performed a cohort study of 1,186 PWH hospitalized in a New York City health system between 2010-2019. Outpatient laboratory values prior and closest to admission (7-365 days) were used to create the VACS index. The VACS index was divided into quartiles (<22, >22 to 34, >34 to 55, >55). AKI was defined by KDIGO criteria.

Multivariable Cox regression adjusting for sociodemographics, diabetes and intensive care unit admission was used to determine the association between VACS quartile and risk of AKI, treating the competing risks of death and discharge as censoring events.

Results: Median age was 53 years (IQR 45, 60), 516 (43.5%) were women, 500 (42.2%) were Hispanic, 522 (44%) were non-Hispanic Black and 195 (23.1%) were coinfected with HCV. Median CD4 count was 465 cells/mm³ (IQR 201, 714) and 65% were virally suppressed (<200 copies/mL). The unadjusted AKI incidence was higher with increasing VACS quartile: 39 (10.7%) in Q1, 41 (18.6%) in Q2, 61 (28.1%) in Q3 and 107 (60.7%) in Q4. Compared to those in the lowest VACS quartile, the adjusted relative hazard (aHR) of AKI was 1.50 times higher (95% CI 0.96, 2.33; p=0.07) in Q2, 1.93 times higher (95% CI 1.28, 2.91) p=0.002) in Q3 and 3.23 times higher (95% CI 2.21, 4.74; p<0.0001) in Q4.

Conclusions: Preadmission VACS index is independently associated with AKI. The VACS index may allow for timely identification of PWH at risk for AKI and initiation of preventative strategies including intravenous fluids, avoidance of nephrotoxic medications and careful drug dosing. Our findings should be replicated in a larger cohort and future studies should evaluate its ability to predict severe AKI and nonrecovery from AKI.

Funding: Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSAs Grant #UL1TR001073

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SA-PO093
Unique Presentation of Hydrencephrosis of a Transplanted Kidney from an Inguinal Hernia

Alexander N. Fleischhacker,1 Shane W. Quo,2 Elissa Klein,1 Mary Parianos,1 Aakash Padodara,2 Ahmed A. Waheed.1 University of Miami Health System, Miami, FL; 2University of Miami, Coral Gables, FL.

Introduction: End stage renal disease (ESRD) increases morbidity and worsens quality of life. Kidney transplants improve clinical outcomes in ESRD. This is a unique case of a post-renal acute kidney injury in a transplanted kidney secondary to a common right inguinal hernia.

Case Description: A 56-year-old male with history of right inguinal hernia and right kidney transplant on immunosuppression presented to the ED with a tender inguinal hernia for two days and inability to completely void. Prior attempts to reduce the hernia had been successful and notably improved his urinary symptoms. However, he could not longer reduce the hernia. On arrival, the patient was found to have a creatinine of 1.81 (baseline 1.1) and BUN of 32. A CT abdomen and pelvis showed a right inguinal hernia containing the distal ureter of the transplanted kidney and portions of the bladder. (Figure 1.) General surgery was able to reduce the hernia. Once reduced, the patient began producing normal range urine output, and creatinine improved. He was transferred to a transplant facility for surgical evaluation. He underwent open inguinal hernia and incisional repair with mesh, which revealed bladder sidewall protruding through the hernia. Post-operatively, the patient continued to clinically improve, and his creatinine was near baseline.

Discussion: Kidney transplants provide an avenue without dialysis dependency and can increase life expectancy. We present a unique case of an AKI of a transplanted kidney due to complications from an inguinal hernia. Renal transplant recipients have unique changes to their anatomy, which can generate uncommon presentations of ordinary medical cases. We hope to raise awareness among physicians to diversify their differentials when encountering a transplant patient.
Kidney Failure Requiring Dialysis due to Renal Metastatic Spread from a Laryngeal Squamous Cell Carcinoma

Niklas Ayasse, Julian Marinez, Clara Daschner, Zoran Popovic, Anne Lammert, Bernhard K. Krämer. Universitätsklinikum Mannheim, Mannheim, Germany.

Introduction: Renal metastatic spread from laryngeal squamous cell carcinoma (SCC) is particularly rare. We here report the unique case of a patient with acute dialysis requiring renal failure due to diffuse metastatic spread of a laryngeal SCC.

Case Description: A 59-year-old man presented with progressive dyspnea, and anuria. His past medical history was remarkable for right sided supraglottic laryngeal SCC diagnosed two and a half years earlier. The histopathological work-up had revealed a squamous cell carcinoma (SCC). A radiochemotherapy had been effectuated and the patient had since then been in remission. The initial diagnostic workup revealed acute kidney failure AKI-3. Initially, a prerenal cause was assumed. Bedside sonography did not show urinary retention. Due to uremia symptoms intermittent hemodialysis was initiated. Since renal function did not improve, a percutaneous kidney biopsy was obtained. The histopathological work-up revealed squamous cell carcinoma infiltrates consistent with renal metastasis from the supraglottic laryngeal carcinoma (Figure 1). The neighboring healthy renal parenchyma showed only few vital glomeruli, without any signs of glomerular damage. We hence concluded that the origin of the kidney failure was a diffuse renal metastatic spread from the primary cancer. Due to persistent anuria, a tunneled dialysis catheter was placed and the patient was started on intermittent hemodialysis three a week.

Discussion: To the best of our knowledge, only 3 previous cases of renal metastasis from laryngeal SCC have been described in the literature (Paul, Harden et al. 1999, Leceouvre, Degardin et al. 2003, Erbag et al. 2013). In contrast to these previous reports dealing with unilateral renal metastasis, our patient case is unique in the way that both kidneys were diffusely infiltrated by metastasis, that led to end-stage kidney disease. This case report highlights that one should always consider renal metastasis as a cause of acute kidney failure in tumor patients.

Recurrent AKI for a Patient with Mutation in the MCP/CD46 Gene and Plasminogen Deficiency

Tariku T. Goda, Melissa Baker, Laura Ferreira Provenzano, Leal C. Herlitz, Robert J. Heyka, Xiangling Wang, Jonathan J. Taliercio. Cleveland Clinic, Cleveland, OH.

Introduction: Complement-mediated thrombotic microangiopathy (CM-TMA) is a systemic disease characterized by hemolytic anemia, thrombocytopenia, and organ damage including acute kidney injury (AKI). Some causes of CM-TMA occur from dysregulation of complement proteins leading to loss of function in regulators and gain of function in effectors. Pathogenic gene variants of plasminogen, a component of the coagulation cascade, are thought to play role for CM-TMA. We present a case report of a patient with plasminogen deficiency and mutation in MCP/CD46 gene presenting with recurrent AKI.

Case Description: 64 years old female patient with history of asthma, alopecia universalis and gout presented for evaluation of recurrent episodes of AKI. She reports around five episodes of AKI over 5 years. She required dialysis and steroids in two occasions with complete kidney recovery. Her symptoms start with nausea, vomiting and flank pain followed by gross hematuria. Past work up was notable for thrombocytopenia, elevated D-dimer and AKI. Kidney biopsies obtained in 2016 and 2019 revealed acute tubular injury without signs of thrombotic microangiopathy (TMA). During her most recent episode, she presented with similar symptoms. Labs showed Hgb 10.9 g/dl, platelet 78.1 K/μl (150 - 400), D dimer >35,200 ng/ml (< 500), creatinine of 4.9 mg/dl (0.6 - 1), LDH of 3417 U/L (135 - 214), haptoglobin <10mg/dl (31 - 238), plasminogen Assay 52% (69 - 137), plasminogen antigen 6.2 mg/dl (7.5 -15.5), schistocytes on peripheral smear, norma ADAM-13 and unrevealing bone marrow. Genetic testing showed a variant in MCP/CD46 gene and a variant in plasminogen. She was treated with steroids, fresh frozen plasma and IVIG for 3 days, and discharged on tapered dose steroids for a month. On subsequent follow up, her kidney recovered within a month.

Discussion: The exact interplay between individual coagulation factors and complement system is not well understood. Plasmin has been shown to have some inhibitory role on complement mediated hemolysis. Pathogenic variants of the coagulation proteins such as plasminogen is found to play a role in CM-TMA such as atypical hemolytic uremic syndrome. In this case, plasminogen deficiency is likely contributing to TMA from MCP/CD46 mutation warranting further studies for better understating.
SA-PO097
Clinical Characteristics and Outcomes of Urolithiasis

Sungyeun Kim,1 Young Eun Choi,1 Yookyang Jang,1 Suk Min Chung,1 Ko Yoon Sook,2 Lee Hee Young,3 Jihyung Yoon,4 Tai yeon Koo,4 Sewon Oh,1 Myung-Gyu Kim,1 Sung-Kyung Jo.1 Korea University, Seongbuk-gu, Republic of Korea; 2Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea.

Background: Recent studies have showed the incidence of urolithiasis is increasing and known to be associated with chronic kidney disease (CKD) and stage kidney disease (ESKD). Although kidney and urter stones are heterogeneous in composition, it is usually considered as single entity. The aim of this study was to compare the different clinical characteristics and outcomes of kidney/urter stone diseases according to compositions.

Methods: We performed a single center retrospective study of symptomatic stone formers with known stone compositions (n=758). Baseline characteristics, blood and urinary excretory profiles, prevalence of diverse comorbid conditions as well as acute kidney injury (AKI) and long-term outcomes including ESKD and death were compared.

Results: Mean age was 58.6 yrs with male predominance (64.5%). Calcium oxalate stone was the most common type (68%) followed by struvite stone (15.5%), uric acid stone (13%) and mixed stones. Uric acid stone formers were significantly older (69yrs) with male predominance (76.5%) and showed higher prevalence of diabetes mellitus, hypertension, ischemic heart disease and cancer. Calcium oxalate stone formers excrete significantly higher levels of glucose and calcium while uric acid stone formers showed lower urinary pH. Incidence of AKI was 36.3% and older age, hypertension, low total CO2, and uric acid stone were found to be independent risk factors of AKI. During the mean follow-up of 456 days, 33 (4.3%) progressed to ESKD and 35 (4.6%) died. AKI was found to be an independent risk factor for both ESKD and mortality regardless of stone composition.

Conclusions: Kidney stone disease is thought to be a heterogeneous condition with different clinical characteristics and long-term outcomes. Occurrence of AKI regardless of stone composition is an important predictor for adverse longterm outcomes. Better understanding of epidemiology, risk factors and pathogenesis of this heterogeneous conditions are needed.

SA-PO098
The Clinical and Pathologic Characteristics of Patients with Oxalate Nephropathy

María Linanos,1 Alvin G. Kwong,2 Lea C. Herlitz,2 Surafel K. Gebreselasie,2 Hanny Sawaf,2 Shane A. Bobart.1 1Cleveland Clinic, Cleveland, OH; 2Cleveland Clinic Florida, Weston, FL.

Background: Oxalate nephropathy (ON) is characterized by deposition of calcium oxalate crystals in the kidney and is commonly unrecognized. Causes of ON include primary hyperoxaluria, enteric hyperoxaluria and ingestion of excess oxalate or its precursors.

Methods: We report the clinical and pathological characteristics of the largest series of native kidney oxalate nephropathy to date, from January 2015 to March 2023 at the Cleveland Clinic.

Results: Of 11900 kidney biopsies, we identified 60 native biopsies with oxalate deposits and excluded patients with clinically insignificant insignificants (n=12) or lack of data (n=71). 31 patients with native oxalate nephropathy were described. The mean age at diagnosis was 66.2 years (±12.1) and 58% were female. 87.1% had hypertension, 58.1% had diabetes, 42% had nephrolithiasis, and 77.4% had underlying CKD with a mean baseline creatinine of 1.8 mg/dL ± 1.7. The mean creatinine at biopsy was 5.2 mg/dL ± 1.7. Patients with oxalate nephropathy were more likely to have high serum oxalate levels and severe proteinuria. The most common cause of death was renal failure (n=34), followed by myocardial infarction (n=7), stroke (n=5), and cancer (n=5).

Conclusions: Oxalate nephropathy presents as AKI or acute on CKD. The diagnosis is poor with most patients requiring dialysis at presentation with high morbidity and mortality. Clinicians need to be aware of the risk factors associated with oxalate nephropathy to aid prompt diagnosis and management.

Funding: Private Foundation Support

SA-PO099
Multifactorial Rhabdomyolysis in an HIV Patient: Management of AKI

Uma D. Gupta,1 Thi My Nguyen Nguyen, Saphal N. Subedi.1 Interface Medical Center, Brooklyn, NY.

Introduction: Rhabdomyolysis is common in HIV patients with drug abuse history, however literature is scarce regarding management. In our multifactorial rhabdomyolysis case, CK level is more than 100,000 with proteinuria, which is a rare presentation. The findings in our case highlight the importance of individualized management approach based on the underlying etiologies and the patient’s clinical status.

Case Description: In our case, a 32-year-old male with unknown past medical history presented to the emergency department with altered mental status. He was diagnosed with Strep Pneumonia, subsequently with HIV, HCV, polysubstance abuse (amphetamine, cocaine, and opiates) and later developed rhabdomyolysis with nephrotic range proteinuria. The patient received conservative treatment with 10-20 mL/kg of isotonic saline with 1 Liter of glucose 5% with 100 mmol of bicarbonate bolus. The goal was to maintain Urine output of 1 to 2 mL/kg/hour. Notably, there was a progressive improvement in the proteinuria, (from 4.5 grams per day to 1.45 grams per day). Considering the decline in proteinuria and the restoration of renal function, a renal biopsy was not planned at this stage. To support the patient’s nutritional needs, a high protein diet was administered via a nasogastric tube, targeting a dosage of 1-1.5 grams per kilogram of body weight.

Discussion: This HIV patient with rhabdomyolysis and nephrotic range proteinuria who developed AKI due to multifactorial causes was treated with various management strategies including pharmacological interventions targeting the specific etiologies, fluid therapy for volume resuscitation and electrolyte balance, and nutritional support. The efficacy of the conservative interventions was evaluated by improvement in renal function and reduction in proteinuria.

Trend of CK level

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Creatine Kinase Level trend

Protein Creatinine Ratio

SA-PO100
The Rise of Rhabdomyolysis in Philadelphia’s Fentanyl Crisis

Rami Bzeih,1 David Jimenez, Jean Lee, Avrum Gillespie. Temple University Hospital, Philadelphia, PA.

Background: Philadelphia has experienced a recent surge of fentanyl use and unintentional overdose, particularly the area served by the Temple University Hospital System (TUHS). Patients admitted to the hospital for overdose are often found to have rhabdomyolysis and acute kidney injury (AKI). While opioids like heroin have been previously associated with causing rhabdomyolysis, it is our belief that fentanyl has exacerbated this problem. In this study, we determine whether there has been a rise in patients developing AKI from drug-associated rhabdomyolysis that correlates with the 50% increase of fatal fentanyl overdoses in Philadelphia over the past 6 years.

Methods: We conducted a retrospective cross-sectional study to examine trends in fentanyl-associated rhabdomyolysis and AKI. Our sample comprised 1060 patients aged 18-60 admitted to TUHS for drug-associated rhabdomyolysis. Data were collected from electronic medical records and screened for inclusion criteria. Patients with end-stage kidney disease or a hospital stay of less than 24 hours were excluded.

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

SA-PO009
Multifactorial Rhabdomyolysis in an HIV Patient: Management of AKI

Uma D. Gupta,1 Thi My Nguyen Nguyen, Saphal N. Subedi.1 Interface Medical Center, Brooklyn, NY.

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Creatine Kinase Level trend

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SA-PO100
The Rise of Rhabdomyolysis in Philadelphia’s Fentanyl Crisis

Rami Bzeih,1 David Jimenez, Jean Lee, Avrum Gillespie. Temple University Hospital, Philadelphia, PA.

Background: Philadelphia has experienced a recent surge of fentanyl use and unintentional overdose, particularly the area served by the Temple University Hospital System (TUHS). Patients admitted to the hospital for overdose are often found to have rhabdomyolysis and acute kidney injury (AKI). While opioids like heroin have been previously associated with causing rhabdomyolysis, it is our belief that fentanyl has exacerbated this problem. In this study, we determine whether there has been a rise in patients developing AKI from drug-associated rhabdomyolysis that correlates with the 50% increase of fatal fentanyl overdoses in Philadelphia over the past 6 years.

Methods: We conducted a retrospective cross-sectional study to examine trends in fentanyl-associated rhabdomyolysis and AKI. Our sample comprised 1060 patients aged 18-60 admitted to TUHS for drug-associated rhabdomyolysis. Data were collected from electronic medical records and screened for inclusion criteria. Patients with end-stage kidney disease or a hospital stay of less than 24 hours were excluded.
Results: From 2016 to 2022, the incidence of drug-associated rhabdomyolysis at TUCH has increased from 8.8 cases per month to 16.4 cases per month. Among those cases, the incidence of AKI rose from 5.8 cases per month to 13.8 cases per month. The greatest increase was noted between 2019 and 2020 (6.5 to 10 cases per month). Fentanyl was first tested in late 2018, and 60% of included patients since then were tested for fentanyl. Of those who were tested for fentanyl, positivity rate steadily increased from 52% in 2019 to 75% in 2023. Since 2016, AKI cases associated with other opioids declined from 67% to 16%. AKI cases positive for cocaine has remained around 43%.

Conclusions: Our findings suggest a strong correlation between the increased incidence of drug-associated rhabdomyolysis and AKI at TUCH and rising fentanyl abuse. This correlation was not observed with other drugs included in toxicology screens. Further research is required to ascertain the potential contribution of adulterants such as xylazine and phencyclidine, and to develop effective harm reduction strategies to mitigate fentanyl-associated rhabdomyolysis and AKI.

SA-PO101

Hantavirus: A Rare Cause of Rhabdomyolysis
Pratiksha Singh,1 Katherine Toma,2 Rutgers Health Community Medical Center, Toms River, NJ; 3Jersey Coast Nephrology and Hypertension Associated LLC, Brick, NJ.

Introduction: Rhabdomyolysis has physical and nonphysical causes including toxins, trauma, and viral infections. Hantavirus presents flu-like symptoms and multisystem involvement including gastrointestinal, renal, and nervous systems.

Case Description: The patient is a 70-year-old male with a history of non-insulin-dependent diabetes, obesity, hyperlipidemia, arthritis, and chronic NSAID use who presented with altered mental status and inability to stand up after a fall eight hours prior. An initial examination found him disoriented, afebrile, and normotensive. Labs revealed a creatinine of 3.37 mg/dl and CK of 59100 U/L. CNS and renal imaging were all within normal limits. An initial examination found him disoriented, afebrile, and normotensive. Labs revealed a creatinine of 3.26 mg/dl and a urinalysis that was positive for hematuria. This prompted testing for hantavirus. The family, treated with aztreonam, vancomycin, cefepime, and empiric coverage with doxycycline. A follow-up examination found him disoriented, afebrile, and normotensive. Labs revealed a creatinine of 1.87 mg/dl and CK of 59100 U/L. CNS and renal imaging were all within normal limits. Further investigations revealed a strong correlation between the increased incidence of drug-associated rhabdomyolysis and AKI at TUCH and rising fentanyl abuse. This correlation was not observed with other drugs included in toxicology screens. Further research is required to ascertain the potential contribution of adulterants such as xylazine and phencyclidine, and to develop effective harm reduction strategies to mitigate fentanyl-associated rhabdomyolysis and AKI.

Investigations

Blood culture: Negative
Urine Culture: Negative
ANA: Negative
Anti-JE: Ab: Negative
P.N.C.: Ab: Negative
Antibody: Negative
Antidrug: Ab: Negative

Discussion: Hoarders are at increased risk of exposure to Hantavirus due to contact with rodent droppings, saliva, urine in poorly ventilated areas. This is easily missed unless emphasis is placed on social history, including hobbies. It is imperative to focus on The Social determinants of health for timely diagnosis and management.

SA-PO102

Assessing Discharge Communication and Follow-Up of AKI: An Opportunity for Quality Improvement
Bader Al-Zeen,1 Peter C. Birks,1 Daniel T. Holmes,2 Rami Elzayat,3 Mark Canney,2 Ognjenka Djurdjevic,2 Yuyan Dong,2 Samuel A. Silver,2 Adeera Levin.3 1The University of British Columbia Faculty of Medicine, Vancouver, BC, Canada; 2Queen’s University, Kingston, ON, Canada; 3University of Ottawa, Ottawa, ON, Canada; 4Provincial Health Services Authority, Vancouver, BC, Canada.

Background: Acute kidney injury (AKI) affects up to 20% of hospitalized patients and is associated with increased chronic kidney disease, mortality, and healthcare costs. Proper documentation of AKI in discharge summaries is critical for optimal monitoring and treatment of these patients once discharged. This study aimed to evaluate the accuracy and quality of documentation of episodes of AKI and then we performed a retrospective chart review of adult patients who experienced AKI during hospital admission between January 1, 2018, and December 31, 2019. Our findings suggest a strong correlation between the increased incidence of drug-associated rhabdomyolysis and AKI at TUCH and rising fentanyl abuse. This correlation was not observed with other drugs included in toxicology screens. Further research is required to ascertain the potential contribution of adulterants such as xylazine and phencyclidine, and to develop effective harm reduction strategies to mitigate fentanyl-associated rhabdomyolysis and AKI.

Methods: We retrospectively reviewed adult patient discharge summaries and identified AKI cases. We then reviewed the discharge summaries for documentation of episodes of AKI and then we performed a retrospective chart review of adult patients who experienced AKI during hospital admission between January 1, 2018, and December 31, 2019. Our findings suggest a strong correlation between the increased incidence of drug-associated rhabdomyolysis and AKI at TUCH and rising fentanyl abuse. This correlation was not observed with other drugs included in toxicology screens. Further research is required to ascertain the potential contribution of adulterants such as xylazine and phencyclidine, and to develop effective harm reduction strategies to mitigate fentanyl-associated rhabdomyolysis and AKI.

Discussion: This case highlights the importance of considering malakoplakia in the differential diagnosis of nephromegaly, even in young patients. It is usually described in patients above age 40 years and is associated with infections and immunosuppressed conditions. We present a case of renal malakoplakia in a young female in the setting of E. coli urinary tract infection (UTI).

Case Description: A 32-year-old female with a history of recurrent UTI, Raynaud’s phenomenon, COVID-19, presented with 2 days of shortness of breath and lower extremity weakness. On examination, she was afebrile, tachycardic, hypotensive with diffuse petechial skin rash and hepatosplenomegaly. Labs showed leukocytosis, anemia, thrombocytopenia and acute kidney injury with creatinine 6.4 mg/dl (baseline 0.64mg/dl). Blood culture grew E. coli. CT abdomen pelvis showed marked bilateral kidney enlargement and continuous renal replacement therapy was started in the setting of worsening septic shock. The differential diagnosis of enlarged kidneys includes diabetes mellitus, cystic disease and infiltrative disease like amyloidosis, lymphoma, IgG4 related disease, hemophagocytic lymphohistiocytosis and malakoplakia. HIV and TB testing were negative. Kidney biopsy demonstrated pyelonephritis with focal micro-abscesses and diffuse CD163 positive inflammatory infiltrate consistent with macrophage/histioctytic cells. Von Kossa stain was positive with round inclusions in histioctyes, typical of Michaelis-Gutman bodies. Biopsy findings consistent with Malakoplakia. She was treated with antibiotics, bethanechol and ascorbic acid with recovery of kidney function sufficient to stop dialysis. Given intermittent fevers, persistent leukocytosis and enlarging left renal abscesses on CT, she underwent left nephrectomy 2 months into hospitalization. She was discharged home on oral minocycline.

Discussion: This case highlights the importance of considering malakoplakia in the differential diagnosis of nephromegaly, even in young patients. It is due to defective phagocytosis by macrophages, although the underlying mechanisms remain unclear. Optimal therapy is uncertain, and this case emphasizes the importance of aggressive care.

SA-PO104

Kidney Epithelium Origin Cell-Free DNA: A Promising Biomarker in Prediction Sepsis-Induced AKI
Kuijian You,1 Xiangming Quan,2 Peng Xia,1 Huadong Zhu,3 Ling Yang,2 Enming Guo,1 1Peking Union Medical College Hospital, Dongcheng-qu, Beijing, China; 2GenePlus-Beijing, Beijing, China.

Background: Sepsis-induced acute kidney injury (SI-AKI) is a common complication of sepsis with a high morbidity and mortality, with the pathogenesis usually described in renal proximal tubule epithelial cells. We report the first case of a renal proximal tubule epithelial cell-derived cell-free DNA (cfDNA) sample that has been used as a biomarker for the prediction of AKI. This study aimed to evaluate the diagnostic correlation of Kidney-ep cfDNA samples for the prediction of AKI. We used a microfluidics-based technology to isolate cell-free DNA from blood samples and evaluated the diagnostic correlation of Kidney-ep cfDNA samples for the prediction of AKI. We used a microfluidics-based technology to isolate cell-free DNA from blood samples and evaluated the diagnostic correlation of Kidney-ep cfDNA samples for the prediction of AKI.

Methods: We extracted plasma cfDNA from 7 sepsis non-acute kidney injury (SN-AKI) and 9 SI-AKI patients for TET-assisted pyridine borane sequencing, used a reference methylation atlas of 40 cell types to analyze sequence reads to quantitate the relative contribution of cfDNA from different cell types by using the UXM fragment-level deconvolution algorithm. We multiplied the contribution by the total concentration of cfDNA, to obtain the concentration of Kidney-ep derived molecules. We determined the correlation of Kidney-ep cfDNA measures to SI-AKI, and then evaluated the diagnostic value of the Kidney-ep cfDNA. Differential methylation regions (DMR) were analyzed, and the standard GO/KEGG pathway enrichment analysis using these DMR-related genes.

Results: Of the 300 discharge summaries reviewed, 38 were excluded. AKI was documented in 362 summaries. AKI occurred in 362 (35%) of summaries had documented recommendations. In summaries that included medications typically held during AKI, only about half made specific reference to those medications. For those with NS-AIDS listed, 64% mentioned holding, and 9% mentioned a discharge plan. For those with ACEI/ARB, 38% mentioned holding these medications, and 46% mentioned a discharge plan. In ones with diuretics listed, 35% mentioned holding, and 51% included a discharge plan.

Conclusions: We found substantial quality and completeness of discharge reporting in patients hospitalized with AKI. This may contribute to inadequate follow up and post hospitalization care for this patient population. Strategies are required for increasing the presence and quality of AKI reporting in discharge summaries.
Results: Compared to healthy controls, all sepsis patients showed significantly elevated concentrations of cfDNA (P < 0.01). Compared to SN-AKI patients, SI-AKI patients had approximately 8.57-fold higher levels of cfDNA, consistent with the disorders of coagulation cfDNA (P = 0.022). The relative contribution and concentration of Kidney-ep cfDNA in SI-AKI patients was higher than in non-AKI patients (P = 0.003). The Area Under Curve (AUC) in differentiating SI-AKI from sepsis patients reached 0.9206, which was higher than that of the cfDNA concentration (0.9206 vs. 0.8889). Also, there was a significant negative correlation between the concentration of kidney-ep cfDNA and the number of days after being diagnosed with SI-AKI (R=0.81, P = 0.028). Except for coagulation dysfunction, the concentration of kidney-ep cfDNA was not affected by age, hypertension or septic shock (P>0.05). The pathways enriched the DMR genes, including complement and coagulation pathway, lymphocyte differentiation, etc.

Conclusions: Our study first showed the kidney-ep cfDNA is a novel biomarker of the SI-AKI diagnosis with real-time functional response.

SA-PO105
Chest Pain, Diarrhea, AKI, and Anemia: Uniting Them
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Introduction: Amyloidosis is a systemic disease with multiorgan involvement affecting 4000 Americans a year. Diagnosis is often delayed and overlooked. In this case a patient presents with many symptoms and a renal biopsy unites them.

Case Description: 69 year old male with pancreas and kidney transplant presents for chronic diarrhea for several weeks, chest pain, acute kidney injury (AKI) and anemia. GI panel positive for sapovirus. Cr improves with IV fluids but with ongoing diarrhea coloscopy is done showing edematous colon. Chest pain persists and catherization showed 60% proximal stenosis of the LAD and 40% left circumflex and RCA stenosis. He is discharged on aspirin. One week later, he has a rash and AKI with a Cr of 13.3. UA has eosinophils and cholesterol emboli is diagnosed. Dialysis is initiated and patient transferred for renal biopsy which is performed. The glomerulus had diffuse mesangial expansion by eosinophilic, amorphous, acellular material, walls of arteries and arterioles were expanded by the same material (Figure 1A). A Congo red stain was positive in glomeruli, arteries, and arterioles (Figure 1B). This is consistent with AL amyloidosis, lambda light chain type. Bone marrow biopsy shows plasma cell neoplasm involving 40 to 50% of bone marrow. Cardiac MRI is consistent with amyloid. Colon biopsy positive for amyloid. Patient was started on chemotherapy but expired.

Discussion: Amyloidosis is deposition of insoluble amyloid proteins that form B-pleated sheets. AL amyloidosis is caused by monoclonal kappa light chains. Light chains deposit in many organs and can present as anasarca, GI bleeding, dysphagia, weight loss, portal hypertension, diarrhea, chest pain, arthrythmia and macroglossia. Diagnosis requires a biopsy of a fat pad or bone marrow and undergo evaluation for extent of organ involvement with MRI, coloscopy and skin biopsy. In this patient, due to his history of transplants, his work up was focused on infectious etiology for diarrhea. With the rarity of this disease, many are diagnosed late or not at all, which is why it is important to consider a unifying diagnosis for what may appear to be independent disease processes.

SA-PO106
Properaive Serum Creatinine-to-Cystatin C Ratio and Risk of AKI After Cardiac Surgery
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Background: Postoperative acute kidney injury (AKI) is a serious complication after cardiac surgery, but risk stratification measures are limited. Decreased muscle mass is linked to negative outcomes, including kidney disease, in various clinical settings. More recently, the creatinine to cystatin C (Cr:Cys) ratio has shown correlation with muscle mass in several patients populations. This study aims to explore the association between preoperative serum Cr:Cys ratio and postoperative AKI in cardiac surgery patients.

Methods: Patients aged ≥ 18 years who underwent cardiac surgery at two tertiary hospitals between 2006 and 2020 were retrospectively evaluated. Their preoperative serum Cr:Cys ratios were categorized into quartiles. Primary outcomes were postoperative mild AKI (KDIGO stage 1) and moderate-severe AKI (KDIGO stage 2-3). Secondary outcome was length of hospital stay.

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

Results: Of the 2,354 enrolled patients (median age, 67.0 years; male, 65.2%), mild AKI and moderate-severe AKI were noted in 803 (34.1%) and 150 (6.4%) patients, respectively. Patients with higher Cr/Cys ratio had lower frequency of postoperative AKI and shorter lengths of hospital stay. Logistic regression analysis revealed that the odds ratios (ORs) [95% CI] for postoperative mild AKI and moderate-severe AKI decreased in a stepwise manner towards higher Cr/Cys ratio quartiles (mild AKI Q2, 0.77 [0.61-0.97]; Q3, 0.75 [0.59-0.95]; Q4, 0.62 [0.49-0.79]; moderate-severe AKI: Q2, 0.67 [0.43-1.02]; Q3, 0.45 [0.28-0.73]; Q4, 0.54 [0.34-0.85] relative to the Q1, both P for trend <0.001. These associations were maintained after adjusting for confounding factors. Multivariable logistic regression analyses revealed that patients in the 4th quartile of the Cr/Cys ratio had shorter hospital stay (-3.32 days, 95% CI, -5.34 to -1.30) stay than those in the 1st quartile.

Conclusions: Higher preoperative Cr/Cys ratios were associated with a lower risk of AKI development after cardiac surgery.

SA-PO107
Determination of Urinary Neutrophil Gelatinase-associated Lipocin (NGAL) Reference Intervals for Healthy Adult and Pediatric Individuals
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Background: Neutrophil gelatinase-associated lipocin (NGAL) is a 25kDa protein implicated in multiple biological processes, including attenuation of apoptosis and differentiation of renal tubule epithelial cells and nephrons. NGAL is also produced and secreted by injured kidney tubule epithelial cells. As such, NGAL can serve as an early biomarker for acute kidney injury (AKI). This multi-site, cross-sectional study aimed to establish reference intervals for urinary NGAL (uNGAL) in healthy pediatric and adult populations using a particle-enhanced turbidimetric assay.

Methods: Apparently healthy individuals, aged ≥3 months, were eligible for this study. Subjects with urinary tract infections, acute kidney injury (AKI) or a history of AKI, stage 4 or 5 chronic kidney disease (CKD), known congenital anomalies of the kidney and urinary tract, known urothelial, urological, or kidney malignancies were excluded from the study. Subjects with uncorrected congenital heart disease, having undergone solid organ or bone marrow transplantation, receiving renal replacement therapy, and having undergone surgery (urologic, nephrectomy, or correction of congenital heart disease) were also excluded. Six hundred eighty-eight (688) subjects were screened, 677 were eligible, and 629 (91.4%) were considered evaluable. Urine samples were collected and tested for NGAL, uNGAL, and UTI.

Results: The following table describes the NGAL summary statistics and upper 95th reference intervals by age and gender.

Conclusions: These data demonstrate the normal urine NGAL reference intervals in apparently healthy pediatric and adult populations.

Funding: Commercial Support - BioPorto A/S

SA-PO108
Improved Outcomes with Early Nephrology Consultation After Biomarker Measurement
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Background: Novel urinary biomarkers, including Tissue Inhibitor Metallo-protease-2 and Insulin-like Growth Factor Binding Protein 7 ([TIMP]-2)[[IGFBP7], T2*], have been developed to predict which patients are at risk for stage 2/3 AKI. While T2* MRI is approved as a risk stratification tool, data on its “real-world” use in conjunction with Nephrology consult and impact on AKI care is lacking.

Conclusions: These data demonstrate the normal urine NGAL reference intervals in apparently healthy pediatric and adult populations.
Methods: We conducted a single-center prospective quality improvement study of ICU patients at risk for AKI or with KDIGO serum creatinine (SCr) stage 1 AKI. T2* measurements and Nephrology consults were at the discretion of the primary ICU team. ICU providers were given KDIGO AKI-guideline-based practice recommendations based on T2*7 results.

Results: Of 116 patients, 86(74%) had elevated T2*I7. Of those, 30(26%) patients received nephrology consultation, 20 of whom had consultation within 1 day of T2*I7 measurement (early consult), and 10 had consultations on days 2 or later (delayed consult). Patients with early and delayed consultations had similar T2*I7 values (mean(SD) 3.0(3.1) vs 3.0(2.9), p=0.89), SCr at T2*I7 measurement (2.0(0.7) vs 2.0(0.5), p=0.75). Despite more exposure to nephrotoxins, patients with early consults had significantly lower incidence of severe AKI, less dialysis, and improved mortality (p<0.05 for all) (Table). With renal consultation, T2*I7 was a poor predictor of severe AKI in days (AUC 0.50(0.32-0.79), p=0.61).

Conclusion: Despite similar baseline characteristics and biomarker values, early nephrology consults were associated with improved outcomes and diminished the ability of T2*I7 to predict severe AKI. Future studies should continue to investigate if early kidney care, prompted by T2*I7, is beneficial in high-risk AKI patients.

SA-PO110

Mortality Associated with the Neutrophil-Lymphocyte Ratio in Septic AKI Requiring Continuous Renal Replacement Therapy

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Background: Sepsis is an important cause of acute kidney injury in intensive care unit (ICU) patients, accounting for 15-20% of renal replacement therapy prescriptions. The neutrophil-lymphocyte ratio, a marker of systemic inflammation and immune response, was previously associated with the mortality rate in multiple conditions. Herein, we aimed to examine how the neutrophil-lymphocyte ratio relates to the mortality rate in septic acute kidney injury patients requiring continuous renal replacement therapy.

Methods: Neutrophil-lymphocyte ratios of 6 and 18 were used for dividing patients into low (<6), medium (6≤18), and high (>18) groups. Multiple regression analysis by identifying independent prognostic factors. The diagnostic ability was calculated using receiver operating characteristic (ROC).

Results: A total of 798 septic acute kidney injury patients requiring continuous renal replacement therapy were classified into three neutrophil-lymphocyte ratio groups: low (< 6), medium (6 ≤ x < 18), and high (x ≥ 18). The in-hospital mortality rates per group were 83.4%, 74.8%, and 70.4%, respectively (Table 1, P < 0.001). The in-hospital mortality rates per group were 83.4%, 74.8%, and 70.4%, respectively (Table 1, P < 0.001). Per the univariable Cox survival analysis after propensity score matching, a high neutrophil-lymphocyte ratio was related to approximately 24% reduced mortality. The survival benefit of high neutrophil-lymphocyte ratio group compared with the other two groups remained consistent across all subgroups, showing any P for interactions > 0.05.

Conclusions: A high neutrophil-lymphocyte ratio is associated with better clinical outcomes, such as low mortality, in septic acute kidney injury patients undergoing continuous renal replacement therapy.

Mortality outcomes according to the NLR results

SA-PO111

Risk Prediction Score for AKI in Critically Ill Septic Filipinos Patients Admitted in Perpetual Succour Hospital: An Analytical Prospective Cohort Single-Center Study

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Background: Acute kidney injury (AKI) is a lethal complication of critical illness characterized by the rapid loss of the kidney’s excretory function encountered in 50% of intensive care unit (ICU) admissions. Its impact on the outcome of critically ill patients makes AKI a significant cause of morbidity and mortality.

Methods: This is a prospective cohort study conducted in a tertiary hospital in Cebu from February to September 2020. The data of 2545 patients were identified by chart review but only 607 patients with a quick Sepsis Organ Failure Assessment Score (qSOFA) score of ≥2 were included in the pre-screening. A total of 198 septic ICU patients were enrolled. Demographic profile, laboratory results and outcome data were collected. Variables were screened then stepwise forward elimination was done to identify the significant predictors. An AKI risk score model was developed with binomial regression analysis by identifying independent prognostic factors. The diagnostic ability of the model was determined by the Area under the Receiver Operating Characteristics (AUC).

Results: AKI developed in 155 (78%) patients. The significant predictors for Acute Kidney Injury were age, hypertension, atherosclerotic cardiovascular disease, weight, white blood count, creatinine, and BUN. An AKI prediction model with a cut-off score of 161.9 was made with a fair diagnostic ability for predicting AKI at 0.79 based on AuROC.

Conclusions: The developed risk prediction tool using routinely available variables is found to be fairly accurate to predict the development of AKI among critically ill septic patients. This can aid clinicians to identify high risk population and will provide strategies for prevention, early diagnosis and treatment.
SA-PO112
Metabolomics Analysis and Classic Biomarkers to Predict Mortality in Patients with AKI and Kidney Replacement Therapy
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Background: Acute kidney injury (AKI) requiring kidney replacement therapy (KRT) is associated with mortality in critically ill patients. Serum metabolic biomarkers and markers of tubular damage might differentiate patients with a high risk of mortality.

Methods: Prospective cohort study of patients with critical COVID-19 in intensive care units (ICU) with invasive mechanical ventilation (IMV) and who required KRT admitted to Mar 2020 - Feb 2022. Patients with CKD stages 4 or 5 and kidney transplant were excluded. Urine SerpinA3, KIM-1, nGAL, HSP-72, and metabolomics analysis were measured on day 0 (start of KRT). Serum IL-6, IL-10, and TNF-alpha were also measured on day 0.

Results: Sixty patients were included, 52% died before discharge. The parameters measured at the beginning of the KRT were not different between living and dead patients (Fig 1). Of the urinary biomarkers studied, KIM-1 was the best mortality predictor (Fig 2a). The rest of the biomarkers had AUC scores 0.5-0.6 to predict this outcome. In the discriminant analysis of differential metabolites between the living (HD-A) and the dead (HD-D), p-cresol glucuronide was present in higher amounts in HD-D (Fig 2b).

Conclusions: In this study it was observed that KIM-1 was the best predictor of mortality. In the metabolomics analysis, p-cresol glucuronide was the metabolite present in highest amounts among the deceased patients.
SA-PO115
Plasma Humanin Level in AKI and CKD Patients
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Background: Humanin is a mitochondrial-derived cytoprotective peptide that reflects mitochondrial damage. Its level in the plasma of patients with AKI and CKD has not been reported yet. We aimed to determine the diagnostic value of humanin for kidney injury.

Methods: A total of 188 patients with kidney disease and 32 healthy controls were collected. Patients with kidney disease were divided into AKI group (n=54) and CKD group (n=134) according to KDIGO definition. The plasma humanin level of each group was detected by enzyme-linked immunosorbent assay (ELISA). A ROC curves were used to analyze the diagnostic performance of humanin for AKI and CKD.

Results: A total of 188 patients (54 AKI, 134 CKD) and 32 healthy people were studied. The plasma humanin level in the AKI group of the plasma AKD patient was significantly higher than that in the healthy control group (57.29±79.6 pg/mL vs 29.6 ± 18.8 pg/mL, p=0.0066 and 32.9±73.61 pg/mL vs 29.6 ± 18.8 pg/mL, p=0.0164, respectively). On the basis of receiver-operating characteristic analysis, humanin could predict AKI and CKD (area under the curve (95% confidence interval) 0.809 (0.74-0.94) and 0.620 (0.52-0.71), respectively). A cut-off point >413.2 pg/mL for humanin had a sensitivity of 0.78 and specificity of 0.91 in predicting AKI and a cut-off point >841.4 pg/mL for humanin had a sensitivity of 0.38 and specificity of 0.89 in predicting CKD.

Conclusions: Humanin is expressed in patients with AKI and CKD and may be a novel biomarker in response to kidney damage.

Funding: Government Support - Non-U.S.

SA-PO116
Dickkopf-3, a Key Driver of Renal Fibrosis, Is Increased in the Urine of Patients with AKI
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Background: The WNT–β-catenin system, an evolutionary conserved signaling pathway involved in morphogenesis and cell organization during embryogenesis, is usually suppressed in adulthood but can be re-activated in organ injury and regeneration. Dickkopf (DKK) proteins serve as inhibitors of WNT–β-catenin signaling. Animal models showed that DKK-3 is released by ‘stressed’ tubular epithelial cells and drives kidney fibrosis. However, the role of DKK-3 in human acute kidney injury (AKI) remains unknown. In the present study, we measured urinary DKK-3 in patients with AKI to test if urinary DKK-3 is useful to monitor the degree of tubular damage and/or recovery in human AKI.

Methods: AKI patients (n=66) who were treated in our department (December 2020 to December 2022) and healthy adults (n=16) were enrolled in this study. Written informed consent was obtained from all patients. Serum and urinary DKK-3 were measured by ELISA. The correlation of urinary DKK-3 with renal function, urinary protein level, clinical parameters and various AKI biomarkers was analyzed. This study was approved by the Ethics Committee on Human Research of our institutions (Approval number 2487).

Results: Compared to healthy subjects, urinary DKK-3 was significantly increased in AKI (1.02 ± 0.06 vs 10.5 ± 1.26 ng/mL, p<0.001). There was no significant difference in urinary DKK-3 level between prerenal and renal AKI, but there was a significant increase according to the stage of AKI. There is a significant correlation of urinary DKK-3 with serum creatinine level, eGFR, urinary NGAL, and urinary bet2-microglobulin, but not with urinary protein level, urinary KIM1, or urinary NAG. Among the causes of AKI, urinary DKK-3 was markedly increased in patients with microscopic polyangiitis, in which urinary DKK-3 was significantly decreased after therapeutic intervention. In cases of kidney transplantation recipients, urinary DKK-3 was markedly increased 1 day after transplantation but was decreased and became undetectable thereafter.

Conclusions: Urinary DKK-3 might be useful as a marker reflecting tubular damage as well as interstitial fibrosis in patients with AKI.

SA-PO117
Urinary DcR2/Cr Level Predicts Renal Outcome in Patients and Mouse Models with AKI
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Background: Acute kidney injury (AKI) is a well-recognized complication of critical illness with poor prognosis. Decoy receptor 2 (DcR2), a senescent marker, is expressed specifically in senescent tubular epithelia. The aim of study is to investigate the association of urine DcR2 with renal outcome of AKI.

Methods: 153 biopsy-proven AKI patients were included from Daping Hospital, Army Medical University from January 2018 to October 2022. A composite renal endpoint included creatinine more than 50% higher than the baseline or ESRD after 90 days. All patients were divided into positive endpoints (n=75) and negative endpoints (n=78). The clinical characteristics were collected, and the uDcR2 levels were measured and related to urine creatinine (uCr) and renal outcome. Univariate logistic regression and Kaplan-Meier curves, we explored the relationship between uDcR2/Cr and kidney outcome. We used experimental animals to further verify, and mice were randomly divided into 3 groups as follows: control, cisplatin, and aristolochic acid.

Results: The level of uDcR2/Cr was positively correlated with cystatin C and renal pathological acute scores, and negatively correlated with eGFR. Univariate logistic regression results increase the risk factors for poor kidney prognosis are age, female, with hypertension or (and) CKD, eGFR, Cystine C and uDcR2/Cr. Multivariate logistic regression analysis showed that the effect of uDcR2/Cr on renal outcome was statistically significant. After a median follow-up of 16 months, 75 participants achieve endpoint. The ROC curve was used to analyze the value of uDcR2/Cr for predicting kidney prognosis in AKI with an area under the curve of 0.72 and the cut-off value of 365 ng/g Cr. The median time from at the time of AKI to endpoint in the uDcR2/Cr ≥365 ng/g Cr group (7.6 months) was significantly shorter compared to the uDcR2/Cr <365 ng/g Cr group (36.6 months). To explore the trend of uDcR2 levels after AKI, uDcR2/Cr levels increased at 3d in cisplatin-induced and aristolochic acid-induced AKI models compared with the control group, and the levels at 7d and 21d were still higher in the two models.

Conclusions: Urinary DcR2/Cr is closely associated to kidney injury and renal prognosis of AKI, suggesting that uDcR2/Cr could serve as a novel biomarker for predicting adverse outcomes in patients and mouse models with AKI.

Funding: Private Foundation Support

SA-PO118
Effects of Lanosterol Synthase Gene on the Development of AKI After Cardiac Surgery
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Background: Acute kidney injury (AKI) is a common post-surgery complication, significantly affecting morbidity and mortality. Recent studies reported that high plasma levels of endogenous ouabain (EO) are associated with worse kidney outcomes after cardiac surgery. Our group demonstrated that EO activity is affected by a missense variant (rs2254524 C → A, Val642Leu) in Lanosterol Synthase (LSS) gene. This work aims to analyze the relationship between this LSS polymorphism and the development of AKI after cardiac surgery.

Methods: 1237 patients undergoing elective cardiac surgery were enrolled in the study. For each patient, preoperative biological samples and LSS genotypes were collected. Primary outcome was AKI development according to KDIGO guidelines. Results: 21.4% of patients developed AKI. Different preoperative clinical variables were analyzed, identifying five independent elements significantly correlated to AKI in multivariate logistic regression analysis: age (p<0.001), FE (p<0.005), NYHA class (p<0.001), reoperation (p=0.002) and complex surgical intervention (p=0.001). No significant differences were observed between preoperative EO plasma levels and allelic variants of the LSS gene; moreover, patients with the less common A allele were not associated with a more severe preoperative clinical presentation, expressed as EuroScore. LSS AA and AC variants (A) turned out to be significantly associated with the incidence of AKI (AA=29.3%; AC=25.3%; CC=17.2%; X2=3.71; p=0.03). This evidence remains significant after correction for covariates associated with AKI previously reported (Log regression p=0.002; RR for AA variant: 2.09 IC95% 1.15-3.78).

Conclusions: Patients with at least one mutated allele of the LSS variant have a higher probability of developing AKI after cardiac surgery. We think these results could be of interest to further understand cellular mechanisms underlying AKI development.
SA-PO119

Low Cardiac Output During Cardiac Surgery Is Associated with Renal Tubular Injury Measured by Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL)


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Background: Low cardiac output (CO) during cardiac surgery may contribute to renal hypoperfusion and AKI. It is challenging to associate intraoperative low CO to renal injury using serum creatinine as it is non-sensitive to injury and its increases are delayed by 24-48 hours after surgery. We assessed the relationship between low CO and urinary neutrophil gelatinase-associated lipocalin (NGAL), which is a sensitive marker of renal tubular injury.

Methods: We enrolled 30 patients with preserved left-ventricular ejection fraction undergoing coronary-artery bypass graft to collect urine samples at baseline, after cardiopulmonary bypass, and at intensive care unit (ICU) arrival. Cardiac index (CI) was calculated from continuous arterial waveform analysis that generates CI every five seconds and value of <= 2 L/min/m² was used as the threshold for low CI. We used the Meso Scale discovery platform to assess NGAL.

Results: Mean age was 62.7+/- 8 and 28% were female. On average, 210 ± 58 minutes of CI readings were available on each patient. Mean Low CI was 100.1 ± 73 minutes per patient. Figure 1a shows log2 NGAL at the three timepoints. Mean (SD) change from baseline to ICU arrival was (3.27 +/-3.89) pg/mL. On multivariable regression analysis adjusted for age, sex, and minutes MAP<65mmHg, each 10 minutes of CI <2 L/min/m² was associated with increased NGAL (beta 0.2; p=.078, fig. 1b). There was minimal association between changes in serum creatinine and low CI.

Conclusions: Low CO during cardiac surgery appears to be associated with renal tubular injury and can be detected by urinary NGAL. This finding was independent of exposure to hypotension (minutes/MAP of 65 mmHg). Additional investigation of low CO and NGAL are warranted.

Figure 1: (a) Log2 NGAL increases from baseline (0), after cardiopulmonary bypass (1) to ICU arrival (2). (b) Low CI is associated with change in NGAL from baseline to ICU arrival.

SA-PO120

Association Between AKI and Biomarkers KIM-1, Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Cystatin C in Patients Undergoing Cardiac Surgery


Background: Patients undergoing cardiac surgery are at risk of developing acute kidney injury (AKI), which negatively impacts short and long-term clinical outcomes. Biomarkers that provide earlier detection of AKI may allow for timely intervention.

Urinary excretion of kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C (CysC) is increased during experimental AKI. We investigated the association between these biomarkers and AKI in patients undergoing elective coronary artery bypass graft (CABG) and/or valve surgery on CPB.

Methods: Urine and plasma samples were collected from 121 adult patients who participated in a Phase 2 study designed to test the ability of an investigational drug (RBT-1) to induce an organ preconditioning response and prevent post-operative complications. AKI was defined as a ≥1.5X increase in serum creatinine (sCr) or oligoanuria through post-op Day 5 or need for dialysis. The study was neither powered nor enriched to test for potential RBT-1-induced AKI protection. Urine and plasma KIM-1, NGAL, and CysC were measured through post-op Day 3.

Results: Of the 121 patients, 22 (18.2%) developed AKI. Urinary levels of KIM-1 (uKIM-1) and CysC (uCysC) were higher in patients who did not develop AKI post-operatively (uKIM-1: 6.27 ng/mL vs 14.41 ng/mL [p=0.013]; uCysC: 2.92 ng/mL vs 6.45 ng/mL [p=0.011] for AKI vs No AKI). While uNGAL was higher in those who developed AKI (10.30 ng/mL vs 6.41 ng/mL), this result was not statistically significant (p=0.472).

Correlation analyses indicated no relationship between max post-op sCr and uKIM-1 (r=0.0572), uCysC (r=0.2953), or uNGAL (r=0.3176). In contrast, plasma levels for these biomarkers were higher in patients who developed AKI post-op (KIM-1: 158 pg/mL vs 101 pg/mL; CysC: 2.39 mg/L vs. 1.61 mg/L; NGAL: 185 ng/mL vs. 126 ng/mL). Correlation analysis also showed a stronger relationship between max post-op sCr and plasma levels of CysC (r=0.7771, p<0.0001) and NGAL (r=0.7585, p<0.0001) at Day 3; no correlation was observed with KIM-1 (r=0.2941, p=0.001).

Conclusions: Urinary KIM-1, NGAL, and CysC did not correlate with AKI in this cohort of adults undergoing cardiac surgery. Plasma KIM-1, NGAL, CysC levels may hold greater promise and should be studied further.

Funding: Commercial Support - Renibus Therapeutics

SA-PO121

Exploring Lipid Biomarkers of Cardiac Surgery-Associated AKI Based on Lipidomics

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Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequently occurring complication. Lipids played important roles in many biological pathways and could work as biomarkers of disease. The purpose of this study was to explore lipid biomarkers of CSA-AKI.

Methods: Plasma samples were collected when patients admitted to the ICU after cardiac surgery from 24 CSA-AKI patients and 31 controls. Lipidomic approach based on liquid chromatography mass spectrometer (LC-MS) was used to analyze plasma lipidomic alterations and potential biomarkers for CSA-AKI patients. Univariate and multivariate statistical analyses were utilized to screen the differential lipids between two groups.

Results: Lipidomics analysis detected 4053 lipid species totally. Differentially expressed lipids were screened based on the criteria variable importance at projection (VIP) value > 1, p value < 0.05, and fold change (FC) > 1.5 or < 0.67. Lipidomics identified that 65 lipids satisfied the criteria. The volcano plot showed the results of differential expression of lipids (figure 1). Heat map presented the relative levels of lipids (figure 2).

Conclusions: Lipidomics profiles could change significantly in CSA-AKI patients, and some lipid species were notably upregulated in the early stage of CSA-AKI, which could serve as potential biomarkers for CSA-AKI.
SA-PO122
Intra-Operative Shedding of Endothelial Glycocalyx in Cardiac Surgery-Associated AKI: A Prospective Longitudinal Cohort
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Background: This novel study aimed to consider the temporal association between microvascular disruption and cardiac surgery-associated acute kidney injury (CSA-AKI) by investigating dynamic endothelial glycocalyx changes.

Methods: We conducted a prospective observational cohort study of 61 patients undergoing non-emergency coronary artery bypass graft (CABG) surgery with serial sampling at set time-points in the pre, intra and post-operative period. We measured plasma syndecan-1 (SDC1), a major endothelial glycocalyx structural component, and calculated a ratio against plasma albumin (SDC1:alb) to take account of intraoperative haemodilution fluctuations. CSA-AKI within 48 hours was assessed using Kidney Disease Improving Global Outcomes (KDIGO) criteria. Demographic, clinical and surgical variables were considered in analysis.

Results: 14/61 (23.0%) participants developed CSA-AKI. Peak intraoperative SDC1:alb and increase from baseline of peak SDC1:alb were significantly higher in participants who subsequently developed CSA-AKI compared to those who did not (P=0.0063; P=0.008). (Figure 1) The best predictor variables of CSA-AKI were peak SDC1:alb (AUC 0.77) and urine protein:creatinine ratio (upCR, AUC 0.840). After adjusting for upCR and other key variables, odds of CSA-AKI in patients with peak SDC1:alb greater than the derived optimal cut-off of 23 were 11 times those with a lower peak SDC1:alb (OR 11.0 (95% CI 1.57 – 106.91, P=0.021)).

Conclusions: This is the first demonstration of increased intraoperative shedding of SDC1, a core endothelial glycocalyx constituent, in CABG patients who subsequently developed CSA-AKI. These findings suggest endothelial glycocalyx disruption and microvascular dysfunction in CSA-AKI may provide a target for early therapeutic intervention and/or facilitate earlier identification of patients at greatest risk.

SA-PO123
Growth Differentiation Factor (GDF)-15, a Stress-Induced Cytokine, Is Increased in Patients with AKI
Takayuki Hamada,1 Momoiko Sekiguchi,1 Izumi Nagayama,1 Kaori Takayanagi,1 Hajime Hasegawa,1 Akito Maeshima,1 Department of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan.

Background: Growth Differentiation Factor (GDF)-15, a member of the TGF-beta superfamily, is one of the stress response cytokines that promotes cell death. Under physiological conditions, GDF-15 is expressed in high levels in the placenta, prostate, and bladder. High circulating levels of GDF-15 have been associated with chronic inflammatory conditions including lung, liver and cardiovascular diseases, rheumatoid arthritis, and cancers. In the kidney, GDF-15 is expressed in renal tubules but its role in acute kidney injury (AKI) remains unknown. To address this issue, we measured urinary GDF-15 in patients with AKI to test if GDF-15 is involved in pathophysiology of human AKI.

Methods: AKI patients (n=86) who were treated in our department (December 2020 to November 2021) were enrolled in this study. Serum and urinary GDF-15 were measured by ELISA. Correlations of urinary GDF-15 with other clinical parameters were analyzed.

Results: Urinary GDF-15 was detectable in healthy adults but was significantly increased in patients with AKI (5.1 ± 1.0 vs. 18.4 ± 1.5 ng/mL, p<0.001). Especially, urinary GDF-15 was markedly elevated in patients with ischemic AKI, drug-induced AKI, and AKAs-associated AKIs. In most cases of AKI, urinary GDF-15 was decreased after therapeutic intervention. In cases of deceased donor kidney transplant recipients, urinary GDF-15 was significantly elevated at 1 day after transplantation but was decreased with improvement of kidney function thereafter. There was a significant correlation of urinary GDF-15 with urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary kidney injury molecule-1 (KIM-1), urinary NAG, urinary β2-microglobulin, and urinary protein level, but not with serum creatinine level or L-FABP.

Conclusions: Collectively, urinary GDF-15 might be useful as a marker reflecting tubular stress and/or damage in patients with AKI.

SA-PO124
Urinary Follistatin Is a Marker Reflecting the Severity of Tubular Damage in Patients with AKI
Izumi Nagayama,1 Kaori Takayanagi,1 Daisuke Nagata,1 Hajime Hasegawa,1 Akito Maeshima,1 Department of Nephrology and Hypertension, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; 2Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke, Japan.

Background: Follistatin is an activin-binding protein that antagonizes the function of activin A, a member of TGF-beta superfamily. In animal models of acute kidney injury (AKI), the blockade of activin A by exogenous follistatin has been shown to attenuate kidney damage and improve renal function, suggesting that endogenous activin A negatively regulates tubular repair after AKI. Follistatin acts as a local modulator of activin A in many tissues. However, the role of follistatin in the kidney remains unknown.

Methods: To address this issue, we examined the localization of follistatin in normal human kidney and measured urinary follistatin in patients with AKI to test if urinary follistatin is useful as a marker for AKI. Patients with AKI (n=131) and healthy adults (n=13) were enrolled in this study. Serum and urinary follistatin was measured by ELISA. Correlations of urinary follistatin with other clinical parameters were analyzed.

Results: Follistatin was localized in renal tubules of normal kidney. Follistatin-producing cells were positive for Na-Ci co-transporter and urorodulin but were negative for aquaporin 1 or aquaporin 2. Urinary follistatin, undetectable in healthy adults, was significantly increased in patients with AKI (0.00 ± 0.00 vs. 458.1 ± 150.4 pg/mL, p<0.05) and was positively correlated with the severity of AKI. Urinary follistatin was significantly increased in patients requiring renal replacement therapy compared to those who did not. There was a significant correlation of urinary follistatin with urinary protein, α-l-microglobulin, urinary NGAL, but not with urinary KIM-1, urinary L-FABP, urinary NAG, urinary β2-microglobulin, serum creatinine. No correlation between urinary and serum follistatin was observed, suggesting that urinary follistatin is originated from the kidney but not from blood.

Conclusions: Collectively, follistatin produced by distal tubules of the kidney become detectable in the urine of AKI patients. Urinary follistatin might be useful to monitor the severity of acute tubular damage.

SA-PO125
Comparative Analyses of Classical Urinary Discriminators in Pre- vs. Biopsy-Proven Intrarenal AKI
Pre- vs. Biopsy-Proven Intrarenal AKI: Biomarkers, Imaging, Interventions
Martin Rusavský, AG Translational Nephrology, Philipps-University Marburg, University Hospital, Center for Internal Medicine, Renal Division, Marburg, Germany.

Background: The clinical distinction between prerenal and intrarenal acute kidney injury (AKI) remains challenging. Many biomarkers have been proposed, yet no comprehensive analyses of their performance has been conducted.

Methods: Classical Urine AKI-Biomarkers of patients with biopsy-proven intrarenal AKI and prerenal AKI have been compared.

Results: Kidney urine composition handling showed alterations according to severity (Figure 1) of AKI in most discriminators. ROC analyses (of AKI 3 prerenal vs. intrarenal) showed some discriminatory power of the investigated classical biomarkers (Figure 2). Best performance was observed with BUN-to-creatinine-ratio (area-under-the-roc / AUROC = 0.79; sensitivity 60%, specificity 83%), worst with urine sodium concentration (AUROC 0.6; sensitivity 50%, specificity 68%). The ratio of FEUrea divided by BUN-to-creatinine-ratio yielded the best discriminatory power (AUROC 0.83; sensitivity 80%, specificity 73%).

Conclusions: This analysis is the first to comprehensively compare the discriminatory power of classic urine biomarkers to distinguish between prerenal and intrarenal AKI. To foster reliability the intrarenal group was based on kidney biopsy diagnosis. Overall, most parameters showed medium performance. We identified a new ratio (FEUrea divided by BUN-to-creatinine-ratio), which performed best according to AUROC analysis.
SA-PO126

Fractional Excretion of Urea for the Differential Diagnosis of AKI: A Systematic Review and Meta-Analysis with Comparison to Fractional Excretion of Sodium
Mohammad O. Abdelhafez,1 Abdurrahman M. Hamadah,2 Kamel A. Gharibeh.3 AQU Collaborators. Al-Quds University, Jerusalem, Palestine; 1St. Luke’s Hospital, Duluth, MN; 3University of Maryland School of Medicine, Baltimore, MD.

Background: Differentiating between intrinsic and prerenal acute kidney injury (AKI) presents a challenge. This study aims to assess the performance of fractional excretion of urea (FEUrea) and compare it to fractional excretion of sodium (FENa) in distinguishing intrinsic from prerenal AKI.

Methods: We searched MEDLINE, Embase, CENTRAL, the Cochrane Library, and Scopus until July 2022. Studies evaluating FEUrea, with or without FENa, for differentiating AKI etiologies in adults were included. We assessed the methodological quality using the QUADAS-2/C tools. We conducted a meta-analysis using the bivariate random effects model, with subgroup analyses to explore the impact of diuretic therapy on FEUrea performance. We performed direct statistical comparisons between FEUrea and FENa in the overall AKI patients and subgroups with and without diuretic therapy. Study protocol: PROSPERO, CRD42022341290.

Results: We included 11 studies with 1108 hospitalized patients. Among 8 studies (915 patients) evaluating FEUrea at 35% threshold, the pooled sensitivity and specificity for distinguishing intrinsic from prerenal AKI were 66% (95% CI, 49-79%) and 75% (95% CI, 60-85%), respectively. In a subset of 6 studies (573 patients) comparing FEUrea at 35% to FENa at 1%, there was no significant difference in sensitivity (69% vs. 86%, P=0.089) but a significant difference in specificity (64% vs. 83%, P=0.038). Additionally, In 302 patients not on diuretics, there were no significant differences in sensitivity (77% vs. 89%, P=0.410) or specificity (80% vs. 79%, P=0.956). In 4 studies with 244 patients on diuretics, FEUrea demonstrated lower sensitivity (52% vs. 92%, P=0.001) but higher specificity (82% vs. 44%, P=0.001) compared to FENa.

Conclusions: Both FEUrea and FENa have limited utility in differentiating intrinsic from prerenal AKI. FEUrea does not provide a superior alternative to FENa, even in patients receiving diuretic therapy.

Table: Direct comparisons between FEUrea at 35% and FENa at 1%.

<table>
<thead>
<tr>
<th>FEUrea</th>
<th>FENa</th>
<th>FEUrea vs FENa</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>35%</td>
<td>1%</td>
<td></td>
<td>69%</td>
<td>86%</td>
<td>0.089</td>
</tr>
<tr>
<td>1%</td>
<td>35%</td>
<td></td>
<td>86%</td>
<td>64%</td>
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<tr>
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<tr>
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<td>FEUrea</td>
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<td>92%</td>
<td>52%</td>
<td>&lt;0.001</td>
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</tbody>
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SA-PO127

Fractional Excretion of Urinary Sodium and Urinary Sediment Microscopy for Prediction of Response to Vasoconstrictors in Hepatorenal Syndrome Type 1
Walter Lam, Terrance J. Wickman, Muner Mohamed, Juan Carlos Q. Velez. Ochsner Health, New Orleans, LA.

Background: Because of diagnostic challenges around differentiating hepatorenal syndrome type 1 (HRS-1) from acute tubular injury ( ATI), proper selection of patients who can benefit from vasoconstrictor therapy (VCT) remains suboptimal. We hypothesized that markers of tubular function or injury may correlate with therapeutic response to VCT.

Methods: Records from hospitalized patients with HRS-1 treated with VCT without shock were reviewed. We selected those who achieved ≥5 mmHg rise in mean arterial pressure (MAP) within 48 hours and had available fractional excretion of urinary sodium (FENa) (marker of tubular function) and microscopic examination of the urinary sediment (MicrExUrSed) (marker of tubular injury). Lower limit for urinary Na was <10 mEq/L. HRS-1 was diagnosed by ICA criteria + FENa <1% + no overt ATI by MicrExUrSed (abundant dark granular casts). Absence of ATI by MicrExUrSed was defined as bland sediment or only hyaline casts. The primary endpoint was percentage of change in serum creatinine (sCr) at the end therapy (day 7-14).

Results: A total of 44 patients with HRS-1 treated for 2-7 days with either norepinephrine (n=40) or midodrine/octreotide (n=4) were included. Median age was 52 (IQR 46-62), 41% female and 57% had alcoholic cirrhosis. At the start of VCT, median MAP was 71 mmHg (IQR 68-74) and median sCr was 3.8 mg/dL (IQR 2.8-4.9). Median FENa was 0.4% (IQR 0.29-0.49). FENa significantly correlated with change in serum Cr (r=0.395, P=0.007). Thus, lower FENa was associated with reduction in sCr. All patients with <30% reduction in sCr had FENa between 0.03 and 0.42% . Among those with MAP rise ≥10 mmHg (n=30), the correlation between FENa and change in sCr turned stronger (r=0.599, P=0.0004). Furthermore, the correlation between MAP rise and improvement
in sCr was stronger among those with absence of ATI by MiceExUrSed (n=24) (r=0.579, p=0.004) compared to those with scattered elements of ATI (n=20) (r=0.23, p=0.32). Among those with MAP rise >10 mmHg, 16 of 16 (63%) of those with no ATI by MiceExUrSed achieved >30% reduction in sCr compared to 4 of 14 (27%) of those with ATI elements (p=0.06).

Conclusions: Functional and injury urinary markers may offer predictive information respect to response to VCT in HRS-1.

SA-PO128
Kinetics of Mature Platelet Fraction as a Tool for Predicting the Time Course of Shiga Toxin-Producing Escherichia coli-Associated Hemolytic Uremic Syndrome (STEC-HUS)
Gianluigi Ardissino, Thomas Ria, Maria Cristina Mancuso, Valentina Capone, Laura Daprai, Valeria Amico, Francesco Spanu. Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy.

Background: Shigatoxin-related Hemolytic Uremic Syndrome (STEC-HUS) is a common thrombotic microangiopathy in children characterized by platelet consumption, hemolysis and kidney dysfunction. Being the time course of the disease relatively regular, the description of platelet kinetics, including reticulated platelets, may provide some useful insights for predicting the short-term course of the disease.

Methods: We considered all patients with STEC-HUS referred to our center during the last 5 years. Blood count for both total and reticulated platelets was performed daily with a XN-9000 hematology analyzer since admission until recovery. Results are expressed as absolute number and percentage of total.

Results: Forty patients with documented STEC-HUS were studied. Results are displayed in the figure showing the time course of total and reticulated platelets in the course of patients (time 0 identifies the nadir of total platelets). When immature platelet fraction reaches the threshold of 10% the resolution of thrombocytopenia, thus the beginning of recovery, is approaching and is expected in 24-48 hours.

Conclusions: During the course of STEC-HUS the rise of immature platelet fraction above 10% anticipates (by 24-48 hours) the increase of total platelets count thus predicting the beginning of disease recovery.

SA-PO129
Through the Haze: Sailing the Turbid Waters of Uremic Ophthalmopathy

Introduction: Ophthalmic disease can be a consequence of many metabolic conditions, rarely is caused by uremia. This is an uncommon etiology of ophthalmic disease. Rarely is caused by uremia. This is an uncommon etiology of ophthalmic disease. Evaluation was remarkable for elevated blood pressure, 168/85 mmHg, and bilateral lower extremity edema. Ophthalmologic evaluation was notable for bilateral optic nerve inflammation. Laboratory results were remarkable for anemia, azotemia and metabolic acidosis with HCO₃⁻ level of 14.5 mmol/L. Uremic encephalopathy UE is a cerebral dysfunction caused by the accumulation of toxins resulting from acute or chronic renal failure. The clinical presentation is broad, and the clinical course is always progressive when untreated. Patients generally exhibit the signs of UE when glomerular filtration rate is less than 15 ml/min/1.73 m² and the symptoms usually include fatigue, nausea, restlessness, drowsiness and diminished ability to concentrate. Paranoia is sometimes described as a uremic presentation, but rarely do patients exhibit acute psychosis.

Case Description: A 65-year-old female with past medical history of CKD stage III with baseline 2.4 mg/dl, coronary artery disease status post percutaneous coronary intervention, HPPEF, DM2 who presented to the hospital after being admitted to a rehabilitation management of mastitis. Her hospital course was complicated by acute kidney injury stage II, mild hyperkalemia and acute psychosis. Her manifestations include vocalization of her displeasure of the hospital, aggressive language, noncompliance to the treatment plan and severe paranoia. Patient did not have any psychiatric history. Her peak BUN was 59 and peak creatinine was 5.68 mg/dl. She was deemed to be competent by the psychiatry team. Anti-psychotics were given for paranoia, but her conditions did not improve. However, her mental status improved drastically after two sessions of dialysis treatment.

Discussion: Timing of dialysis initiation is an important topic in nephrology. The current practice is to delay dialysis unless there is an absolute indication. Uremic encephalopathy is a clinical diagnosis and can have various presentations, most notably catatonia or hypactive symptoms. Acute psychosis is a very atypical presentation of uremia and can be missed as an indication for dialysis initiation. In our patient, delayed dialysis would significantly impacted the delivery of her overall care due to her psychosis.

SA-PO131
A Case of Atypical Manifestation of Uremic Encephalopathy: Acute Psychosis

Introduction: Uremic encephalopathy UE is a cerebral dysfunction caused by the accumulation of toxins resulting from acute or chronic renal failure. The clinical presentation is broad, and the clinical course is always progressive when untreated. Patients generally exhibit the signs of UE when glomerular filtration rate is less than 15 ml/min/1.73 m² and the symptoms usually include fatigue, nausea, restlessness, drowsiness and diminished ability to concentrate. Paranoia is sometimes described as a uremic presentation, but rarely do patients exhibit acute psychosis. Here we present a patient with acute psychosis as her first sign of uremic encephalopathy.

Case Description: The patient is a 66-year-old female with past medical history of CKD stage III with baseline 2.4 mg/dl, coronary artery disease status post percutaneous coronary intervention, HPPEF, DM2 who presented to the hospital after being admitted to a rehabilitation management of mastitis. Her hospital course was complicated by acute kidney injury stage II, mild hyperkalemia and acute psychosis. Her manifestations include vocalization of her displeasure of the hospital, aggressive language, noncompliance to the treatment plan and severe paranoia. Patient did not have any psychiatric history. Her peak BUN was 59 and peak creatinine was 5.68 mg/dl. She was deemed to be competent by the psychiatry team. Antipsychotics were given for paranoia, but her conditions did not improve. However, her mental status improved drastically after two sessions of dialysis treatment.

Discussion: Timing of dialysis initiation is an important topic in nephrology. The current practice is to delay dialysis unless there is an absolute indication. Uremic encephalopathy is a clinical diagnosis and can have various presentations, most notably catatonia or hypactive symptoms. Acute psychosis is a very atypical presentation of uremia and can be missed as an indication for dialysis initiation. In our patient, delayed dialysis would significantly impacted the delivery of her overall care due to her psychosis.
SA-PO132

Cystatin C as a Diagnostic Marker for a Postoperative Urine Leak
Rahul Maheshwari, Jeffrey Kott, Holly M. Koncicki. Icahn School of Medicine at Mount Sinai, New York, NY.

Introduction: Evaluating kidney function after urologic procedures can be challenging in the presence of complications such as urine leaks. This case report illustrates a scenario where serum creatinine provided misleading Glomerular Filtration Rate (GFR) estimations, prompting the use of cystatin C for diagnostic accuracy.

Case Description: A 67-year-old male with a history of prostate cancer underwent an uneventful robotic assisted laparoscopic prostatectomy. Postoperatively, serum creatinine rapidly increased from a baseline of 0.9 mg/dL. On postoperative day (POD) 1, significant output from a Jackson-Pratt (JP) drain indicated possible urinary leak. However, a CT scan on POD 2 did not show obstruction or leak. Due to ongoing suspicion, nephrology consultation recommended obtaining daily cystatin C, hypothesizing that elevated serum creatinine mirrored urine resorption rather than a GFR decline. On POD 3, discrepant serum creatinine and cystatin C values (10.95 mg/dL, 1.5 mg/L respectively) along with a JP drain fluid creatinine of >40 mg/dL led to the placement of nephrostomy tubes. Post-procedure, serum creatinine and cystatin C levels normalized and JP output decreased.

Discussion: This case highlights the use of cystatin C in diagnosing postoperative urine leaks and the limitations of using serum creatinine as the sole kidney function marker after urologic procedures. Despite a non-diagnostic CT scan, the divergent serum creatinine and cystatin C pointed towards a urine leak. The mild cystatin C elevation, which improved post nephrostomy tube placement, suggests some obstructive uropathy or intrinsic kidney injury. Our case aligns with a case by Saro-Nunez et al. 2018, where cystatin C, correlates or intrinsic kidney injury. The mild cystatin C elevation, which improved post nephrostomy tube placement, suggests some obstructive uropathy or intrinsic kidney injury. Our case aligns with a case by Saro-Nunez et al. 2018, where cystatin C, correlates or intrinsic kidney injury.

 dances: This case highlights the use of cystatin C in diagnosing postoperative urine leaks and the limitations of using serum creatinine as the sole kidney function marker after urologic procedures. Despite a non-diagnostic CT scan, the divergent serum creatinine and cystatin C pointed towards a urine leak. The mild cystatin C elevation, which improved post nephrostomy tube placement, suggests some obstructive uropathy or intrinsic kidney injury. Our case aligns with a case by Saro-Nunez et al. 2018, where cystatin C, correlates or intrinsic kidney injury.

SA-PO133

Comparison of eROCK, KDIGO, and Their Combined Criteria for Detecting AKI in Hospitalized Adults with CKD
Ling Sun,1 Luxi Zou,2 Xuzhou Central Hospital, Xuzhou, China; 2Xuzhou Medical University, Xuzhou, China.

Background: Acute kidney injury (AKI) in chronic kidney disease (CKD), also known as acute-on-chronic kidney disease (ACKD) increases the risk of CKD progression, major adverse cardiovascular events (MACEs), and all-cause mortality. Hou et al. set up a reference change value (RCV) of the serum creatinine (SCr) Optimized Criterion for AKI in CKD (eROCK), which is defined as a >25% increase of SCR over 7 days. This study aimed to evaluate the ability of the novel criterion of eROCK to detect ACKD patients and then compared the effects of the criteria of eROCK and KDIGO in predicting long-term outcomes in ACKD patients.

Methods: This was a retrospective observational study with a 3-year follow-up period. The electronic medical records data of inpatients admitted to Xuzhou Central Hospital between January 2016 and June 2018 were screened. All included patients with CKD stage 3 were evaluated using CRECK, KDIGO, and their combined criteria. The renal composite endpoints, MACEs, and all-cause mortality were recorded as the clinical outcomes.

Results: A total of 812 patients was enrolled and assigned to 4 groups depending on the KDIGO and eROCK criteria (Fig 1). The baseline and follow-up data were described in Table 1. The eROCK detected 8.5% more ACKD events than KDIGO criterion (67.98% vs 59.48%, P < 0.001). During the 3-year follow-up, 683 patients experienced renal composite endpoints events, with groups ranked from high to low percentage of free events as KDIGO(-)&eROCK(-), KDIGO(+)&eROCK(-), KDIGO(-)&eROCK(+), and KDIGO(+)&eROCK(+) (Fig 2A). 650 patients developed MACEs, with groups ranked as KDIGO(-)&eROCK(-), KDIGO(+)&eROCK(-), KDIGO(-)&eROCK(+), and KDIGO(+)&eROCK(+) (Fig 2B). 405 patients died with trends similar to MACEs (Fig 2C).

Conclusions: Compared to the KDIGO criterion, the eROCK detected more ACKD events. Combining the eROCK and KDIGO criteria might improve the predictive ability for long-term outcomes in ACKD patients.

Funding: Government Support - Non-U.S.

SA-PO134

Smaller Kidney Volume Is Associated with AKI Following Cardiovascular Surgery, Especially Among Patients Treated with Renin-Angiotensin System Inhibitors

Background: Kidney volume might reflect atherosclerotic changes in the vascular bed in the kidney independent of eGFR and thus might be independently associated with post-operative AKI.

Methods: In this retrospective cohort study, we enrolled adults who underwent cardiovascular surgery from 2014 to 2021 at our facility and computed tomography (CT) scans within 6 months before surgery. We excluded those with multiple or large cysts, single kidney, serum creatinine >4 mg/dL, or undergoing kidney replacement therapy. Exposure of interest was height-adjusted total kidney volume (htTKV) measured by software using the three-dimensional CT reconstruction. The outcome was postoperative AKI defined by the KDIGO creatinine criteria. We employed logistic regression models and the results were shown as cubic spline curves. Effect modifications by renin-angiotensin system inhibitors (RASi, defined as angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers), loop diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) were assessed.

Results: Among 433 patients, 147 (33.9%) developed AKI. Those with smaller htTKV were older, less likely to be diabetic, had lower eGFR, and higher prevalence of CV comorbidities. Smaller htTKV tended to be associated with AKI even after adjustment for eGFR. Smaller htTKV was associated with AKI especially among the users of RASi (p for interaction 0.02). Loop diuretics and NSAIDs did not significantly modify the association between htTKV and AKI (p for interaction 0.44 and 0.42, respectively).

Conclusions: Smaller htTKV was associated with postoperative AKI independent of eGFR, especially among patients using RASi. Among patients with smaller htTKV, withdrawing RASi before CV surgery might be protective against post-operative AKI.
SA-PO135

**Combining Arterial and Venous Intrarenal Doppler Assessment for the Prediction of AKI After Cardiac Surgery**

*Cameron Giles,1 André Denault,2 William Beaulieu-Souligny,2 McMaster University, Hamilton, ON, Canada; 2Universite de Montreal, Montreal, QC, Canada.*

**Background:** Acute kidney injury (AKI) is common after cardiac surgery and often hemodynamically mediated. The roles of ultrasonographic measures of intrarenal perfusion to predict AKI after cardiac surgery have been evaluated. The objective of this study was to determine if point-of-care ultrasound Doppler measures of intrarenal arterial and venous flow predict AKI after cardiac surgery.

**Methods:** We conducted a secondary analysis of a prospective cohort study of adult patients undergoing cardiac surgery in whom ultrasonographic assessments were performed at ICU admission after surgery. AKI was defined by the KDIGO creatinine criteria. Intrarenal arterial markers included renal resistive index (RRI) and velocity-time integral normalized to peak systolic velocity (VTI/PSV), while venous markers included intrarenal venous flow (IVF) category and renal venous stasis index (RVSI). The area under the receiving operating characteristic (AUROC) curves were used to determine the predictive characteristics for post-operative AKI. The performance of individual markers were compared to a combined RRI and RVSI logistic regression model using the net reclassification index (NRI) and AUROC were compared with the DeLong test.

**Results:** We included 131 patients in total, with 47 patients (35.9%) developing post-operative AKI. All studied ultrasound markers showed moderate discrimination for the subsequent development of AKI (Table 1). More complex measurements (VTI/PSV and RVSI) were not superior to simpler indices (RRI and IVF). In a multivariable model, both RRI (OR 1.70; CI 1.09-2.66; p = 0.02) and RVSI (OR 0.85; CI 0.64-0.98; p = 0.048) remained associated with AKI. The predicted probabilities from the model were slightly better than each index taken individually according to the NRI. However, the AUROC were not significantly different (Table 1).

**Conclusions:** Intrarenal arterial and venous Doppler indices moderately predict the development of post-operative AKI in cardiac surgery patients. However, combining arterial and venous Doppler indices only marginally improves prediction.

**Echographic Parameters and AKI After Cardiac Surgery**

<table>
<thead>
<tr>
<th>Echographic Parameter</th>
<th>Postoperative AKI</th>
<th>P</th>
<th>Odds Ratio (95% CI)</th>
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<td>RRI</td>
<td>OR 1.70 (1.09-2.66)</td>
<td>0.02</td>
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**SA-PO136**

**Association of Aortic Pulsatility Index with Clinical Outcomes and In-hospital eGFR Slope Among Patients Admitted for Acute Decompensated Heart Failure Requiring Hemodynamic Monitoring**

*Banlengchit,1,2 Hocine Beaubien-Souligny,1 Marcelle Tighiouart,1 Jeffrey L. Sarnak,1 Wendy Sarnak,1 I. Jeffrey McCallum.1,* 1Tufts Medical Center, Boston, MA; 2UCSF Medical Center, San Francisco, CA; 3Tufts Medical Center Institute for Clinical Research and Health Policy Studies, Boston, MA; 4Yale School of Medicine, New Haven, CT; 5Tufts University School of Medicine, Boston, MA.

**Background:** Aortic pulsatility index (API), a non-invasive measure using arterial pulse wave analysis, may serve as a useful tool to assess mortality and cardiovascular outcomes among patients admitted for acute decompensated heart failure (ADHF). Mortality and end stage renal disease (ESRD) events were linked to the electronic medical record. Cox proportional hazards regression models were used to evaluate the risk of AKI after cardiac surgery.

**Methods:** We included 131 patients in total, with 47 patients (35.9%) developing post-operative AKI. All studied ultrasound markers showed moderate discrimination for the subsequent development of AKI (Table 1). More complex measurements (VTI/PSV and RVSI) were not superior to simpler indices (RRI and IVF). In a multivariable model, both RRI (OR 1.70; CI 1.09-2.66; p = 0.02) and RVSI (OR 0.85; CI 0.64-0.98; p = 0.048) remained associated with AKI. The predicted probabilities from the model were slightly better than each index taken individually according to the NRI. However, the AUROC were not significantly different (Table 1).

**Conclusions:** Intrarenal arterial and venous Doppler indices moderately predict the development of post-operative AKI in cardiac surgery patients. However, combining arterial and venous Doppler indices only marginally improves prediction.

**Echographic Parameters and AKI After Cardiac Surgery**

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<td>VTI/PSV</td>
<td>OR 0.85 (0.64-0.98)</td>
<td>0.048</td>
<td>0.85 (0.64-0.98)</td>
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<td>RVSI category</td>
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<td>RVSI</td>
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**SA-PO137**

**The Impacts of Skeletal Muscle Mass and Quality on Kidney Recovery of Patients with AKI Receiving Continuous Renal Replacement Therapy**

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**Background:** Although there are increasing interests in kidney recovery after acute kidney injury (AKI), little is known about patients with severe AKI requiring continuous renal replacement therapy (CRRT). It is known that sarcopenia is associated with poor prognosis and mortality in chronic inflammatory conditions but also in acute disease. Recent studies revealed that muscle mass and quality were significant determinants of mortality in patients with CRRT. However, few studies evaluated the effect of sarcopenia on kidney recovery in patients receiving CRRT.

**Methods:** We collected 2015 AKI patients who underwent CRRT from eight medical centers between 2006 and 2021. The skeletal muscle area (SMA) was measured from the automated software from CT images at 3rd lumbar vertebra within 15 days of CRRT initiation, and classified as normal attenuation muscle area (NAMA) and low attenuation muscle area (LAMA) according to muscle density. We used Fine and Gray model to investigate the effects of muscle mass index adjusted by body mass index (BMI) on kidney recovery.

**Results:** Of the 813 CRRT survivors, 682 (83.9%) patients were discharged without RRT. Increased SMA/BMI was independently associated with decreased risk of RRT dependence. Also, the 4th quartile of NAMA/BMI was significantly associated with decreased RRT dependence risk. However, no significant effects of LAMA/BMI were observed.

**Conclusions:** In patients with severe AKI receiving CRRT, not only the quantity but also the quality of muscle affects RRT dependence.

**SA-PO138**

**Contract Induced Nephropathy in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis**

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**Background:** Kidney transplant recipients (KTR) may be at higher risk of contrast induced Nephropathy (CIN) because of associated risk factors. The incidence proportion of CIN in native kidneys was reported to be 9% in a recent meta-analysis with 1.5% requiring renal replacement therapy (RRT). We aimed to determine the incidence proportion of CIN in KTR.

**Key:** TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Methods: Medline, Embase, and Cochrane databases were used to search the studies assessing the incidence of CIN in KTR from inception until January 2023. We applied Random effect model to estimate the incidence of CIN in KTR.

Results: Sixteen studies, including 805 contrast studies in KTR, were included in the analysis. The estimated incidence of CIN in KTR and CIN requiring RRT was 9.3% (95% CI: 7.5% to 11.1%) and 1.1% (95% CI: 0.6% to 1.4%), respectively. None of the CIN patients required permanent RRT. In subgroup analysis, the incidence of CIN in KTR who received iso-osmolar (300 mOsm/kgH2O) vs hypo-osmolar CM (350 mOsm/kgH2O) was 5.0% (95% CI: 0.8% to 11.2%) and 8.7% (95% CI: 5.6% to 12.3%), respectively. An estimated incidence of CIN in KTR who underwent coronary angiography was 14% (95% CI: 8% to 22%). Angiograms, including all graft renal artery angiograms (without angioplasty/stenting) and CT scans resulted in CIN in 12% (95% CI: 4% to 18%), in 8.6% (95% CI: 5% to 12%), respectively. CIN in KTR who underwent angioplasty/stenting to relieve renal artery stenosis (RAS) was 3%. There was complete reversal of CIN with successful therapeutic intervention for RAS, renal function improved above baseline. No graft loss was reported within 30 days post CM administration regardless of the type of CM administered.

Conclusions: The estimated incidence of CIN in KTR is 9.3%, equal to the incidence of CIN in native kidneys (9%). Therefore, it appears that the risk of CIN in KTR patients is not different than the general population.

SA-PO139
Effect on Kidney Function Recovery Guiding Decongestion with Venous Evaluation by Ultrasound System (VExUS) in Patients with Cardiorenal Syndrome 1, A Randomized Control Trial
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Background: In cardiorenal syndrome type 1 (CRS1) vascular congestion is a common complication, the Venous Evaluation by Ultrasound System (VExUS) could guide decongestion with diuretics effectively and thereby improve renal function and outcomes.

Methods: In this double-blind randomized clinical trial, patients with CRS1 were randomized to guide decongestion with VExUS compared to usual clinical evaluation. The primary and secondary endpoint was to assess kidney function recovery (KFR), days of hospitalization, mortality, changes in brain natriuretic peptide (BNP) and CA-125. Protocol registration number is HCG/CEI-0836/22.

Results: During the period from March 2022 to February 2023, a total of 140 patients were randomized, 70 in the VExUS group and 70 in the Control group. KFR improve in the VExUS group, compared to Control, no significant difference was found. VExUS improve in more than twice the speed (in days) with which decongestion is achieved (OR 2.6, CI 1.9-3.6, p=0.01). With VExUS is two-fold more likely to reach a decrease of BNP ≥30% (OR = 2.4; CI 1.3-4.1, p = 0.01). Survival at 90 days was similar between groups. Reconditioning, CA125 and mortality were similar between groups.

Conclusions: In patients with CRS1, we observed that VExUS guided decongestion, compared to clinical evaluation, did not improve the probability of KFR, but decongestion could be achieved more efficiently in fewer days.

SA-PO140
Discordance Between the Initial Etiological Diagnosis of AKI and that of the Nephrologist Based on a VExUS Study of Patients with AKI in an Acute Care Setting
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Background: Acute kidney injury (AKI) is associated with high morbidity and mortality. The correct diagnosis is essential for appropriate management because the treatments are very different between volume depletion, cardiorenal syndrome, hepatorenal syndrome, and acute tubular necrosis (ATN). We compare the initial diagnosis on presentation of AKI and the likely diagnosis based on the evaluation of a nephrologist on a later chart review of the clinical course and diagnostic results.

Methods: In this single center, prospective, cohort study of ICU and ward patients who developed AKI during the admission we sought to determine the application of venous excess ultrasounds of intra-abdominal organs in discriminating the cause of AKI. We performed bedside US using a Logiq e BT12 machine, chart review and collection of baseline characteristics of all enrollees for 3 consecutive days. Baseline characteristics included: vital signs, 2D-echocardiogram, central venous pressure, right heart catheterization, urine electrolytes, urine protein-to-creatinine ratio, urine sediment. Ultrasound scanners were blinded to the clinical diagnosis.

Results: We enrolled 80 patients with the initial diagnosis of AKI established by the primary care. Primary teams suspected ATN (23.5%), volume depletion (39.5%), hepatorenal (8.6%), cardiorenal (26%), and other causes (2.5%). The diagnoses posed by the primary care team were correct in 75% of the cases. ATN was mistakenly categorized as volume depletion 24% of the time and volume depletion as hepatorenal 29% of the time. Granular casts were present in 45% of ATN cases and 8% of non-ATN cases (p=0.0001), sensitivity 45%, specificity 92%. This includes 41% of misdiagnosed cases. For VExUS, 70% of ATN cases were Grade 0, 64% of volume depletion, 50% of hepatorenal, and 33% of cardiorenal.

Conclusions: In a single-center prospective study of 80 patients with an initial diagnosis of AKI, the cause of AKI determined by the primary care team was discordant to that of the nephrology specialist in only 25% of the case. Urine sediment remained a useful tool in the diagnosis of AKI than VExUS. Future research is needed to examine the role of VExUS as a diagnostic tool.

SA-PO141
Hepatic Duplex: Can the Liver Be of Service to the Kidney in Diagnosing AKI?
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Background: Acute kidney injury (AKI) has a significant morbidity and mortality. The correct diagnosis is essential for appropriate management because the treatments are very different between volume depletion, cardiorenal syndrome, hepatorenal syndrome, and acute tubular necrosis (ATN). We examined whether bedside venous excess ultrasounds of intra-abdominal organs differs in different causes of AKI.

Methods: A prospective single-center study of patients with cardiorenal, hepatorenal, acute tubular necrosis(ATN), and volume depletion acute kidney injury (AKI). Arteriographies and body mass index (BMI)>30 were exclusions. Clinical data were obtained via chart review. Inferior svena cava diameter(IVC); hepatic vein and renal vein patterns; and Renal Resistive Indices(RRI) were obtained via Logic e BT-12 ultrasound. Sonographers were blinded from diagnoses. We used analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

Results: We enrolled 81 AKI subjects, 34% with volume depletion, 19 cardiorenal, 35%ATN, 6% hepatorenal, and 3% other. Participants’ mean creatinine 2.74 (±1.47) mg/dL. The IVC diameters in ATN, volume depletion, hepatorenal, and cardiorenal were, 762
SA-PO142
Association of Kidney Biopsy Needle Gauge with Post-Procedure Complications and Biopsy Adequacy

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Background: Narrower kidney biopsy gauge needles are thought to lower post-biopsy complications but could risk inadequate sampling for diagnosis. We examine the association of needle gauge with post-biopsy complications and sampling adequacy.

Methods: Using data from participants enrolled in the Yale biopsy cohort between 7/2020 and 4/2023, we tested the association of needle gauge (16G vs. 18G or 20G) with biopsy-related complications and number of glomeruli sampled using a chi-squared test for proportions for categorical outcomes or a Wilcoxon rank sum test for continuous outcomes.

Results: Of the 511 adult participants, median age was 60 (43.70), 49% were female, 60% were White, 33% were hospitalized and 52% underwent a biopsy for acute kidney injury. Of those with 18G were more likely to have AKI (60% vs. 48%, P=0.01) and be hospitalized (40% vs. 29%, P=0.007). Smaller needle gauge was not associated with seeking adverse post-biopsy complications, but participants who underwent a biopsy with narrower needle gauge required more imaging studies after biopsy (21% vs. 11%, P=0.004) primarily driven by concerns of hemoglobin drop. Narrower needle gauge was associated with fewer glomeruli available for diagnosis (11.5 [7.9-17.0] vs 14.0 [9.0-20.0], P=0.001).

Conclusions: Our data show that the narrower gauge biopsy needle was associated with fewer glomeruli available for diagnosis and greater need for postoperative imaging. However, we cannot rule out confounding by indication such that those at higher risk of complications undergo biopsy with narrower needle gauge. Further investigation into the complications associated with biopsy needle size controlling for detailed risk factors for post-biopsy complications is needed to confirm these findings.

Funding: NIDDK Support

SA-PO143
Erroneous Diagnosis of Acute Interstitial Nephritis on Gallium-67 Scintigraphy

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Introduction: Acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) are common etiologies for acute kidney injury (AKI) in a patient with infection being treated with antibiotics. Kidney biopsy is the gold standard to distinguish between these diagnoses, but gallium-67 scintigraphy is sometimes used if a biopsy is considered high risk.

Case Description: We present a case of a 32-year-old male admitted for right elbow swelling, associated with fever to 100.4 for one day. Physical exam was significant for chronic venous manifestations on the right arm, one of which was now tender to touch and palpation. Thrombophlebitis was suspected. Creatinine was 1.62 mg/dL which improved to 1.19 after 2 Liters of normal saline. Piperacillin/Tazobactam and Vancomycin were started. Blood cultures grew Pasteurella Multocida. Antibiotics were tailored towards this infectious agent. However, the patient remained febrile for three days after the bacteremia had cleared. Meanwhile, his creatinine rose from 1.19 to 2.81 in 72 hours. Urinalysis showed 100mg/dl protein, sterile pyuria and few granular casts. Renal ultrasound showed normal size and echogenicity. A gallium scan was done to identify the source of ongoing fever and revealed intense activity in the kidneys suggestive of interstitial nephritis.

Kidney biopsy was done to confirm the diagnosis. Empiric Prednisone 1mg/kg/day was started while waiting for biopsy results. The biopsy showed ATN. Prednisone was then discontinued. Creatinine improved to 1.0 one week after discharge.

Discussion: Kidney biopsy is the gold standard for diagnosing acute interstitial nephritis but is not always attainable. Gallium-67 scintigraphy has emerged as an alternative modality to diagnose AIN. Graham et al showed 100% specificity but poor sensitivity when using an uptake cutoff of grade 5, which means the intensity of radioisotope uptake in the kidney is higher than in the liver. Few older studies have shown varying degrees of sensitivity and specificity. Our patient had a grade 5 uptake, yet the biopsy did not show AIN. Thus, our case highlights the limitations of the gallium scan in diagnosing AIN and confirms that when the clinical picture is unclear, biopsy may be preferred.

SA-PO144
Catheter-Directed Thrombectomy in Acute Renal Vein Thrombosis

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Introduction: Renal vein thrombosis (RVT) is a rare condition that can lead to severe complications including acute kidney injury or renal failure. Malignancy and nephrotic syndrome are the most common etiologies accounting for up to 66% and 20% of cases, respectively. The standard treatment for RVT is anticoagulation, but in the presence of declining renal function or contraindications, catheter-directed thrombectomy (CDT) can be considered.

Case Description: A 64-year-old female with CKD stage IIa, hypertension and nephropathia presented with acute left flank pain, AKI (creatinine 1.35mg/dL) and a 7cm left renal subcapsular hematoma with large RVT. Urinalysis revealed trace blood and protein with urine ACR of 8.2mg/mmol. On day three, kidney function declined to creatinine of 2.1mg/dL. Due to the rapid decline in kidney function and renal hematoma, precluding anticoagulation, CDT was performed. The clot was successfully retrieved and renal flow was restored. The creatinine approached baseline within a few days. Interestingly, the pathology demonstrated fragments of renal cell carcinoma within the thrombus despite no clear evidence of malignancy on CT or MRI imaging.

Discussion: We present the successful use of CDT for acute RVT secondary to renal cell carcinoma for diagnostic and therapeutic purposes. CDT permits rapid recanalization of the renal vein and facilitates faster renal recovery. Direct access permits interventions including venoplasty or stent placement for persistent stenosis or elastic recoil. To our knowledge, there are no previously reported cases of thrombectomy for acute RVT secondary to tumor thrombus. CDT is a potentially safe and effective treatment option for acute RVT, especially in the setting of declining renal function or contraindications to anticoagulation.

SA-PO145
Urinoma Treated with Transcatheter Arterial Embolization for Renal Artery: A Case Report


Introduction: Transcatheter arterial embolization (TAE) for renal artery was generally performed for renal cancer, aneurysm, polycystic kidney disease and bleeding. Here, we report a case of urinoma with the renal abscess successfully treated with TAE.
Case Description: A 79-year-old man with a past medical history of bladder cancer with total cystectomy and ileal conduit and ureterolithiasis with left ureteral stent was admitted to our hospital. He showed septic shock and disseminated intravascular coagulation (DIC) with the left renal abscess due to the dislodged left ureteral stent. He also showed acute kidney injury (AKI) and his serum creatinine was elevated to 7.37 mg/dL from baseline of 3.43 mg/dL a month before admission. He was given antibiotic for septic shock and underwent hemodialysis for AKI. He was also found to have hemorrhage from dorsal branch of the left renal artery due to DIC and performed the emergent TAE for that branch. After the TAE, we performed percutaneous drainage from the left renal abscess. However, fluid was continued to drain away from a tube inserted into the abscess. Laboratory findings showed the creatinine in the fluid was 17.09 mg/dL, and then we diagnosed as a urinoma. To treat the urinoma with infection, we performed TAE against the left renal artery to completely disrupt the renal function (Figure). After that, the fluid was dramatically decreased, the urinoma size was reduced, the abscess was fully improved, and the drainage tube was removed, though the maintenance dialysis was required.

Discussion: In this case, TAE was performed for disruption of renal function to treat the urinoma. Radical nephrectomy was also considered, but it was suspected difficult due to adhesions after infection. TAE may be the one of the treatment options for the urinoma.
SA-PO148
Meprin β Regulates Protein Kinase A-Mediated TGF-β Signaling in Ischemia/Reperfusion-Induced Kidney Injury
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Background: Ischemia/reperfusion (IR) is a leading cause of acute kidney injury (AKI) and is associated with high morbidity and mortality rates. Meprins, zinc metalloproteases have been implicated in the pathology of IR. Meprins are capable to proteolytically processing the catalytic subunit of protein kinase A (PKA-C) and several mediators of inflammation. The protein kinase A (PKA) signaling pathway plays an important role in renal fibrosis, promoting the production of transforming growth factor-β (TGF-β) and/or TGF-β-dependent molecules. The TGF-β signaling is involved in wound healing and tissue repair of injured kidneys. Activation of Smad2 and Smad3 is the major downstream event of the TGF-β signaling pathway. The objective of the current study was to determine how meprin β expression impacts PKA-C-mediated TGF-β signaling in IR-induced kidney injury.
Methods: We used surgical procedures to achieve unilateral IR with contralateral nephrectomy in wild-type (WT) and meprin β knockout (JKO) mice. The mice were sacrificed at 96 h post-IR and kidney tissues obtained for analysis. Real-time PCR, and immunohistochemical staining, were used to evaluate the expression levels of PKA-C and TGF-β. Statistical analysis utilized two way ANOVA.
Results: Real-time PCR data showed significant increases in mRNA levels of PKA-C only in JKO kidneys after IR. In contrast, the mRNA levels for TGF-β were higher in both WT and JKO at all time points. Similarly, the mRNA levels for TGF-β were higher in meprin β deficient mice. Immunohistochemical data showed significant increases in the levels of PKA-C proteins in select kidney tubules of both genotypes after IR. Similarly, staining intensity for TGF-β were higher in select kidney tubules of both WT and meprin β deficient mice at 96 h IR. Immunofluorescence of kidney tissues with anti-meprin β antibodies showed a positive correlation between meprin β expression and tubular PKA-C and TGF-β levels in kidneys subjected to IR.
Conclusions: These findings suggest that meprin β regulates PKA-C-mediated TGF-β signaling pathways underlying kidney IR-induced kidney injury and provides new insights on the mechanisms underlying meprin β modulation of the pathophysiology of IR-induced renal injury.
Funding: Other NIH Support - NIH/NIGMS Grant # R35GM141537

SA-PO149
Role of LTBP4 in Kidney Injury: A Study on the Effect of LTBP4 on Angiogenesis and Inflammation in Renal Fibrosis
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Background: Transforming growth factor beta (TGF-β), a key protein in renal fibrosis, is regulated by latent transforming growth factor binding protein 4 (LTBP4). We hypothesize that LTBP4 also plays a role in angiogenesis and inflammation, both TGF-β related and TGF-β independent. This is significant because the role of angiogenesis and inflammation in kidney injury is widely recognized.
Methods: We employed wild-type (WT) and Ltbp4 KO mice at 96 h IR. Immunofluorescence analysis of kidney tissues with anti-meprin β antibody and harvested kidneys 3 weeks later.
Results: Our study demonstrated increased expression of LTBP4 in mice after kidney injury. Fourteen days post-IR, Ltbp4+/− mice showed more pronounced fibrosis than WT mice. Immunohistochemistry analysis revealed stronger positive staining for CD31, an endothelial marker, in WT mice than in Ltbp4−/− mice. Moreover, WT mice exhibited higher expression of vascular endothelial growth factor (VEGF) than Ltbp4−/− mice after undergoing IR injury. Transcriptomic analysis revealed upregulation of genes linked to angiogenesis in LTBP4-overexpressed HK-2 cells. Cellular studies reflected similar results in HK-2 cells, where VEGF expression was lower in LTBP4 knockdown compared to non-targeting siRNA knockdowns. Furthermore, podocyte-specific knockouts of Ltbp4 showed increased protein expression of TGF-β in the glomerular filtration barrier were quantified by transmission electron microscopy.
Conclusions: These findings suggest that LTBP4 plays a key role in regulating angiogenesis and inflammation during kidney injury. We demonstrated that LTBP4 partly has a protective effect in the progression of kidney disease. The increased angiogenesis and reduction in inflammation aid in the recovery of kidney injury and potentially mitigates long-term complications. These findings highlight the potential therapeutic avenues for utilizing LTBP4 in managing kidney injury.

SA-PO150
Role of SMPDL3b in Radiation-Induced Nephropathy
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Background: The kidneys are radiosensitive and dose-limiting organs for radiotherapy (RT) targeting abdominal and paraspinal tumors. Excessive radiation doses to the kidneys lead to radiation nephropathy (RN). In this study, we investigated a novel role for the lipid-modifying enzyme, sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b), in regulating the response of renal podocytes to radiation injury.
Methods: Podocytes were irradiated with either 4 Gy or 8 Gy and Ezrin, and apoptosis, DNA damage, and survival were quantified at different time points post-RT. For in vivo studies, 10–14 weeks old C57Bl/6 received bilateral kidney irradiation of 14Gy or 6x5Gy with or without rituximab (50 mg/kg IP, 1h before RT). 20 weeks post RT, glomerular filtration rate (GFR) was measured by transdermal monitors. Urine and serum samples were analyzed to quantify urinary albumin-to-creatinine ratio (ACR), serum BUN, and creatinine levels. Kidney cortex sections were stained with H & E, Periodic Acid-Schiff, Picrosirus red, and Masson’s trichrome staining. Ultrastructural Changes in the glomerular filtration barrier were quantified by transmission electron microscopy.
Results: Podocyte survival decreased in a dose-dependent manner post-RT. SMPDL3b expression was more prominent in uninjured kidneys than in cultured podocytes. 24 h post-RT, Podocyte DNA damage and apoptosis increased significantly more in podocyte-specific knockout (pSMPDL3b-KO) mouse kidney cortex than in SMPDL3b wild-type mice (p = 0.0166 and p = 0.0302, respectively). Fibrosis, glomerular basement membrane thickening, (GBM), podocyte foot process width, mesangial expansion score, BUN, creatinine ACR increased significantly more in pSMPDL3b-KO mice than in SMPDL3b wild-type mice (p = 0.05). GFR decreased significantly in SMPDL3b wild type and pSMPDL3b-KO mice 20 weeks post-RT (p < 0.05). Rituximab treatment to SMPDL3b wild-type mice prevented SMPDL3b deficiency and reduced inflammation, podocyte loss, reduced fibrosis, mesangial expansion score, GBM thickness, and foot process width and significantly improved renal function (BUN, Creatinine, and ACR) post-RT (p < 0.05).
Conclusions: Rituximab treatment restored SMPDL3b basal expression levels and reduced decreased radiation-induced podocyte injury and albuminuria. Our findings suggest SMPDL3b as a potential therapeutic target in radiation-induced renal damage.
Funding: Other NIH Support - NIH/NCIPO12 R01C01227493; W81XWH-22-1-0305; UM S1G 2023-01; 2SL12, Other U.S. Government Support

SA-PO151
Renal IsolG-Containing Antigen-Presenting Cells Modulate Endothelial Cells of Lymphatic Vessels via ET-3/ERB During Kidney Injury
Ashley L. Pitzer,1 Jiaying Zheng,1 Haichun Yang,1 Annet Kirabo,2 Valentina Kon. Vanderbilt University Medical Center, Nashville, TN.
Background: Previously, we showed that sodium (Na+) promotes the formation of the lipid oxidation product, isoleucylglycine (IsoLGs) in antigen-presenting cells (APCs) during kidney injury. More recently, we have been interested in the role of podocyte-endothelial cell interactions. Lymphangiogenesis accompanies multiple experimental and human kidney diseases. Our recent studies show that albuminuric kidney injury leads to a high Na+ environment in the kidneys and promotes renal accumulation of IsoLGs.
Methods: To induce nephrotic injury in mice, we used a sheep anti-glomerular basement membrane antibody and harvested kidneys 3 weeks later.
Results: We observed a 370% increase in albumin: creatinine ratio, a 30% decrease in GFR, and increased systolic blood pressure (+20.1 mmHg) in nephrotoxin injured vs uninjured controls. Immunostaining of renal F4/80 expression, a macrophage marker, revealed a stronger increase in the interstitium of nephrotic mice vs controls. Using flow cytometric analysis, nephrotic-injury kidneys were found to have elevated IsoLGs in monocytes and dendritic cells when compared to controls. Lymphatic endothelial cells (LECs) in co-cultured together with a high Na+ environment have increased expression of IsoLGs as well as expression of endothelin receptor B (ETB), which are blocked with 2-hydroxybenylamine (2-HOBA) treatment. Additionally, when co-cultured with LECs, dendritic cells have increased IsoLG expression and vasoactive peptide Endothelin-3 (ET-3) in response to a high Na+ environment. Similarly, these observed increases are blocked by 2-HOBA treatment. Using RNA sequencing data and informatics in LECs co-cultured with APCs, we found high Na+ significantly increased ET-3 in immune cells and ETB receptor in LECs.
Conclusions: These findings were validated using RT-PCR. Taken together, this data suggests LEC uptake of IsoLGs is potentiated by high Na+ environment and interaction with inflammatory immune cells, and IsoLGs may play a role in the ET3/ETB ligand: receptor interaction and crosstalk with LECs. The work was supported by NIH T32HL144446, 1PO1HL116263, K001HL13049, R03HL155041, and K01HL144491.
Funding: NIDDK Support, Other NIH Support - NHLBI, Other U.S. Government Support
SA-PO152

Exposure to Systemic Hypoxia After Renal Ischemia Reperfusion Injury (IRI) Promotes Kidney Repair

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Background: and others have shown that activation of hypoxia signaling prior to renal ischemia reperfusion injury (IRI) exerts renoprotective effects. However, it is unclear whether induction of hypoxia (Hx) after injury regulates kidney recovery. Here, we investigated how exposure to systemic hypoxia regulates post-IRI kidney repair.

Methods: Male C57BL6 mice were subjected to uIRI via clamping for 25 minutes. 6-hrs post-injury, groups were placed in hypoxia chamber at 8% O2 for 24 or 72 hrs, while control groups remained in normoxia (Nx). Mice were then sacrificed and kidneys collected for bulk RNA-Seq, metabolomic analysis and histology, while serum was collected for metabolomic analysis.

Results: After exposure to 72 hrs of Hx or Nx following IRI, the Hx group was found to have significantly lower injury via kidney injury scoring on H&E stained tissue sections (3.3±0.5 Nx vs 2.2±0.4 Hx, P<0.02, n=4 Nx, n=4 Hx) and Kim1 gene expression (2.5 fold suppression compared to Nx, P=0.002, n=4 Nx, n=4 Hx). Hypoxia exposure for 24 hours did not significantly reduce kidney injury scores, but did reduce Kim1 expression (P=0.03). KEGG/GO pathway analysis of RNA-Seq data at 72 hours revealed a prominent inflammatory signature in the downregulated genes, such as cytokine-cytokine receptor interaction, TNF and NF-kB pathways (KEGG), as well as immune response, inflammation response and cytokine production (GO), indicating hypoxia exposure promotes post-ischemic inflammation. On the other hand, pathway analysis of upregulated genes showed significant enrichment for metabolic pathways such as tryptophan metabolism, PPAR signaling, glutathione metabolism, fatty acid degradation and retinol metabolism. Furthermore, quantitative assessment of kidney and serum metabolic profile using a comprehensive LC-MS metabolite panel, as well as a targeted LC-MS assay for tryptophan related metabolites were carried out. Here, we found significant increases in tryptophan pathway metabolites in kidney tissue and serum, such as kynurenine, xanthurenic acid, 3-hydroxyanthranilic acid and NAD+.

Conclusions: 1) In summary, exposure to hypoxia in the context of established ischemic injury promotes early reparative processes. Among the altered metabolic pathways, changes in tryptophan metabolism may contribute to the mechanisms by which hypoxia promotes adaptive repair.

Funding: NIDDK Support

SA-PO153

Modulation of Stimulator of Interferon Genes (STING) Signaling Differentially Affects Outcomes of AKI

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Background: Activation of cGAS/STING signaling leads to both type I interferon production and NRF2-dependent transcription in a Tbk1-dependent manner. During acute kidney injury (AKI), we recently described a population of innate immune cells expressing galectin D to be recruited to the surroundings of acute tubular necroses. Interestingly, these GSDMD+ cells seemed to signal back on the ongoing cell death, a mechanism which promotes kidney repair.

Methods: Male C57BL6 mice were subjected to uIRI via clamping for 25 minutes. 6-hrs post-injury, groups were placed in hypoxia chamber at 8% O2 for 24 or 72 hrs, while control groups remained in normoxia (Nx). Mice were then sacrificed and kidneys collected for bulk RNA-Seq, metabolomic analysis and histology, while serum was collected for metabolomic analysis.

Results: After exposure to 72 hrs of Hx or Nx following IRI, the Hx group was found to have significantly lower injury via kidney injury scoring on H&E stained tissue sections (3.3±0.5 Nx vs 2.2±0.4 Hx, P<0.02, n=4 Nx, n=4 Hx) and Kim1 gene expression (2.5 fold suppression compared to Nx, P=0.002, n=4 Nx, n=4 Hx). Hypoxia exposure for 24 hours did not significantly reduce kidney injury scores, but did reduce Kim1 expression (P=0.03). KEGG/GO pathway analysis of RNA-Seq data at 72 hours revealed a prominent inflammatory signature in the downregulated genes, such as cytokine-cytokine receptor interaction, TNF and NF-kB pathways (KEGG), as well as immune response, inflammation response and cytokine production (GO), indicating hypoxia exposure promotes post-ischemic inflammation. On the other hand, pathway analysis of upregulated genes showed significant enrichment for metabolic pathways such as tryptophan metabolism, PPAR signaling, glutathione metabolism, fatty acid degradation and retinol metabolism. Furthermore, quantitative assessment of kidney and serum metabolic profile using a comprehensive LC-MS metabolite panel, as well as a targeted LC-MS assay for tryptophan related metabolites were carried out. Here, we found significant increases in tryptophan pathway metabolites in kidney tissue and serum, such as kynurenine, xanthurenic acid, 3-hydroxyanthranilic acid and NAD+.

Conclusions: In summary, exposure to hypoxia in the context of established ischemic injury promotes early reparative processes. Among the altered metabolic pathways, changes in tryptophan metabolism may contribute to the mechanisms by which hypoxia promotes adaptive repair.

Funding: NIDDK Support
SA-PO156

Reno-Protective Effect of Ginsenoside Rg3 in Ischemia Reperfusion Injury Mice by Inducing Autophagy Flux

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Background: The protective effects of Ginsenoside Rg3 (Rg3) have been demonstrated through different mechanisms. Nevertheless, the specific evaluation of its renal-protective effect and the involvement of autophagy remain unclear. This study aims to examine how Rg3 induces autophagy flux and diminishes renal cell death in renal ischemia reperfusion injury (IRI).

Methods: C57Bl/6 mice were categorized into the subsequent groups: sham; sham treated with Rg3; IRI mice treated with saline; IRI mice treated with Rg3. Kidneys and blood samples were obtained 24 hours after the surgical procedure (sham and I/R operation). Renal function, kidney histology, and the protein expression of autophagy markers were assessed.

Results: In the IRI mouse group, there was an elevation of BUN and s-Cr levels compared to the sham group. However, the administration of Rg3 resulted in a reduction of BUN and s-Cr levels in the IRI mice. Furthermore, Rg3 treatment led to a decrease in renal injury, as evidenced by a lower renal tubular cell detachment and necrosis score in the IRI mice. The Rg3-treated IRI mice exhibited reduced oxidative stress and improved autophagy, characterized by increased expressions of LC3 and Beclin-1, decreased levels of p62, and higher levels of renal ATPase compared to the IRI mice treated with saline. Additionally, Rg3 treatment promoted the phosphorylation of AMPK in the kidneys of IRI mice.

Conclusions: Rg3 exhibits renal protection against renal IRI by enhancing autophagy flux.

SA-PO157

OTUD5 Mediates GPX4 Stability and Ferroptosis in Renal Tubular Cells During Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI) is a severe kidney disease often linked with renal tubular cell ferroptosis, an iron-dependent, non-apoptotic cell death characterized by lipid peroxide accumulation. This can be triggered by ischemia-reperfusion (I/R) and typically results from decreased glutathione peroxidase 4 (GPX4) expression. However, the specific molecular events underlying GPX4 reduction following I/R remain poorly understood.

Methods: Our research involved identifying and characterizing the role of GPX4-interacting proteins in renal tubular cells. We also studied the susceptibility of renal regions to I/R injury using spatial transcriptomics. Both in vitro assays and in vivo experiments using mice with conditionally deleted Otud5 were employed to evaluate the function of OTU deubiquitinase 5 (OTUD5) in ferroptosis and AKI.

Results: OTUD5 was found to interact with and stabilize GPX4, conferring resistance to ferroptosis in renal tubular cells. During I/R, the inability of OTUD5 to deubiquitinate, triggered by mTORC1-mediated macroautophagy, led to GPX4 degradation and ferroptosis. Spatial transcriptomics revealed hyperactivity of cell ferroptosis and autophagy in the region between the kidney’s inner cortex and medulla, susceptible to I/R injury. Functionally, OTUD5 deletion resulted in heightened renal tubular cell ferroptosis in vitro, and mice with tubular epithelial cell-specific Otud5 deletion demonstrated exacerbated AKI in response to I/R. Conversely, adenovirus-mediated Otud5 delivery reduced ferroptosis and promoted renal function recovery.

Conclusions: Our findings unveil a novel autophagy-dependent ferroptosis module: I/R-induced OTUD5 macroautophagy leads to GPX4 degradation and tubular cell ferroptosis. Targeting this pathway may offer a potential therapeutic strategy for I/R-related kidney diseases.

Funding: Other U.S. Government Support

SA-PO158

Kidney HMGCS2 Protects Against Ischemic Kidney Injury

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Background: Evidence for abnormal renal fatty acid oxidation (FAO) in kidney disease suggests that dysregulated metabolism is a key component of kidney disease pathogenesis. Ketogenesis is a central metabolic pathway in which ketone bodies are produced from FAO. While the liver is the main ketogenic organ, the rate-limiting enzyme for ketogenesis, mitochondrial Hydroxymethylglutaryl-CoA synthase 2 (HMGCS2), is induced in the proximal tubule of the kidney during fasting. We previously demonstrated that HMGCS2 induced in the kidney does not contribute to the circulating pool of ketones during fasting and cannot compensate for hepatic ketogenic deficiency. We hypothesized that kidney HMGCS2 may be acting locally within the kidney to maintain normal function during metabolic stress or injury.

Methods: Six2-Cre;Hmgcs2fl/fl (Six2CreHmgcs2) mice with kidney-specific Hmgcs2 deletion and Hmgcs2fl/fl littermate controls were subjected to ischemia/reperfusion injury (IRI). An acute kidney injury model with right nephrectomy and left IRI was used. Plasma creatinine and/or kidney mRNA/protein expression were assessed 24 hours after IRI. Using novel mouse models with proximal tubular hemagglutinin (HA)-tagged mitochondria with (Ggt1-Cre;Hmgcs2fl/fl-MITO-Tag, Ggt1Cre;Ggt1Cre;MITO-Tag) or without (Ggt1-Cre;MITO-Tag, Ggt1Cre-MITO-Tag) Hmgcs2 deletion, proximal tubular-specific mitochondria were isolated using anti-HA magnetic beads after unilateral IRI. Fatty acid oxidation (FAO) capacity was measured using palmitoylcarnitine as a substrate and oxygen consumption rate was determined by Seahorse.

Results: Six2CreHmgcs2 mice had significantly higher plasma creatinine levels and expression of kidney injury markers (Kim) 24 hours after IRI compared to Hmgcs2fl/fl littermate controls. Kidneys lacking HMGCS2 also had an increase in lipid droplet accumulation accompanied by a decrease in Pparα expression, however there was no significant difference in renal de novo lipogenesis gene expression. Proximal tubular-specific mitochondria isolated 24-hour post IRI from Ggt1Cre-MITO-Tag and Ggt1Cre;MITO-Tag kidneys demonstrated that mitochondria lacking HMGCS2 had significantly lower basal and ADP-stimulated FAO capacity.

Conclusions: Our data provide evidence that proximal tubular HMGCS2 may play an important role in maintaining mitochondrial function and FAO capacity, resulting in protection against ischemic kidney injury.

Funding: Other NIH Support - NIGMS

SA-PO159

Peroxisomal Inhibition Abolishes Dicarboxylic Acid-Mediated AKI Protection

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Background: Peroxisomes play important roles in metabolism, including in fatty acid oxidation (FAO). Interestingly, post-translational modification of lysine residues by succinylation promotes FAO and has also been linked to acute kidney injury (AKI). In addition, octanecosoy acid (DC) is a dicarboxylic acid that, upon FAO, promotes hyperuricinuria. Finally, studies suggest that 10,12-tetracosadiynoyl-CoA (TDYA) inhibits peroxisomal activity. Therefore, we hypothesized that DC promotes AKI via hyperuricinuria of renal peroxisomes and that TDYA blocks this response.
Methods: To test the role of DC, in AKI, mice were fed with control or 10% w/w DC diet 4 days prior to renal ischemia-reperfusion injury (IRI) and examined for AKI. Mice underwent contralateral nephrectomy and were euthanized the following day. Supplementation was provided until sacrifice. To test if TDYA would promote an opposite response, we treated another cohort of animals with or without daily doses of 2mg/kg TDYA (Sigma-Aldrich). Animals were fed on 10% DC, and underwent IRI as previously. Biochemical, histologic, and proteomic analyses were performed together with mitochondrial and peroxisomal activities.

Results: DC, prevented the rise of renal injury markers in IRI mice and improved morphological changes. On day 3, TDYA completely protected animals, which was confirmed by immunofluorescence and peroxisomal FAO activity, indicating mitochondrial fragmentation. In vitro, AA treatment reproduced this phenotype in PTCs, as dedifferentiated PTCs had greatly reduced mitochondrial volume and network length, demonstrating efficient protection against AKI. Proteomics evidenced a substantial increase in peroxisomal succinylation in DC-fed animals, which was confirmed by immunofluorescence and peroxisomal FAO activity, while mitochondrial activity was shown to be preserved. Furthermore, TDYA completely abolished the protective responses of DC, as it inhibited peroxisomal activity.

Conclusions: DC supplementation drives renal hyperfusion, promoting a shift from mitochondrial to peroxisomal FAO, and protecting against AKI. Meanwhile, peroxisomal inhibition with TDYA completely inhibits this protection and confirms the important role of peroxisomal succinylation in AKI protection following DC administration.

SA-PO160 Mitochondrial Morphology Regulates Proximal Tubule Cell Differentiation Status
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Background: Acute Kidney Injury (AKI) frequently occurs in hospitalized patients and predisposes them to developing chronic kidney disease (CKD). Our lab and others have shown prolonged proximal tubule cell (PTC) dedifferentiation in the context of maladaptive repair contributes to this AKI-to-CKD transition. One of the most striking histological features of dedifferentiated PTCs is fragmentation of the mitochondria, which occurs in the mitochondrial fission pathway involving dynamin-related protein 1 (Drp1). While it is known mitochondrial fragmentation reduces mitochondrial function, it is unclear if fragmentation contributes to PTC dedifferentiation.

Methods: Mitochondrial morphology in kidney tissue was monitored using super-resolution imaging of kidney tissue, we found that dedifferentiated PTCs had greatly reduced mitochondrial volume and network length, indicating mitochondrial fragmentation. In vitro, AA treatment reproduced this phenotype by inducing mitochondrial fragmentation early after injury, which was followed by dedifferentiation at later time points. Pharmacological inhibition of mitochondrial fragmentation prevented PTC dedifferentiation. Similarly, knocking down Drp1 in vivo after kidney injury improved mitochondrial morphology and reduced markers of dedifferentiation in all three injury models tested. Improved mitochondrial morphology was observed in vivo with reduced kidney fibrosis in all three models.

Conclusions: Inhibition of mitochondrial fragmentation prevents proximal tubular cell dedifferentiation and reduces renal fibrosis. Interventions targeting mitochondrial health may lead to novel therapeutics to improve chronic kidney injury.

SA-PO161 A Novel RIPK3/BRD4 Small Molecule Inhibits Arsenical-Induced AKI
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Background: Arsenicals such as lewisite, cause blistering of the skin as well as lung, kidney, and nerve damage. The development of arsenical warfare agents to warfare agents is a priority of the NIH CounterACT Program. To this end, we used single nucleus RNA sequencing (snRNAseq) to explore the nephrotoxic effects of phenylarsine oxide (PAO), a lewisite mimic, in an unbiased manner and synthesized a novel dual inhibitor (duali) that targets two necroptotic markers that are upregulated after lewisite exposure: receptor-interacting serine/threonine kinase 3 (RIPK3) and bromodomain-containing protein 4 (BRD4). BRD4 plays a critical role in inflammation and redox metabolism. Here we identify transcriptional alterations in the kidney following arsenical-induced damage and test the hypothesis that the duali protects against injury using in vivo and in vitro models.

Methods: snRNAseq was performed on kidneys from mice treated topically with PAO (4mg/kg) or vehicle for 6 and 24 hours. Protective effects of duali were evaluated in vitro utilizing proximal tubule cells (PTCs). Cells were pretreated with duali 1 h before PAO and examined for necroptosis, western blots, and qPCR at 4, 20, or 24 hours. In vivo efficacy was assessed 24 post PAO (4-6mg/kg). Duali was applied topically 30 min post PAO exposure.

Results: Duali treatment inhibits phospho- mixed lineage kinase domain-like pseudokinase (MLKL) and total RIPK3 and MLKL transcripts (p < 0.05) in vitro. We also observed a recovery of glomerular filtration rate in PAO treated mice following duali treatment, which was associated with decreased expression of pRIPK3. snRNAseq in PAO treated mice revealed that fatty acid (FA) β-oxidation, FA biosynthesis, and PPAR-α pathways were regulated by duali and protected against AKI.

Conclusions: While the treatment with duali ameliorated PAO induced kidney injury, the mechanism of action remains to be elucidated. We have shown that cutaneous PAO exposure alters gene transcription and upregulates FA metabolism suggesting a compensatory response following metabolic perturbation. We conclude that our duali may be used as a potential therapeutic in arsenical-induced AKI. Future studies aim to confirm the precise mechanisms behind BRD4- and duali-mediated improvements of renal function.

Funding: Other NIH Support

SA-PO162 Continuous Antithrombin III Infusion in a Clinically Relevant Sepsis Model
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Background: Despite unacceptably high mortality and economic burden, effective therapeutic strategies for sepsis remain elusive. Disparities between septic patients and animal models may be caused by drug pharmacokinetics, route, and timing of drug administration. Antithrombin III (AT) is an anticoagulant that might ameliorate sepsis-induced multiorgan dysfunction, though clinical trial results are conflicting due to variation in patient selection and drug regimens. AT has not been tested in clinically relevant sepsis models. AT has a short half-life, so we devised a method to continuously infuse drugs starting 6-12 h after cecal ligation and puncture (CLP). We asked, “Is AT effective in a clinically translatable sepsis model, and does the route of administration matter?”

Methods: We catheterized the mouse jugular vein, then connected the catheter to an osmotic minipump containing saline. After 1 wk stabilization, we performed CLP and topically infused saline or the containing AT or saline. We set a 6-12 h-time delay between sepsis induction and treatment by incorporating a 4 cm saline-filled catheter in the circuit. We measured the actual time lag with FITC-sinistin and measured its systemic appearance with a transdermal fluorescence detector. Survival studies were conducted in separate experiments, we collected blood, kidney, liver, and lung at 48 h for biochemical and histological tests. To examine the effect of administration route, we compared continuous AT infusion with saline infusion, and a conventional bolus AT injection.

Results: First, we detected a sustained fluorescence signal in the systemic circulation 5–6 hours after adding FITC-sinistin to our drug administration system. Second, delayed, continuous AT infusion significantly improved 7-day survival compared to saline-infusion (65% vs. 29%, n = 21/group, p = 0.018). Continuous AT infusion markedly improved survival vs. a single injection of AT (65% vs. 19%, n = 21 group, p = 0.003). Continuous AT attenuated liver injury but not renal or lung injury in the histology and biochemistry analyses.

Conclusions: We created a clinically relevant murine sepsis model with both a continuous infusion and time lag. Survival was higher in continuous AT infusion than either single bolus injection or vehicle. Future studies will elucidate the mechanism of the survival benefit.

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

SA-PO163 Quantitative Proteomics Analysis of Differentially Expressed Proteins in Septic Mice Kidney With Humanin Treatment
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Background: Sepsis-associated acute kidney injury (SA-AKI), which carries a high morbidity and mortality in patients, has no effective therapeutic strategies and its mechanisms are not fully understood. Increasing evidence have already showed that renal mitochondrial dysfunction plays a pivotal role in sepsis. We aimed to determine the effects of humanin, a mitochondrial-derived cytotoxic peptide on kidney injury in septic mice, and look for differentially expressed proteins after humanin treatment.

Methods: A murine model of sepsis (C57BL/6 mice, 8-10 weeks, male, n=6 for each group) was constructed by one single dose of intraperitonially lipopolysaccharide (LPS) injection (10mg/kg, LPS group) or PBS (Control group). Humanin (a potent analog of humanin) was intraperitonially injected 15 minutes later with a dose of 1mg/kg (HN group). Blood was collected (4 hours) after injection. Serum creatinine (Scr) and KIM-1 was determined, kidney histology staining, renal inflammatory cytokines, mitochondrial function were evaluated. To analyze the global proteome of the kidney tissue, the 4D-Label-free quantification analysis was applied to screen differentially expressed proteins in 3 groups (n=3 for each group). The parallell reaction monitoring (PRM) was used to verify the selected target proteins.

Results: HNG significantly reduced serum levels of Scr and BUN in a dose-dependent manner (0.2mg/kg, 0.4mg/kg and 1mg/kg), inhibited renal expression of IL-6, IL-1β and HMGB1 and reduce the damage of mitochondria in renal tubular epithelial cells in LPS-induced AKI. Collectively, 5960 proteins were identified in the label free quantification mass spectrometry, 5111 of which were quantifiable. NF-kappa B, Toll-like receptor, NOD-like receptor or IL-17 signaling pathways were significantly enriched,among which 7 proteins were selected for verification by PRM, and they were CD14, Casp3, Rela, Gbp2, Gbp3, Gbp5 and S100a9.

Funding:

Underline represents presenting author.
Conclusions: Humanin improves mitochondrial function and alleviates renal tubular injury in LPS-induced AKI. The map of the global proteomics enables further understanding of SA-AKI and will provide great help for seeking more potential therapeutic targets for SA-AKI.

Funding: Government Support - Non-U.S.

SA-PO164

Differential Renal Responses to Dexamethasone in Rats and Mice Following AKI

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Background: Acute kidney injury (AKI) is a common cause of kidney failure and mortality. No treatments are approved, but the availability of novel diagnostic tools and biomarkers and better understanding of human pathogenesis have increased the likelihood of developing an effective therapy. A major missing link to support successful clinical trials in this area is the lack of evidence that efficacy in preclinical models of AKI is translatable into humans. Because there is existing evidence of dexamethasone (dexa) benefit in human (DECS trial) and rodent AKI, dexa was evaluated in ischemia-reperfusion (IR) induced AKI in rats and mice.

Methods: Dexamethasone was administered via IP injection to mice (12mg/kg) and rats (3mg/kg) 30 min before kidney ischemia reperfusion (IR). Plasma creatinine (pCr), transcutaneous GFR (tGFR) and kidney gene expression were evaluated 24h after the procedure. Results: Dexa reduced plasma creatinine, kidney proinflammatory genes (IL-6, CCL2, IL-1β) and increased tGFR on day 1 after IR in rats but not in mice. Consistently, dxatreatment reduced plasma corticosterone levels (translational target engagement (TE) biomarker) only in rats. Kidney mRNA level of glucocorticoid receptor NR3C1 was downregulated in mouse IR but remained unchanged in rat IR. Similar plasma dexa concentrations were detected in rat and mice.

Conclusions: While the interpretation of these data is limited by the lack of availability of TE and plasma exposures in the DECS clinical trial, the differential responses observed in rat and mice may be attributed to downregulation of steroid receptor expression in mouse kidneys. Appropriate omics characterization together with translational biomarkers and compound exposures in humans and animals may provide significant insights and increase preclinical model translatability in AKI.

Funding: Commercial Support - Janssen

SA-PO165

Acute Exposure to Particulate Matter Affects Renin-Angiotensin System in the Kidneys

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Background: Recent studies have shown that exposure to fine particulate matter (PM) leads to systemic inflammation and furthermore increases the risk of cardiovascular disease. Epidemiologic studies have shown a significant association between exposure to PM and chronic kidney disease and progression to end-stage renal disease. In order to understand the underlying mechanism of PM to systemic effects, we examined the effects of acute exposure to high-concentration PM on kidney injury in an experimental mice model.

Methods: Unilateral Ureteral Obstruction (UUO) was induced in 10-week-old Sprague Dawley rats. For fine PM, we used Carbon black CP(CAS No 1333-86-4) dispersed in a specialized inhalation chamber. SD rats were exposed to high-concentration CP particles for 3 hours for 3 days in a nose-only inhalation chamber. Groups were divided into 1) Control, 2) UUO, 3) PM, 4) UUO + PM, 5) UUO+ PM+ ARB L158809 (Merck & Co, Inc, NJ, USA) by drinking water (1.5mg/kg/d).

Results: Weight loss was apparent in rats exposed to carbon black and PM exposure group. Blood pressure was also increased after the study in the PM and UUO groups. In the lung of PM exposure, renin, angiotensinogen, AT2R gene expression significantly increased and ACE2 decreased. In the kidney, the expressions of renin, and angiotensinogen were not changed after PM exposure, but ACE2 expression significantly decreased in the kidney and UUO further diminished the expression. ARB treatment restored the expression.

Conclusions: Altogether, these findings suggest that exposure to PM can affect the renin-angiotensin system in the kidney, in a different manner from other organs.

Funding: Private Foundation Support

SA-PO166

Functioning and Molecular Mechanism of Histone Lactylation in AKI

Zhenzhen Functioning and Molecular Mechanism of Histone Lactylation in AKI: Mechanisms - III

Republic of Korea

Methods: Although lactylation has been widely studied in the context of cancer, inflammation, and regeneration, its role in AKI remains poorly understood. To address this gap, we conducted a comprehensive investigation into the effects and mechanisms of lactylation in ischemic AKI, utilizing flow cytometry, Western blot, PCR, immunofluorescence, Seahorse in vivo and in vitro.

Results: Our findings demonstrated that pan-lactylation and HJ1k18 lactylation were significantly reduced in tubular epithelial cells (HK-2 cells) and renal tissue under ischemia in vitro and in vivo. Interestingly, we found that ING2 expression were significantly reduced under ischemia and overexpression of ING2 could inhibit apoptosis in HK-2 cells. In mechanism, ING2 knockdown or overexpression could regulate lactylation. Finally, ING2 could regulate lactylation through p300 and promoting histone lactylation could reverse ischemia-induced HK-2 cells injury and ischemia-reperfusion induced AKI in mice.

Conclusions: These results suggested that an unrecognized role of lactylation in kidney injury and a promising target for therapeutic intervention of AKI.

SA-PO167

Assessment of Extracellular Vesicles Isolated from the Culture Medium of Ischemic Renal Proximal Tubular Epithelial Cells

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Background: Extracellular vesicles (EVs) are membranous particles released by a cell into the extracellular environment. They play an emerging and important role in cell communication and have been implicated in a variety of pathological conditions including acute kidney injury and chronic kidney diseases. Our objective was to characterize the dynamics of extracellular vesicle release by proximal tubular epithelial cells exposed to hypoxia and reoxygenation (H/R).

Methods: Primary human renal proximal tubule epithelial cells (hPTECs, n=3) were exposed to 24 hours of 1% hypoxia followed by 3 hours of reoxygenation. Proximal tubule EVs were isolated by megalin immunofluorescence and EVs were isolated from the conditioned culture medium by ultracentrifugation (100,000g for 1h30min). Extracellular vesicle size and quantity were assessed by nanoparticle tracking analysis (NTA) and EV protein quantification.

Results: The immunofluorescence analysis indicated hPTECs were megalin-positive and this was not altered by H/R. NTA indicated that the H/R exposed cells released ~2-fold more EVs than normoxia (p<0.05). This was further supported by an increase in EV protein in conditioned media of H/R vs normoxia (1.08±0.17 vs 0.75±0.12 μg/ml, p<0.05). The mean particle sizes were not significantly different between H/R (153.5nm) and normoxia (145.8nm) groups.

Conclusions: Our initial data suggest that under hypoxia induces a shift in EV release from proximal tubule cells with greater EV release. These findings suggest that proximal tubule EV release may be altered in the context of ischemic kidney disease. Such changes may contribute to disease pathogenesis.

Funding: Government Support - Non-U.S.

SA-PO168

The Blood Transcriptome Is Reflective of Renal Tissue Injury in Endotoxin-Associated Acute Kidney Failure

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Background: MicroRNA (miR) regulate the translation of RNA involved in renal injury and recovery processes in endotoxin-associated acute kidney injury (sAKI). We previously identified the renal tissue response in sAKI as a series of temporally unique stages consisting of inflammation progressing to translation shutdown and organ failure. We hypothesize the blood miR and RNA transcriptome exhibits a response reflective of underlying renal tissue sAKI stage.

Methods: Kidney bulk RNAseq and miRNAseq were performed in an established murine model of sAKI at 0 (baseline) and 1.16 hr (injury) after endotoxin tail vein injection (LPS, n = 5 per timepoint). Total RNA (consisting of RNA and miRNA) extracted from bulk kidney tissue and whole blood (blood), DNAsese treated, and globin depletion (blood) only performed. For each miR and RNA, libraries prepared and sequenced (miR-10: 100 ng lead depth; RNA-25-30 million reads per sample, RNA-25-30 million reads per sample) to miR-10 transcriptome (STAR). Counts were TMM normalized, log-transformed (counts-per-million, EdgeR), generating expression data. Pearson correlation between blood and kidney performed and common genes with r >0.8 and FDR <0.05 considered significantly correlated and pathway analysis performed (Pathfinder).

Results: Transcriptome analyses performed in the blood and the kidney revealed positively correlated miR (n=133 r = 0.8) and RNA (n= 388, r =0.99) shared between the blood and kidney at each timepoint. Pathway analysis revealed significant upregulation (p <0.05) of inflammatory, extracellular matrix/membranous pathways at 1 hr after LPS (NFkB pathway, cell-matrix adhesion, endothelial cell migration). At 16 hr after LPS there were shared alterations in transcription processing, miR regulation, viral responses, and catalytic processes. Analysis of the transcriptome shared between the blood and the kidney revealed parallel activation of RNA involved in the innate immune response and metabolic processes, regulated by miR (miR-144/Cxcl10, miR-298/Cd46, miR-545/Saa2).

Conclusions: Our data suggest that miR regulate RNA in several important sAKI-related pathways. These data demonstrate that the blood transcriptome may be reflective of underlying sAKI tissue state and the utility of these transcriptomic biomarkers.

Funding: Private Foundation Support
Background: IL-10 is a cytokine with multiple effects in immunoregulation and inflammation. IL-10 can protect the kidney from ischemia-reperfusion injury (IRI) to be acutely protective, long-term alterations in kidney lymphatics following initial injury have never been assessed.

Methods: C57BL/6 mice subjected to bilateral IRI for 30 mins. The rats were divided into 3 groups: sham, IR, and IR+C21 (AT2R agonist, i.p. 0.3 mg/kg b.wt). After 3 days kidney cells were isolated and analyzed with flow cytometry for investigating CD45+, CD3+, CD4+, and FoxP3+ T cells. Also B6 mouse splenic CD45+ T cells were isolated using magnetically labelled anti-CD4, which were activated with anti-CD3/anti-CD28/IL-2/TFG and treated with C21 alone or in the presence of AT2R antagonist PD123319. NO synthesis inhibitor LNAME, PP2A inhibitor okadaic acid.

Results: The female rats showed CD45+, CD3+ and CD4+ T cells infiltration 3days after IR. However, the renal accumulation of CD45 and CD45 is lower in female (~1% of total kidney cells) compared to 3 days IR data in male (7%) rats- suggesting a sex difference, C21 administration reduced the CD45+ T cells infiltration, and increased CD4+FoxP3+ regulatory T cells population and reduced kidney injury as evident by reduced plasma creatinine. However, BUN and proteinuria analysis did not suggest any significant changes with AT2R activation at 3 day post-IR. The ex-ovo splenic CD4+ T cells revealed that C21 treatment modulated the CD45+ T cells into CD45-Treg cells as determined by 2-fold increase in transcription factor FoxP3 expression. AT2R antagonist PD123319 reduced 2-fold, suggesting the involvement of AT2R. The PP2A inhibitor okadaic acid remarkably attenuated C21-induced FoxP3 increase indicating while the NO synthase inhibitor L-NAME caused only a moderate reduction in C21-induced FoxP3 expression.

Conclusions: IR causes a lower immune cell infiltration in females than males and the AT2R-mediated protection and Treg modulation occurs via PP2A pathway.

Funding: Other NIH Support - NIH R01DK117495 and NIHRO1DK061578 support

SA-POI171

Macrophage Subtypes Affect the Damage and Repair of Sepsis-Associated AKI by Regulating the Phagocytic Function of Kidney Epithelial Cells

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Background: Different subtype macrophages play different roles in acute kidney injury, but how they work is still not fully defined. This research highlighted the mechanism underpinning the clearance of dying cells and its impact on the surrounding environment including the phagocytotic function of kidney epithelial cells.

Methods: Mouse RAW264.7 cells (peritoneal macrophage cell line) were cultured, in which LPS or IL-4 was used to induce the M1 or M2 phenotype macrophages. The changes of phenotype were verified by Western Blot and flow cytometry. M1 and M2 macrophages were then co-cultured with TCMK-1 cells (kidney epithelial cell line) with or without LPS treatment for 24 h in a trans-well system. Inflammation cytokines were detected by quantitative real-time PCR (qPCR). Apoptotic cell death was assessed by Annexin V/Propidium iodid staining, while the phagocytic capacity of TCMK-1 cells was evaluated by the uptake of FITC-labelled pHrodo E.coli Bioparticles® Conjugate, and then detected by a flow cytometer.

Results: RAW264.7 cells were successfully induced into M1 and M2, which were verified by increased iNOS expression, F4/80+CD206+ cells and F4/80+Arg-1+ cells in M2 macrophages. In trans-well culture, M1 macrophages increased pro-inflammatory mediators including IL-1β, IL-6 and TNF-α in TCMK-1 cells, especially with LPS stimulation, but M2 macrophages raised anti-inflammation mediators. A similar change trend was revealed in the percentage of apoptotic TCMK-1 cells, together with Bax and EPOR protein expression. Most importantly, regardless of LPS, the phagocytic function of TCMK-1 cells was decreased by co-cultured M1 macrophages, but it was enhanced by cocultured M2 macrophages.

Conclusions: M1 macrophages affect adjacent kidney epithelial cells by releasing inflammatory mediators, inducing apoptotic cell death, compromising phagocytic function and further repair, whereas M2 macrophages have opposite impacts.

SA-POI169

An IL10Ra-Mediated Regulation of T Regulatory Cells by Myeloid Cells in AKI

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Background: IL-10 is a cytokine with multiple effects in immunoregulation and inflammation. IL-10 can protect the kidney from ischemia-reperfusion injury (IRI) - a condition that causes tubular injury and dysfunction due to hypoxia and inflammation. IL-10 binds to its receptor (IL-10R) on the cell surface and activates intracellular signaling pathways that suppress the production of pro-inflammatory cytokines and pro-apoptosis factors. However, the mechanistic role of IL-10Ra has not been investigated in AKI, especially during the resolving phase.

Methods: We generated IL10Ra+/- Lym-MCre mice for specific deletion of IL10Ra in myeloid cells and subjected them to bilateral or unilateral IRI (uIRI) followed by reperfusion for 13 days. The mice were analyzed for immunophenotypic, histopathological, biochemical, and molecular analysis to evaluate immune profile and pathophysiology. Bioenergetics with parameters of oxidative phosphorylation and glycolysis, along with differentiation assays were performed to gain a mechanistic view of immunomodulation.

Results: Myeloid-cell-specific deletion of IL-10Ra led to a significant increase of CD4 effector memory cells and a marked reduction of regulatory T cells in the spleen as compared to IL-10Ra-sufficient controls. The expression of pro-inflammatory cytokines, co-stimulatory markers as well as activated CD8 T cells and CD8 effector memory T cells were also elevated in the KO mice as compared to the control. There were no differences observed in kidney function in KO mice subjected to bilateral IRI for 24 hours (Acute phase). However, when subjected to uIRI, the IL10Ra deletion led to reduced kidney function as shown by increased plasma Creatinine and BUN, increased tubular Injury score, and marked elevation of injury biomarkers KIM1 and NGAL. Interestingly, KO macrophages subjected to bioenergetics analysis revealed a reduction in mitochondrial respiration and altered potential in generating FoxP3+ T-regulatory cells (Tregs).

Conclusions: Our findings reveal a previously unrecognized link between microglial dysfunction, Treg-differentiation, and IL10Ra signaling in resolving of AKI, and could also serve as a potential target for therapeutic modulation.

SA-POI170

Angiotensin II Type 2 Receptor (AT2R) Modulates CD4+ T Cells into Regulatory T Cells (Tregs) in Kidney Ischemia-Reperfusion Injury in Rats: Role of PP2A

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Background: Kidney ischemia reperfusion injury (IRI) is the common pathophysiology of acute kidney injury (AKI) associated with immune cell infiltration including T cells. Male kidney is more susceptible to AKI than females. Recently, we have shown that IR causes infiltration of CD4+ T cells in male rats and AT2R activation reduced renal CD45+ T cells infiltration and modulated CD4+ T cells into anti-inflammatory Tregs ameliorating AKI. Infiltration of these cells in females and the mechanism of AT2R-mediated modulation of CD4+ T cells into Tregs are unknown.

Methods: Bilateral IR was performed on female SD rats for 30 mins. The rats were divided into 3 groups: sham, IR, and IR+C21 (AT2R agonist, t.p. 0.3 mg/kg b.wt). After 3 days kidney cells were isolated and analyzed with flow cytometry for investigating CD45+, CD3+, CD4+, and FoxP3+ Treg cells. Also B6 mouse splenic CD45+ T cells were isolated using magnetically labelled anti-CD4, which were activated with anti-CD3/anti-CD28/IL-2/TFGF and treated with C21 alone or in the presence of AT2R antagonist PD123319. NO synthesis inhibitor LNAME, PP2A inhibitor okadaic acid.

Results: The male rats showed CD45+, CD3+ and CD4+ T cells infiltration 3days after IR. However, the renal accumulation of CD45 and CD45 is lower in female (~1% of total kidney cells) compared to 3 days IR data in male (7%) rats- suggesting a sex difference, C21 administration reduced the CD45+ T cells infiltration, and increased CD4+FoxP3+ regulatory T cells population and reduced kidney injury as evident by reduced plasma creatinine. However, BUN and proteinuria analysis did not suggest any significant changes with AT2R activation at 3 day post-IR. The ex-ovo splenic CD4+ T cells revealed that C21 treatment modulated the CD45+ T cells into CD45-Treg cells as determined by 2-fold increase in transcription factor FoxP3 expression. AT2R antagonist PD123319 reduced 2-fold, suggesting the involvement of AT2R. The PP2A inhibitor okadaic acid remarkably attenuated C21-induced FoxP3 increase indicating while the NO synthase inhibitor L-NAME caused only a moderate reduction in C21-induced FoxP3 expression.

Conclusions: IR causes a lower immune cell infiltration in females than males and the AT2R-mediated protection and Treg modulation occurs via PP2A pathway.

Funding: Other NIH Support - NIH R01DK117495 and NIHRO1DK061578 support
Impact of HIF Stabilizer ICA on Nr2f2/Kap1 Pathway in Macrophages
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Background: Mice treated with HIF-stabilizer 2-[(1-chloro-4-hydroxysoquinoline-3-carboxamido) aceta (ICA) were protected from ischemia-reperfusion induced AKI, as were mice after treatment with Nr2f2-induced 1-[2-cyano-3,12-dioxooleana-1,9(11)-diien-28-yl]imidazole (CDDO-im). However, the potential interactions of HIF and Nr2f2/Kap1 pathways have not been studied in this context.

Methods: Bone marrow was isolated from wildtype (WT) and HIF1α-KO mice and differentiated into bone marrow-derived macrophages (BMDM). Cells were cultured for 5 days before treatment with vehicle, CDDO-im (50nM), ICA (250nM) or CDDO-im+ICA (50nM+250m) for 24 hours. Cells were harvested and mRNA expression of Nr2f2 (Nqo1) and HIF1α-target genes (Hmxox1, Glut1, Ldha) using quantitative real time PCR was analyzed. Protein expression of Keap1, Nqo1 and HIF1α was studied by Western blotting. Statistical analyses were performed using one-way ANOVA and Dunnett post hoc test.

Results: In BMDM from WT mice, treatment with CDDO-im, ICA or the combination of both (CDDO-im+ICA) resulted in an upregulation of Nqo1 mRNA expression (Vehicle: 1αβ vs. CDDO-im: 4.4±1.3 (p<0.05); vs. CDDO-im+ICA:4.4±1.5 (p<0.05)) and Hmxox1 expression (Vehicle: 1αβ vs. CDDO-im: 1.7±0.4 (p<0.05); vs. ICA: 5.0±1.3 (p<0.001); vs. CDDO-im+ICA: 4.1±0.6 (p<0.001)). This effect was not reversed in HIF1α-KO cells for Nqo1 (Vehicle: 1αβ vs. CDDO-im: 5.4±1.3 (p<0.05); vs. ICA: 3.6±0.9 (p<0.005); vs. CDDO-im+ICA: 4.8±0.6 (p<0.01)). However, HIF1α-target genes Hmxox1, Glut1 and Ldha were significantly upregulated by ICA treatment in WT mice, but not by CDDO-im or vehicle treatment. Western blotting confirmed these results at the protein level with a decrease of Keap1 expression (Vehicle: 1αβ vs. ICA: 0.7±0.3) and an increase of Nqo1 expression (Vehicle: 1αβ vs. ICA: 1.3±0.2 vs. CDDO-Im: 4.4±1.4 (p<0.05); vs. ICA: 5.0±1.3 (p<0.001); vs. CDDO-Im+ICA: 4.1±0.6 (p<0.05)).

Conclusions: These in vitro studies demonstrate an upregulation of the Nr2f2-target gene Nqo1 following HIF-stabilizer, ICA, treatment. However, this effect was HIF1α independent. These results indicate a potential overlap of the two pathways HIF and Nr2f2/Kap1 playing important roles in ischemic AKI. In vivo studies in AKI-models are warranted to assess the impact on these dual effects.

Funding: Government Support - Non-U.S.

Neutrophil Extracellular Traps (NETs) in the Peritoneal Cavity
Contribute to Septic AKI (SAKI) via IL-17A Production in a Mouse Model

Background: There are no specific treatments for SAKI. We previously showed that PAD4 KO and 17A KO protected against SAKI, therefore studied DPT cells in normal and diseased mouse and human kidneys. AMNIS imaging flow cytometry confirmed the presence of both CD4 and CD8 co-receptors on individual DPT cells. DPT cells had significant percentages of CD4 and CD8+ T cells in normal mouse kidneys. We thereon studied DPT cells in normal and diseased mouse kidneys.

Methods: PAD4 KO, IL-17A KO and wild-type (WT) controls were studied to CLP. We assessed kidney function and IL-17A levels in peritoneal lavage fluid (PLF) and blood. Leucocyte infiltration in PLF, blood, and kidney were assessed by flow cytometry. NET formation in the cells in PLF was assessed by immunocytochemistry. To further investigate the effect of NETs on SAKI, we collected neutrophils from WT PLF at 18h after CLP and administered them intra-peritoneally into PAD4 KO mice immediately after CLP.

Results: PAD4 KO and IL-17A KO attenuated SAKI and PAD4 KO decreased IL-17A levels in PLF and blood at 18h after CLP. CLP upregulated neutrophil infiltration into PLF, blood, and kidney at 18h. IL-17AKO attenuated neutrophil increase in blood and infiltration into kidney, but not in PLF. The cells in PLF at 18h after CLP contained >70% of neutrophils and formed NETs without any adaptive transfer of WT neutrophils partially counteracted the protective effect of PAD4 KO on SAKI.

Conclusions: We found that PAD4 KO and 17A KO protected against SAKI, and PAD4 KO decreased IL-17A production in plasma and peritoneal cavity. IL-17A promoted neutrophil infiltration into blood and kidney after CLP. Adoptive transfer of WT neutrophils into the peritoneal cavity reversed the beneficial effect of PAD4 KO on CLP-induced SAKI. These findings suggest that NETs in the peritoneal cavity might contribute to a distant organ effect of SAKI via IL-17A production.

Funding: NIDDK Support

Distant Organ Consequences of Renal Ischemia and the Effect of Renal Extracellular Vesicles (Exosomes)
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Background: Acute kidney injury is common, expensive and deadly. Morbidity and mortality remain very high; there is no specific treatment, yet the cause of death is frequently due to failure of extra-renal organs. We and others have demonstrated remote organ dysfunction and systemic inflammation following renal ischemia. We have also shown beneficial effects of extracellular vesicles (EV, exosomes) in models of renal injury. We hypothesized that EV would also decrease remote organ inflammation following renal ischemia. However, the effect of EV in the presence of renal failure could be limited.

Methods: The studies were performed in a well-characterized model of renal ischemia. Multiple time periods of ischemia were used in order to assess the effect of EV treatment independent of renal function. Both tissue and systemic inflammation as well as cell death were quantified.

Results: As in previous studies, markedly improved renal function and structure were found postischemia in groups treated with renal EV, given 24 hours after renal ischemia when renal failure had been established. Systemic inflammation, quantified as serum interleukin-1, -6 and tumor necrosis factor alpha, was significantly decreased in the treated group, even in the presence of prolonged ischemia. Tissue inflammation varied with the organ examined. The number of neutrophils in the heart decreased in the renal ischemia/EV group (figure 1). Anti-inflammatory interleukin-10 was significantly increased in all organs evaluated in the EV treated group, from 110–130% of sham levels. Evidence of apoptotic cell death was decreased in the heart in the EV treated groups.

Conclusions: Systemic and remote organ manifestations of inflammation after renal ischemia are amenable to treatment. Exosomes derived from renal tubule cells improve multiple abnormalities following renal ischemia.

Funding: Other NIH Support - NIAID, Veterans Affairs Support

Analysis of TCRβ+CD4+CD8+ (Double Positive) T Cells in Normal and Diseased Kidneys in Both Mice and Humans

Background: The roles of CD4, CD8 and double negative (DN) T cells are being increasingly recognized in normal and diseased kidneys. However, there is little information about kidney TCRβ+CD4+CD8+ (double positive, DP) T cells. We therefore studied DPT cells in normal and diseased mouse and human kidneys.

Methods: Flow cytometry and single cell RNA-seq (scRNA-seq) were used to analyze kidney DPT cells in C57BL/6 mice at baseline, after ischemia reperfusion (IR) and cisplatin-induced AKI in comparison to CD4, CD8 and DN T cells. Effects of LCMV (virus) infection as well as gut microbiome were studied. Human kidneys from patients with renal cell carcinoma, with and without underlying ESRD were studied.

Results: DPT cells constituted a minor (0.16±0.03%) population of the total TCRβ+cells in normal mouse kidneys. AMNIS imaging flow cytometry confirmed the presence of both CD4 and CD8 co-receptors on individual DPT cells. DPT cells had significant K67 (87.4±3.3%) and PD1 (22.7±3.6%) expression. DPT cells had effector (69.6±7.5%) and central (18.3±3.5%) memory phenotype with significant IFNγ, TNFα and IL-17 expression. DPT cells expressed the metabolism-related proteins namely HKII, CPT1a and pS6. Percentage of DPT cells increased after ischemic AKI (0.47±0.11%, P=0.048) and cisplatin-induced AKI (0.40±0.14%, P=0.17) in 24 hrs compared to baseline. LCMV infection elevated kidney DPT cell percentage (0.40±0.08% vs 0.16±0.03%, P<0.01) and induced distinct functional and metabolic changes. Germ-free mouse kidney DPT cell proportions and functional properties were comparable to WT mice. scRNA-seq analysis showed increased expression of Ki67 and Ccr7 and enrichment of TNFα and oxidative phosphorylation signaling related genes in DPT cells. Human kidneys contained high proportions of TCRβ+CD4+CD8+ DPT cells.
DPT cell populations in both adjacent normal (median (IQR) = 0.97±(0.44)) and cancerous (0.29±(10.40)) tissue.

**Conclusions:** TCRε+CD4+CD8+ double positive T cells constitute a minor population of both mouse and human kidney T cells, with distinct features in normal and diseased kidney compared to other T cells. Future studies of this T cell population are needed to evaluate their roles in normal and diseased kidney.

**Funding:** NIDDK Support

### SA-PO177

**Coronin-1α Remodels Inflammatory Microenvironment to Dictate AKI Progression**

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**Background:** T-cell-mediated immune response is a key mechanism in AKI onset. Our proteomics data indicate that coronin-1α is markedly induced in the kidneys of AKI, and it is highly expressed in T cells and macrophages to regulate immune cell activation, migration, and phagocytosis. As a protein first noted for its role in modulating actin dynamics and phagocytosis-host interactions, coronin-1α is spread throughout the cytoplasm and the cell cortex when the cell is resting. Once a pathogen enters the cell, coronin-1α binds to the phagosomal membrane, ensuring the binding and activation of calcineurin, ultimately stopping the fusion of lysosomes with phagosomes. Whether coronin-1α plays a role in AKI is unknown.

**Methods:** Male and female coronin-1α knockout (Coro1A-/-) mice were used to induce AKI by renal ischemia-reperfusion injury (IRI) at 1, 2, and 3 days (d) or cisplatin at 3d, respectively. A 3-month IRI model was constructed to evaluate AKI long-term outcomes in Coro1A-/- mice. AKI patients samples were employed. Global-phospho-proteomics and single-nucleus RNA-Seq were utilized.

**Results:** After AKI, serum creatinine and blood urea nitrogen levels were largely preserved in Coro1A-/- mice compared with wild-type mice. Kidney morphological damages and the expression of the tubular injury markers and chemokines were consistently decreased in Coro1A-/- mice. Knockout coronin-1α effectively increased the clearance of apoptotic cells by macrophages. As a consequence, tubular cell proliferation was enhanced in Coro1A-/- mice. In the 3-month IRI model, Coro1A-/- mice exhibited significantly improved kidney function, histology and less fibrotic lesions. Mechanistically, global phospho-proteomics revealed that inflammation-related signaling pathways were repressed after deleting coronin 1α, and T-lymphokine-activated killer-cell-originated protein kinase (TOPK) was the topmost differentially expressed protein in Coro1A-/- mice diseased kidneys. Single-nucleus RNA-Seq showed higher expression of TOPK in the isolated Coro1A-/- immune cells. In vivo and ex vivo TOPK regulated an inflammatory microenvironment formation, enhancing apoptotic neutrophil clearance and providing favorable conditions to prime tubule repair and regeneration.

**Conclusions:** Coronin-1α is vital in determining AKI prognosis, and TOPK is a potential immune checkpoint in mitigating AKI.

**Funding:** NIDDK Support

### SA-PO178

**Glutamine Blockade After Severe AKI Reduces Kidney Fibrosis by Controlling Translational Initiation Factor Phosphorylation**

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**Background:** In several inflammatory kidney diseases, circulating blood neutrophils migrate to sites with high cytokine but low oxygen concentrations. Migrating neutrophils interact with extracellular matrix proteins via β2-integrins. We hypothesized that β2-integrins control hypoxia-inducible factor 1α (HIF1α) activation under basal and inflammatory conditions.

**Methods:** HIF1α in human neutrophils was studied by immunoblotting, qPCR, bulk mRNA sequencing. Neutrophil suspension was achieved on polyHEMA, and adhesion on fibronectin (FN). Prolact hydroxylases (PH) were inhibited with Roxadustat (ROX) and normobaria hypoxia (1% O2). β2-integrin signaling was analyzed by blocking and activating antibodies.

**Results:** We observed HIF1α protein in ROX-, but not GMCSF-treated neutrophils after 4h with a 3-fold synergistic effect by combined GMCSF/ROX treatment. Increased HIF1α protein was observed in neutrophils cultured on FN but not under stringent serum conditions. Importantly, HIF1α protein in combined ROX-GMCSF-treated neutrophils on FN was strongly reduced by blocking β2-integrins and, conversely, induced by activating β2-integrins antibodies on polyHEMA. The synergistic ROX/GMCSF effect as well as the blocking β2-integrin effect for HIF1α protein were recapitated under hypoxic conditions. Mechanistically, the HIF1α mRNA increase by O2 was necessary but not sufficient to explain the adhesion-dependent HIF1α protein induction. Importantly, GMCSF increased serine phosphorylation of eEF2 and 4EBP1 HIF1α translation initiation factors in neutrophils on FN in an β2-integrin dependent manner. Synergistic HIF1α protein induction was demonstrated in neutrophils that transmigrated through FN towards GMCSF and ROX in vitro. Neutrophil bulk mRNA sequencing revealed a HIF1α-dependent enrichment of cytoskeletal gene sets under inflammatory conditions. Finally, PH inhibition by ROX or hypoxia enhanced cytoskeleton-dependent neutrophil adhesion.

**Conclusions:** β2-integrin engagement restricts HIF1α activation to neutrophils that emigrate from the blood to inflammatory sites under pharmacologic or hypoxic conditions.

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

### SA-PO180

**Clonal Hematopoiesis of Indeterminate Potential Associates with Severe AKI**

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**Background:** Clonal hematopoiesis of indeterminate potential (CHIP) is the clonal expansion of hematopoietic stem cells due to somatic mutations like TE2 gene mutation, without evidence of hematologic malignancy or cytopenia. CHIP is associated with a pro-inflammatory state. The role of inflammation in acute kidney injury (AKI) among individuals with CHIP remains unclear.

**Methods:** Bone marrow cells (BMC) were collected from recipient mice (CD45.1 isotype). Tet2-deficient and control mice (CD45.2 isotype). Lethally irradiated male recipient mice underwent retroorbital injection of 5 × 10^7 BMC, consisting of 80% recipient cells and 20% Tet2-deficient (Tet2-/-) or control (Tet2+/+) cells. Flow cytometry confirmed successful engraftment and clonal expansion of Tet2-deficient cells, and then BMC were collected. Tet2-/- mice underwent unilateral kidney vascular clamping with contralateral nephronecrosis (Unx-IRI). Renal function was assessed by BUN and creatinine levels, and kidney macrophages were isolated for analysis.

**Results:** The chimeric mice with Tet2-/- BMC developed CHIP, indicated by flow cytometry of peripheral blood cells. Tet2-/- mice exhibited increased CD45.1 cells in the intrinsic myeloid kidney cell population. Following Unx-IRI, Tet2-/- mice had more severe kidney injury compared to control mice. Higher levels of tubule injury markers (KIM-1, NGAL) and more severe tubule injury were observed in Tet2-/- mice at 8 days after Unx-IRI. The kidneys of Tet2-/- mice displayed elevated expression of proinflammatory cytokines (Tnf, Il6, Il1b), chemokines (Ccl2, Ccl3), prostaglandins (Tgfb, Cgfl, Acta2), and extracellular matrix-associated genes (Col1a1, Col3a1, Fn, Vm) compared to Tet2+/+ mice. Macrophages isolated from the kidneys of Tet2-/- mice exhibited increased expression of proinflammatory cytokines both before and after injury. Additionally, increased co-expression of NLRP3 inflammasome and IL-1β with CD8-positive macrophages was observed in kidneys only in the CD45.2 macrophages and not in the CD45.1 macrophages.

**Funding:** NIDDK Support
Deficits and Endothelial Leakage

Background: Acute respiratory distress syndrome and acute kidney injury frequently occur in multiple organ failure patients and couple high mortality due to a lack of mechanistic understanding and therapeutic options. Pre-clinical animal models of this clinical kidney-lung interaction reveal that AKI induces remote lung inflammation with accumulation of neutrophils and interstitial macrophages in the lung, interstitial edema, and hypoxemia. How this remote lung inflammation is established and causes hypoxemia lacks understanding.

Methods: Flow-cytometry was used to determine the amount of classical/non-classical monocytes and of lung intravascular, marginated or extravasated neutrophils in the lung 24 hours after bilateral renal ischemia-reperfusion injury (IRI). Single-cell RNA sequencing (scRNAseq) analysis was used to study the remotely injured lung after AKI. In-vivo two-photon imaging was used to image lung neutrophils and monocytes after AKI. In vitro, permeability assays using primary lung endothelial cell monolayers were employed.

Results: After AKI, classical monocytes and neutrophils increased in the lung. Lung neutrophils accumulated in lung capillaries, impeded blood flow, and did not extravasate, unlike in LPS-induced direct lung injury, suggesting ventilation-perfusion deficits as an important cause of the observed hypoxemia. scRNAseq analysis revealed that monocytes enter the lung and transition into interstitial macrophages. Depletion of CCR2+ classical monocytes, but not of non-classical monocytes, blocked lung interstitial macrophage and neutrophil accumulation after AKI. In vitro, primary lung endothelial cell permeability in the presence of AKI serum was strongly enhanced when neutrophils from AKI mice, but not shunt mice, were added.

Conclusions: CCR2+ classical monocytes are required for neutrophil recruitment in remote lung inflammation after AKI and give rise to lung interstitial macrophages. In contrast to direct lung injury, AKI-induced remote lung inflammation after AKI shows unique inflammatory patterns with neutrophil plugging of vessels that impede capillary perfusion and thus oxygen uptake. This oxygenation deficit is further negatively influenced by AKI. In vivo, two-photon imaging was used to image lung neutrophils and monocytes after AKI. In vitro, primary lung endothelial cell permeability in the presence of AKI serum was strongly enhanced when neutrophils from AKI mice, but not shunt mice, were added.

Conclusions: CCR2+ classical monocytes are required for neutrophil recruitment in remote lung inflammation after AKI and give rise to lung interstitial macrophages. In contrast to direct lung injury, AKI-induced remote lung inflammation after AKI shows unique inflammatory patterns with neutrophil plugging of vessels that impede capillary perfusion and thus oxygen uptake. This oxygenation deficit is further negatively influenced by AKI. In vivo, two-photon imaging was used to image lung neutrophils and monocytes after AKI. In vitro, primary lung endothelial cell permeability in the presence of AKI serum was strongly enhanced when neutrophils from AKI mice, but not shunt mice, were added.

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SA-PO185
Uromodulin Alleviates Intestinal Fibrosis in AKI to CKD Transition in a Cisplatin-Treated Rat Model via the Inhibition of EGFR Pathway

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Background: Severe or recurrent acute kidney injury (AKI) episode is liable to cause the occurrence and acceleration of chronic kidney disease (CKD). Uromodulin has been reported as a protective factor for AKI and CKD. Here, we explored its role in the AKI-CKD transition.

Methods: Wild-type SD rats and UMOD+/+ rats were given cisplatin at 3.2mg/kg for 4 times every 2 weeks to induce the transition of AKI-CKD. Serum, urine and kidneys were collected to assay the protective effect of uromodulin. Western blots, IHC and qPCR were used to investigate mechanisms. HK-2 cell culture in cisplatin was treated with or without uromodulin for further validation.

Results: UMOD−/− rats didn’t develop spontaneous kidney injury or fibrosis. However, uromodulin deficiency accelerated the progression of AKI to CKD in our rat model, as evidenced by more severe kidney insufficiency and fibrosis. The levels of SCR, BUN, urinary KIM1 and NGAL were significantly increased in cisplatin-treated UMOD−/− rats compared with UMOD+/+ rats. PAS and Sirius staining showed heavier renal lesion and fibrosis in UMOD−/− rats. During the transition of AKI-CKD, UMOD−/− rats showed elevated levels of fibrosis markers and over-activation of EGFR/ERK, according to Western blot and IHC. The native uromodulin supplement to cisplatin-stimulated HK-2 cells decreased the expressions of fibroblast markers and down-regulated the EGFR/ERK signaling.

Conclusions: Uromodulin deficiency may exacerbate the progression of AKI-CKD transition induced by cisplatin via the overactivation of EGFR.

Funding: Government Support - Non-U.S.

SA-PO186
Kidney Damage Associated with Liver Fibrosis Is Differentially Orchestrated by YB-1 Depending on Its Cellular Origin

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Background: Acute kidney injury is a common and life-threatening complication of liver disease. In a previous study, we showed that the Y-box-binding protein (YB-1) modulates the liver-kidney crosstalk. In a model of liver fibrosis (biliary duct ligation; BDL), mice with half-maximal Ybx1 expression (Ybx1−/−) exhibited significantly reduced liver damage, but the resulting kidney damage was increased. The purpose of the present study was to clarify the influence of organ/cell specific YB-1 expression on liver and kidney damage after induction of liver fibrosis.

Methods: For this purpose, BDL was performed as a liver fibrosis model in conditional Ybx1−/− knockout animals with specific depletion in hepatocytes (Ybx1−/−Pax5fl/fl) and in renal tubular cells (Ybx1−/−Pax8fl/fl).

Results: We found that targeting Ybx1 in hepatocytes reduced liver fibrosis and kidney damage (e.g. tubular damage, Ngal mRNA expression)/fibrosis (e.g. collagen1A staining). Compared to WT animals, BDL mice with Ybx1−/−specific knockout in myeloid immune cells showed significantly reduced serum levels of liver enzymes but increased evidence of kidney damage and fibrosis. Finally, decreased expression of YB-1 in kidney tubular cells resulted in increased expression of fibrosis markers in the liver.

Conclusions: In summary, cell-specific YB-1 expression has a major influence on the respective organ damage in the context of the liver-kidney crosstalk. In addition, we document that renal YB-1 expression also has implications for liver fibrosis. Furthermore, the previously observed reduced liver damage with increased kidney damage occurring in the Ybx1−/− animals is best mimicked by a specific YB-1 reduction in immune cells.

Funding: Government Support - Non-U.S.

SA-PO187
Effects of Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i) on Renal Vascular Reactivity in Cirrhotic Rats

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Background: Variceal bleeding-associated hypotension may activate endogenous vasoconstrictors, leading to renal vasocostriction and subsequent acute kidney injury (AKI) in cirrhotic patients. Sodium-glucose cotransporters-2 inhibitors (SGLT2i) are a new class of oral anti-hyperglycemic drugs with pleiotropic effects. In addition to the reduction in blood pressure and body weight, SGLT2i showed improvements in renal outcomes. The possible mechanisms included inhibition of inflammation and oxidative stress and a reduction in glomerular hyperfiltration via afferent arteriolar vasoconstriction. Cirrhotic kidney has the same picture of renal hyperfiltration with diabetic kidney. Therefore, the renoprotective role of SGLT2i in cirrhotic kidneys is worth evaluating.

Methods: Liver cirrhosis was induced in S-D rats with common bile duct ligation (CBDL). Rats received oral distill water or SGLT2i (Empagliflozin, 30 mg/kg/day) for 28 days. On the 28th day, AKI was induced by ischemic-reperfusion injury (IRI). On the 29th day, the following was investigated: (a) hemodynamic parameters, (b) serum glucose, BUN, Cr, ALT, AST, IL-1, IL-6, TNF-α, (d) in-situ kidney perfusion, (e) oxidative stress and western analysis of kidneys.

Results: SGLT2i treatment showed no significant change in serum parameters, but lower TNF-α (p < 0.05) in CBDL rats. Renal IRI enhanced renal vascular reactivity to endothelin-1 (ET-1) and led to significant increases in serum BUN and Cr (all p < 0.05), suggesting AKI. Compared with DW-treated rats, SGLT2i treatment abrogated IRI-related renal vascular hyper-reactivity to ET-1 (Fig) and showed lower BUN and Cr following IRI (all p < 0.05). The exact mechanisms of renal protection remained under analysis.

Conclusions: In conclusion, our results demonstrated beneficial effects of SGLT2i in kidneys of CBDL rats, including reduced inflammation, abrogated IRI-related renal vascular hyper-reactivity to vasoconstrictor, and protection from AKI. Therefore, SGLT2i might be recommended for cirrhotic patients.

Fig. IRI increased renal vascular response to ET-1 in CBDL rats (A). SGLT2i treatment abrogated renal vascular hyper-reactivity to ET-1 following IRI (B).
SA-PO188

Transient Inhibition of the Sodium-Glucose Cotransporter 2 After Ischemia/Reperfusion Injury Ameliorates CKD in Rats

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Background: A severe episode of Acute Kidney Injury (AKI) can lead to Chronic Kidney Disease (CKD). The sodium-glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin, has exhibited nephroprotective actions in CKD, but the specific mechanisms remain elusive. We evaluated if a transient administration of Dapa after ischemia/reperfusion injury (IRI) prevents CKD.

Methods: Forty-one male Wistar rats (300-350 g) were randomized in: Sham surgery, IRI for 30 min (IR), and IRI + dapagliflozin (IR+Dapa). Daily treatment with Dapa was initiated 24 h after IRI and maintained only 10 days. After this period, one third of rats was euthanized for kidney functional, histological, and molecular analyses. The other half was followed for 5 months. Proteinuria was determined monthly; kidney function and fibrosis were evaluated at the 5th month. Differences between groups were analyzed through ANOVA with a significance level of p<0.05.

Results: Ten days after IRI, rats receiving Dapa exhibited an early restoration of renal blood flow (RBF) with a notorious reduction in RVR and a recovered Creatinine Clearance (CCr) compared to the IR group alone. Importantly, IRT persisted with detrimental changes in renal histology compared to a significant decrease in Sirtuin-3, a low Mitofusin/Drp1 ratio, and an abnormal mitophagy process with PINK1 up-regulation and reduced Parkin. There was a reduction in OXPHOS Complex I and less total NAD/NADH levels in this group. Interestingly, all these changes were prevented with SGLT2 inhibition. We also demonstrated that this short treatment prevented AKI after five months as indicated by proteinuria, CCr, and fibrosis.

Conclusions: A short treatment with dapagliflozin after IRI is enough to prevent maladaptive repair and CKD in rats. This renoprotective effect seems to be mediated by improved renal circulation and restoration of mitochondrial homeostasis. These findings highlight the relevance of the initial days of reperfusion, indicating that maladaptive repair and CKD in rats. This renoprotective effect seems to be mediated by improved renal circulation and restoration of mitochondrial homeostasis. These findings highlight the relevance of the initial days of reperfusion, indicating that maladaptive repair can be modulated after severe AKI to prevent the development of long-term consequences.

Funding: Government Support - Non-U.S.

SA-PO189

Empagliflozin Protects Kidney by Preventing Autophagic Stagnation via Reducing Megalin-Mediated Reabsorption of Lipotopic Albumin

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Background: Evidence from clinical studies such as DAPA-CKD and EMPA-REG demonstrate that SGLT2 inhibitors prevent further renal functional decline in patients with chronic kidney disease. However, mechanisms involved in the renoprotection are unclear.

Methods: We investigated the following aspects: 1) the impact of empagliflozin (EMPA) on lipotopic in kidney proximal tubular epithelial cells (PTECs) in both wildtype and inducible megalin knockout mice, 2) the effect of EMPA on albumin reabsorption in PTECs, 3) the influence of EMPA on autophagic activity, and 4) the effect of EMPA on ischemia/reperfusion injury (IRI) when autophagy and/or megalin are blocked.

Results: High-fat diet (HFD) induced the formation of cytosolic vacuoles (enlarged lysosomes containing phophoglucoms) in PTECs, which was alleviated by EMPA. Since vacuolar formation was rarely observed in HFD-fed inducible megalin knockout mice, we assessed megalin-mediated fluorescent albumin reabsorption in PTECs. HFD led to hyperreabsorption of albumin in both S1-2 and S3 segments, which was restored by EMPA. Subsequently, we measured plasma levels of 24 fractions of free fatty acids bound to hyperreabsorption of albumin in both S1-2 and S3 segments, which was restored by EMPA. Subsequently, we measured plasma levels of 24 fractions of free fatty acids bound to albumin. EMPA improved the imbalanced lipolipidosis induced by HFD. Furthermore, employing inducible Atg5 knockout mice and GFP-MAP1LC3 transgenic mice, we found that EMPA mitigated the HFD-induced increase in autophagic demand and alleviated the stagnation of autophagosome formation. Finally, we aimed to determine whether the reduced reabsorption of lipotopic albumin and restoration of autophagic flux by EMPA improve the HFD-induced susceptibility to ischemic stress. The renoprotective effect of empagliflozin against IRI-induced acute kidney injury was attenuated when megalin and/or autophagy were abated.

Conclusions: The reduction of toxic albumin reabsorption and prevention of autophagic stagnation in PTECs may be crucial for SGLT2 inhibition-mediated renoprotection.

Funding: Commercial Support - Japan Boehringer Ingelheim

SA-PO190

Gut Dysbiosis and Altered Gut-Derived Metabolites in Patients with Active Lupus Nephritis

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Background: Lupus nephritis (LN) is an important cause of acute kidney injury and chronic kidney disease. Emerging evidence suggests that gut dysbiosis may contribute to LN pathogenesis. We investigated gut dysbiosis and changes in gut-derived metabolites in LN patients.

Methods: Fecal samples were collected from 69 patients with kidney biopsy-proven Class III/IV/EV LN (16 patients with active LN and 53 patients in remission). Age- and sex-matched samples from healthy subjects (n=15), patients with non-renal lupus (n=27), and patients with non-lupus chronic kidney disease (n=37) served as controls. Bacterial DNA was isolated from fecal samples and submitted to Novogene for shotgun metagenomic sequencing. A total depth of 41 million paired end reads with a read length of 150bp. Sequenced reads were processed to remove adapter regions and low-quality bases, and Phix and human contamination were filtered. High-quality reads were taxonomically profiled at different taxonomic levels using MetaPhan4. Microbial pathways and predicted metabolite abundance was assessed using HUMAnN3.6 pipeline and MolMolPan respectively.

Results: Three samples (1 LN and 2 non-renal lupus) failed quality control and were removed from analysis. Alpha and beta diversity were comparable between LN patients and controls. Active LN was accompanied by an increase in the abundance of Megamonas funiformis and Ruminococcus torques and a decrease in Candidatus Accumulibacter coaeicum and Atistipes shahii compared to LN patients in remission and control groups (P<0.05, for all). Microbial pathways were similar in patients with active LN and remission, whereas fatty acid oxidation, hestiol degradation, ornithine degradation, and NAD salvage pathways were enriched in LN patients compared to healthy subjects. Analysis of microbiota-derived metabolites showed increased abundance of ADMA and chenodeoxycholate, and downregulation of pyridoxine and nicotinic acid in patients with active LN compared to remission (P<0.05, for all).

Conclusions: LN is associated with gut dysbiosis and altered metabolite abundance. Whether these changes are of pathogenic significance remains to be established.

Funding: Government Support - Non-U.S.

SA-PO191

ACE2 Overexpression Mediates Spatial Distribution of Pathologic Features in AKI

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Background: Acute kidney injury (AKI) is a widespread health problem often caused by ischemia. Angiotensin II (AngII) drives pathologic changes in AKI. Angiotensin converting enzyme 2 (ACE2) metabolizes AngII and extinguishes its effects. While several studies have examined the role ACE2 plays in chronic kidney disease and hypertension, less is known about ACE2 in AKI. We hypothesize that ACE2 overexpression promotes recovery after AKI via AngII metabolism.

Methods: We use K18-hACE2 mice which overexpress human ACE2 in epithelial cells. Unilateral renal ischemia reperfusion (IRI, 25-min ischemia) with contralateral nephrectomy was performed on age-matched K18-hACE2 and wildtype (WT) littermates. Blood urea nitrogen (BUN), plasma creatinine (Cr), and histology was performed.

Results: Blood urea nitrogen (BUN), plasma creatinine (Cr), and histology was performed.

Conclusions: We show that K18-hACE2 mice are a valuable tool for understanding ACE2 in the context of kidney injury. Reduced brush border injury scores in the corticomedullary junction (CMJ) of K18-hACE2 kidneys (13.4 ± 11.6 in WT vs 4.7 ± 4.7, p<0.01, 2A, B). In the cortex, overexpression of hACE2 caused lower levels of necrosis (23.2 ± 14.0 vs 10.9 ± 11.1 in WT, p<0.01, 2C).

Funding: NIDDK Support, Private Foundation Support
SA-PO192

Loss of Tubular Angiotensin-Converting Enzyme 2 (ACE2) into the Urine with ACE2 Casts: A Key Pathophysiologic and Diagnostic Alteration in AKI?

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Background: In acute kidney injury (AKI) the renin angiotensin system (RAS) is overactive. ACE2 is a tissue RAS enzyme that is highly expressed in the apical tubular border in kidney cortex and corticomedullary region where it controls Angiotensin II degradation to form Angiotensin 1-7. We hypothesize that in AKI there is a loss of apical tubular ACE2 that amplifies RAS overactivity and results in worsening of proximal tubular injury.

Methods: We used the mouse model of AKI by ischemia-reperfusion-injury (IRI) in male C57BL/6 mice by clamping of the left renal pedicle for 30min followed by removal of the right kidney (unilateral IRI). Kidneys were harvested 48hrs after the surgery and stained for ACE2 by immunohistochemistry (IHC) and immunofluorescence (IF). Kidney ACE2 protein was assessed in membrane protein lysates and enzymatic activity measured using a fluorogenic substrate. ACE2 protein by western blot and enzymatic activity were assessed in mouse urine collected 48hrs post IRI.

Results: IHC and IF revealed a striking maldistribution of tubular ACE2 (Fig. A, B) compared to healthy control kidneys including spillage into the tubular lumen and presence of ACE2 positive luminal casts in the medulla (C) where ACE2 is usually absent. ACE2 protein in membrane lysates and enzymatic activity were reduced (37±3 vs. 100±5.6 ACE2/µg total protein/h, p=0.006). In the urine the full-length membrane bound ACE2 protein was increased (2606±1764 vs. 100±47 ACE2/µl urine, p=0.04) and activity in the urine sediment was increased as well (7.7±1.9 vs. 2±0.2 RFU/µg Cr, p=0.01). Moreover, ACE2 containing casts were recovered in the urine sediment.

Conclusions: In a mouse model of AKI caused by IRI there is a marked loss of ACE2 from the apical tubular border with deposition of ACE2 positive material in the medulla and increased urinary excretion of the full length membrane-bound ACE2. The deficiency of apical ACE2 not only results in the loss of its kidney protective effects but may also serve as a diagnostic marker of AKI.

Funding: Other NIH Support - NIAID, Private Foundation Support

SA-PO193

Urinary mRNA Profile in Recipients of Allogeneic Hematopoietic Cell Transplant with AKI

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Background: Allogeneic hematopoietic cell transplantation (HCT) is curative for hematologic malignancies but carries risk of acute kidney injury (AKI) in up to 80% within the first 100 days. The etiology of AKI is multifactorial and includes non-immune (ischemic, drug toxicity) and immune-mediated mechanisms. Herein we investigated whether AKI in HCT recipients is associated with a urinary cell three-gene signature validated for kidney graft recipients to detect intragraft inflammation (Suthanthiran et al. NEJM 2013).

Methods: We prospectively collected urine specimens at baseline, weekly while inpatient, and monthly outpatient until day 100, from individuals who had their first allogeneic HCT at MSKCC. AKI was defined as ≥ 7-day elevation of ≥ 1.5x baseline serum creatinine. Urine samples closest to the time of AKI and time from transplant-matched samples from patients without AKI were analyzed. Using RT-qPCR assay, we measured the absolute quantity of panel of mRNAs (T cell marker CD3e, proinflammatory chemokine CXCL10/IP10, and cytokine TGFβ1), and 18sRNA in urinary cells and calculated the CTOT04 molecular signature.

Results: A total of 32 urine samples from 32 HCT recipients were analyzed; 16 with AKI and 16 without AKI. There was no statistically significant difference in the urinary cell molecular signature score between the group with AKI and without AKI (Table).

Conclusions: Our findings suggest that AKI in HCT recipients is not associated with increased trafficking of activated T cells through the kidney. Ongoing studies in our laboratory to profile the transcriptome of urines of individuals in an unbiased way using RNA-seq would likely yield molecular clues to differentiate causes of AKI in this patient population that is difficult to biopsy.

Key points: Viral, cellular and inflammatory inflammatory factors are found in a wider range of tubular and glomerular diseases. There is significant variability in MBGC and WxC size. We aimed to determine whether cast dimensions may correlate with clinical parameters.

MBGC: Urine specimens from patients seen in inpatient nephrology consultation were collected. Cases with specimens containing MBGCs or WxC were sampled. At least 12 cases per case were imaged using SeBaCam® and SeBaView at 40x to 400x magnification. Using ImageJ, each cast was measured lengthwise 3 times and widthwise 6 times for MBGC, and 10 times for WxC. Clinical data was extracted from medical records. Data was analyzed by Spearman correlation and t-test.

Results: Twenty-one patients with MBGC and 18 patients with WxC were included. The primary etiology of acute kidney injury (AKI) was ischemic AT in 61%, toxic AT in 11% and acute glomerulonephritis in 28%. Mean (range) length for MBGC was 102 (33-317) µm and 223 (28-1714) µm for WxC. Mean (range) width for MBGC was 35 (9-110) µm and 43 (5-253) µm for WxC. For MBGC, width significantly correlated with height (r=0.535, p=0.012), whereas length significantly correlated with age (r=0.436, p=0.048), FENa (r=0.698, p=0.008), urine chloride (r=0.896, p=0.001) and urine phosphate (r=0.717, p=0.03). Further, mean MBGC length was found to be significantly longer in patients that received dialysis (p=0.057). WxC length did not correlate with age, need for dialysis or any other parameter, whereas WxC width significantly correlated with serum creatinine (sCr) value at the time of urine microscopy (r=0.855, p<0.001).

Conclusions: MBGC and WxC dimensions significantly correlated with various anatrophic, chemical and clinical parameters. Correlation of MBGC length with need for dialysis as well as WxC with sCr suggest that cast dimensions may correlate with severity of AKI. With implementation of automated image scanners and computational model training, these observations suggest that urinary cast dimensions may provide valuable diagnostic and prognostic information. Further larger studies are needed to verify and expand these observations.
The Spectrum of Thrombotic Microangiopathy Related to Monoclonal Gammopathy

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Background: Patients with thrombotic microangiopathy (TMA) should be classified according to etiology to indicate targets for treatment, having impact on treatment and prognosis. Recent studies showed a high prevalence of monoclonal gammopathy (MG) in patients with TMA aged over 50 years. TMA was provisionally added as a MG of renal significance (MGRS) lesion by the International Kidney and MG Research Group. Recent studies suggested that complement dysregulation is common in this group. Here, we studied this premise in 7 patients with TMA and coexisting MG using complement measures, functional ex vivo endothelial cell tests, and genotyping.

Methods: Patients with TMA on kidney biopsy and/or peripheral blood were recruited from the Limburg Renal Registry and prospective COMPETE cohort. Patients with ADAMTS13-activity <10% or Shiga-toxin mediated disease were excluded. Patients were screened for rare variants and rearrangements in complement genes. Massive ex vivo CS59 formation on endothelial cells, factor H autoantibodies (FHAA) or pathogenic variants in complement genes defined complement dysregulation. IgG was purified from serum to study monoclonal mediated complement activation. As a control, kidney biopsies of 27 patients with MGRS lesions were studied for morphologic features of TMA.

Results: Eighty-four out of 113 patients with TMA were screened for MG. Seven out of 84 patients presented with MG, classified as MGRS (n=6) and multiple myeloma (n=1). MG clustered in patients aged over 50 years (n=6/32, 19%). Severe acute kidney injury was noted in all patients. Four out of 7 patients presented with normal complement levels. CS59 was found massive ex vivo CS59 formation on the perturbad endothelium. Neither IgG nor C4d were found. No pathogenic variants were found. FHAA were present in 2 patients, without homoygous deletion of CFHR3-1. None of the MG patients presented with coexisting TMA on kidney biopsy or massive ex vivo CS59 formation on the endothelium.

Conclusions: MG clustered in patients with TMA aged over 50 years. One patient with MG related TMA presented with alternative pathway activation. We found no evidence of TMA in a MGRS control group. With little evidence for complement dysregulation, the mechanism of MG induced TMA should be studied further.

Monoclonal Gammopathy of Renal Significance (MGRS) Without Detectable Clones: Clinical Treatment Dilemma

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Background: Monoclonal gammopathy of renal significance (MGRS) is characterized by monoclonal immunoglobulin deposition in kidneys. However, monoclonal immunoglobulin is not always detectable in blood, urine, or bone marrow (BM). Treatment response and kidney outcome of MGRS without a detectable clone remains unclear.

Methods: In this single-center, retrospective cohort study, we identified 192 cases of monoclonal immunoglobulin deposition disease (MIDD) from our biopsy repository between 2010 to 2022, of which 86 had follow-up at our center. Inclusion criteria were: (1) negative serum protein electrophoresis and immunofixation, (2) normal serum free light chain ratio adjusted for kidney function, (3) no clone identified in BM, and (4) no monoclonal IgM kappa and polyclonal IgG. IgM Cryoglobulin resulted at 17mg/dL with IgM kappa M protein at 0.09g/dL and a free light chain kappa to lambda ratio of 4.04 (nl: 0.26-1.65). A kidney biopsy showed membranoproliferative glomerulonephritis and IgM kappa restricted deposits. Serum cryoglobulins resulted as positive, type II with a monoclonal IgM G and polyclonal IgG. IgM Cryoglobulin resulted at 17mg/dL with IgA and IgG cryoglobulins at 3 and 15mg/dL respectively. A clinicopathologic diagnosis of cryoglobulinemia related MPGN was thus made. A bone marrow biopsy unmasked an underlying lymphoproliferative disorder consistent with MZL. CT imaging showed borderline diffuse adenopathy. As such, patient was started on Rituximab, Cytoxan, Vincristine and Prednisone. His kidney function worsened requiring dialysis. Despite cryoglobulins clearance, he remains dialysis dependent while on therapy for his MZL at four months post-diagnosis.

Discussion: Despite an improvement in recognition, MGRS remains a foreign entity both in the nephrology and hematopathology fields. It is frequently thought of in the context of plasma cell neoplasms. This case illustrates an MGRS case occurring with an underlying B-cell clone and manifesting as MPGN with progressive kidney dysfunction and nephrotic range proteinuria. A high index of suspicion and a low threshold for kidney biopsy were key to making the diagnosis. As in this case, the kidney biopsy might be the only clue to the underlying lymphoma and a crucial diagnostic step with paramount therapeutic implications, both for kidney and overall patient survival.

Beyond Plasma Cell Disorders: Monoclonal Gammopathy of Renal Significance with Marginal Zone Lymphoma

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Introduction: Monoclonal Gammopathy of Renal Significance (MGRS) is well recognized with pre-malignant plasma cell disorders. We report a case of MGRS with nephrotic range proteinuria and rapid loss of kidney function in the context of Marginal Zone Lymphoma (MZL).

Case Description: A 65-year-old man with diabetes mellitus and heart failure is admitted for progressive kidney dysfunction. He has chronic kidney disease, baseline proteinuria of 3.5 g/dl, creatinine (Cr) 1.5mg/dl, presumably due to diabetes. On presentation, Cr was 2.1mg/dl. Urinalysis with 2+ proteins and 11-25 RBCs/HPF. 24h urine collection revealed proteinuria at 3.5g. 12.5cm kidneys of normal parenchymal thickness and echogenicity were noted on US with no hydropnephrosis. Further workup showed Cr 3.5mg/dl (nl: 86-166) and C4<2mg/dl (nl: 13-46). Serum monoclonal testing revealed a low-grade IgM kappa M protein on 0.09g/dL and a free light chain kappa to lambda ratio of 4.04 (nl: 0.26-1.65). A kidney biopsy showed membranoproliferative glomerulonephritis and IgM kappa restricted deposits. Serum cryoglobulins resulted as positive, type II with a monoclonal IgM G and polyclonal IgG. IgM Cryoglobulin resulted at 17mg/dL with IgA and IgG cryoglobulins at 3 and 15mg/dl respectively. A clinicopathologic diagnosis of cryoglobulinemia related MPGN was thus made. A bone marrow biopsy unmasked an underlying lymphoproliferative disorder consistent with MZL. CT imaging showed borderline diffuse adenopathy. As such, patient was started on Rituximab, Cytoxan, Vincristine and Prednisone. His kidney function worsened requiring dialysis. Despite cryoglobulins clearance, he remains dialysis dependent while on therapy for his MZL at four months post-diagnosis.

Discussion: Despite an improvement in recognition, MGRS remains a foreign entity both in the nephrology and hematopathology fields. It is frequently thought of in the context of plasma cell neoplasms. This case illustrates an MGRS case occurring with an underlying B-cell clone and manifesting as MPGN with progressive kidney dysfunction and nephrotic range proteinuria. A high index of suspicion and a low threshold for kidney biopsy were key to making the diagnosis. As in this case, the kidney biopsy might be the only clue to the underlying lymphoma and a crucial diagnostic step with paramount therapeutic implications, both for kidney and overall patient survival.
**SA-PO199**

**The Clinicopathologic Characteristics of Patients with Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition**

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**Background:** Proliferative glomerulonephritis with monoclonal immunoglobulin (Ig) deposits (PGNMID) is a rare form of monoclonal gammapathy of renal significance (MGRS). However, the Monoclonal (M) protein and hematologic clone is found in less than half of the cases.

**Methods:** We identified all patients with PGNMID from the Cleveland Clinic Kidney Biopsy Epidemiology Project from January 2015 to March 2023. Retrospective chart review was performed to obtain demographic and clinical characteristics.

**Results:** From 34 patients with PGNMID, 16 patients were excluded due to insufficient data. Of the 18 remaining patients, 67% were male and 78% of patients self-reported as white. The median age was 60 years, with 22% of patients < 50 years. Clinically, features at kidney biopsy were: hypertension (78%), acute kidney injury (72%), hematuria (78%), nephrotic syndrome (22%), and hypocomplementemia (23%). M protein was identified in 33% with an underlying clone identified in only 17% (3/18) of cases (MM, CLL and B cell lymphoma). Mean serum creatinine and proteinuria at biopsy were 3.2mg/dl (0.64 - 9.0) and 4.3 gm/dl (0 - 14.0gm) respectively. Regarding pathology, endocapillary hypercellularity (55%), pure mesangial (28%) and MPGN (16%) patterns were most common. The majority of patients (>75%) had mild chronicity and 1 case had crescents. IgG/Kappa was the predominant finding (83%), one patient had IgM/Kappa. Of 13 patients with IgG subclass staining, 77% had IgG3 and one case each of IgG1, IgG2 and IgG4. CyBord and CyBord-Daratumumab were the most common chemotherapy regimens used, each accounting 35% followed by Rituximab in 12% of cases. Regarding recurrence, 18 patients had follow up data, with 8 (44%) progressing to ESKD post biopsy with mean duration of 7.8 months (0 - 13) and 44% had either complete (< 0.5 g) or partial remission (proteinuria >50% with stable eGFR) during follow up. No clinicopathologic variables were predictive of response on univariate and multivariable analysis.

**Conclusions:** Our study adds to growing evidence of low clonal detection rate among patients with PGNMID and high rate of disease progression despite treatment. More studies are needed to better understand the true nature of this disease to hopefully guide therapeutic interventions.

**SA-PO200**

**Triple Monoclonal Protein-Related Kidney Lesions in a Patient with Plasma Cell Dyscrasia**

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**Introduction:** Toxic monoclonal protein typically results in a single type of kidney pathology due to biophysical properties of monoclonal protein. Multiple type of lesions is rarely reported. We report a patient with monoclonal gammopathy who has light chain cast nephropathy (LCN), light chain proximal tubulopathy (LCTP) and thrombotic microangiopathy (TMA).

**Case Description:** A 57-year-old male with history of dermatomyositis and sarcoidosis on mycophenolate mofetil and prednisone who presented with fever, nausea, and loose stool for 3 days. He was diagnosed with concealed ruptured diverticulitis. He had a baseline creatinine (Cr) of 0.8-1.0 mg/dl but it was 1.47 mg/dl 3 months ago. Upon presentation, Cr was 2.81 mg/dl which continued to rise and peaked at 9.29 mg/dl requiring hemodialysis. Platelet (Plt) and Hemoglobin (Hb) were normal upon admission but continued to decrease along with the presence of hemolysis marker. ADAMTS13 activity was 21% of normal with mean platelet volume (MPV) of 7.17. Serum electrophoresis showed IgG kappa with M- spike of 0.2 g/dl. His urine analysis showed blood and granular cast, and his protein to creatinine ratio of 1.33 mg/mg. He underwent a kidney biopsy which showed kappa LCCN, TMA and non-calcineurin. Bone marrow biopsy showed less than 3% of kappa-restricted plasma cell. Complement study showed elevated sC5b-9. Given the finding of progressive TMA, he underwent plasma pheresis for 3 sessions as a bridging therapy before initiating anti-plasma cell therapy with daratumumab, bortezomib and dexamethasone. Due to recent infection, eculizumab was on hold. After the 3rd cycle, he is still dialysis dependent but kappa free light chain came down to 3.83 mg/dl with K/L ratio 1.32. Hb and Plt improved but still has positive hemolysis marker so the plan is to start Eculizumab and continue chemotherapy.

**Discussion:** This case highlights the importance of toxic properties of monoclonal protein in causing kidney diseases. Triple monoclonal protein related kidney lesions can occur but rare. LCCN is a myeloma defining event but his LC (<50 mg/dl) and plasma cell burden is low (<10%) which makes this case very unusual. Sepsis-induced low flow stage may induce LCCN in this patient. Aggressive therapy is likely needed to eradicate the clone in order to achieve organ response.

**SA-PO201**

**A Case of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposition Presenting as Hypertensive Emergency**

**Keith L. Sauer, Evan A. Farkash, Markus Bitzer. University of Michigan Michigan Medicine, Ann Arbor, MI.**

**Introduction:** Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID) is a subtype of monoclonal gammapathy of renal significance (MGRS), resulting from deposition of intact monoclonal IgG in glomeruli. Herein, we present the case of a 65-year-old who presented for new headaches and hypertensive emergency and was subsequently found to have PGNMID.

**Case Description:** A 65-year-old female with no significant past medical history developed new headaches and was treated with ibuprofen 800 mg TID for 5-months. Subsequently, she was found to have new hypertension with BP of 190/90 mmHg, serum creatinine of 1.0 mg/dl and nephrotic-range proteinuria of 3.4 g/g creatinine. Urinalysis and was positive for protein and blood with no dysmorphic RBCs or casts on urine sediment. Labs also revealed new anemia and thrombocytopenia with elevated LDH, undetectable haptoglobin, and normal peripheral blood smear. Further serologic evaluation for C3, C4, ANA, cryoglobulin, ANCA, HIV, HBV, HCV, Anti-PLA2R, DAT, and ADAMST13 activity were normal/negative. Paraproteinaemia evaluation with SPEP and UPEP were without evidence of M-protein, aside from a marginal free Kappa/lamba light chain ratio (1.8). Despite cessation of NSAIDS and adequate blood pressure control with amlopidine and losartan, proteinuria persisted with rising creatinine. Therefore, kidney biopsy was pursued which showed neutrophilic glomerulitis with a membranoproliferative pattern and rare fibrocellular crescents. Immunofluorescence showed only mesangial and capillary C3 and C1q deposits; however, pronase treated paraffin tissue unmasked IgG-kappa restricted subendothelial and mesangial deposits, diagnostic of PGNMID. She was treated with six cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBord) resulting in initial improvement in proteinuria and serum creatinine. Repeat bone marrow was without residual plasma cells on flow cytometry.

**Discussion:** PGNMID is a MGRS that does not meet criteria for multiple myeloma or Waldenström’s and a monoclonal gammopathy of undetermined significance (MUGS). However, the M protein and hematologic clone is found in less than 30% of cases. Pronase treatment of paraffin tissue to reveal masked immunoglobulin deposits can provide insightful guidance in glomerular deposition diseases when routine immunofluorescence is not diagnostic.

**SA-PO202**

**Proliferative Glomerulonephritis with Monoclonal IgG Deposits: A Mysterious Renal Disorder**

**Umair Khan, Zehra N. Kocas, Kostas Papamarkou. University of Massachusetts Chan Medical School - Baystate Regional Campus, Springfield, MA.**

**Introduction:** Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a rare form of glomerulonephritis characterized mainly by linear staining deposits. It predominantly presents with nephritic range proteinuria and renal dysfunction. A third of patients with PGMID progress to ESRD. It is a renal-limited disorder, however, rare cases of PGNMID in association with CLL have been reported. Herein, we present a case of severe renal failure due to PGNMID in the setting of underlying CLL.

**Case Description:** An 88-year-old female with CLL presented with oliguric renal failure. Labs revealed an elevated serum creatinine level of 7.9 mg/dl (baseline 1.1 mg/dl), and nephrotic range proteinuria. Renal biopsy showed kappa-restricted immune complex-mediated proliferative and mesangial glomerulonephritis and linear staining deposits of glomerular capillary loops for IgG (3+), and kappa (3+) suggestive of PGNMID. It was presumed that her PGNMID was due to CLL and hence decision was made to continue withibrutinib and assess hematological response.

**Discussion:** PGNMID, a rare form of GN, appears as one of the most mysterious renal disorders associated with monoclonal gammapathy. When present, it should raise the possibility of an underlying secondary etiology as hematological malignancies, especially CLL, have been recognized as a rare cause of PGNMID. Early recognition of PGNMID is a key factor for long term renal survival. Treatment therapy is aimed at both monoclonal proliferation and hematological response. Identification of pathogenic clone is vital to guide treatment. The usual absence of any detectable clonal proliferation

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makes its management challenging. Further studies in understanding the mechanisms of monocolonal deposition would help refine treatment strategies. This case highlights the importance of close monitoring and individualized treatment plans in the management of PGNMID.

SA-PO203

Prognostic Factors Associated with Renal Survival and Mortality of Renal Involvement Proven by Biopsy Associated with Monocolonal Gammopathy

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Background: Monocolonal gammopathies can generate a wide and diverse renal compromise that can condition the patient’s prognosis. This study seeks to determine those factors associated with renal survival and mortality.

Methods: A retrospective cohort study of 98 patients older than 18 years with biopsy-proven renal involvement due to monocolonal gammopathy was conducted. For the analysis of renal and patient survival, the Kaplan-Meier method was obtained, renal survival curves were compared with the histological diagnosis and the Log Rank Test was obtained. To determine the predictive factors at the time of biopsy that correlate with death and ESKD, univariate and multivariate cox analyzes were performed.

Results: The need for RRT was related to the combined outcome of ESKD and death (HR 4.86 CI 2.01-11.79). A GFR at the time of biopsy less than 30ml/mn/1.73 was correlated with an increased risk of ESKD (HR 4.02 CI 1.38-11.71). Amyloidosis and age over 60 years are factors associated with higher mortality (HR 2.38, IC 1.22-4.86 and 1.96 IC 1.06-3.61 respectively). The presence of tubulopathy (myeloma Kidney) in renal biopsy was associated with better survival compared with other histological compromises (p 0.05).

Conclusions: The requirement of RRT and GFR less than 30 ml/min/1.73 were associated with adverse outcomes in patients with MGRS. Amyloidosis and age are factors negatively related to patient survival.

Funding: Private Foundation Support

Combined death and end stage chronic kidney disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Combined (n=98)</th>
<th>Monocolonal (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;65 years</td>
<td>1.36 (CI 0.88-2.05, p=0.32)</td>
<td>1.36 (CI 0.73-2.76, p=0.32)</td>
</tr>
<tr>
<td>GFR at biopsy ≤ 30 ml/mn/1.73</td>
<td>3.51 (CI 1.10-10.64, p=0.020)</td>
<td>1.21 (CI 0.48-3.04, p=0.68)</td>
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<td>Amyloidosis</td>
<td>1.08 (CI 0.66-1.72, p=0.70)</td>
<td>1.26 (CI 0.73-2.24, p=0.41)</td>
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</tbody>
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Discussion: The need for RRT and GFR less than 30 ml/min/1.73 were associated with adverse outcomes in patients with MGRS. Amyloidosis and age are factors negatively related to patient survival.

SA-PO204

A Rare Case of Proliferative Glomerulonephritis with Monocolonal IgA Lambda Deposits with Crescents

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is an uncommon condition under the spectrum of renal disorders grouped under monocolonal gammopathies with renal significance (MGRS). Even more uncommon is the type of immunoglobulin (Ig) deposition other than IgG subclasses (IgG3 heavy chain being most common type of deposition) in PGNMID, which may be IgA or IgM as well as light chain only deposition.

Case Description: We report a 65 y/o Caucasian female patient (pt) with history of hypertension, recurrent urinary tract infections and non-obstructive nephro lithiasis with recent worsening of creatinine (Cr) to 1.3-1.6 mg/dL, with albuminuria 1.8 g/g, proteinuria 2.2 g/g and hematuria and negative nephritic workup. While awaiting hematology consultation and renal biopsy the pt was admitted with low back pain and was noted to have low kappa/lambda light chain ratio (0.14) with significantly elevated free lambda light chains (206.23). No significant abnormalities were noted on serum protein electrophoresis, serum immunofixation electrophoresis or urine protein electrophoresis. While awaiting hematology consultation and renal biopsy the pt was admitted with low back pain and was noted to have new retroperitoneal mass/adenopathy concerning lymphoma. Pt developed progressive renal failure necessitating initiation of hemodialysis (HD). Retroperitoneal mass biopsy positive for diffuse large B-cell lymphoma (DLBCL) with renal biopsy notable for proliferative glomerulonephritis with monoclonal IgA lambda deposition with crescents in the setting of lymphoma and MGRS w/ monoclonal IgA lambda. The pt was started on R-CHOP chemotherapy (CT) for management of her DLBCL while continuing her on HD. Pt eventually achieved DLBCL remission as well as renal recovery with discontinuation of HD with 2 R-CHOP and 4 R-COEP cycles.

Discussion: PGNMID is a rare cause of renal disorder. Though it is usually recognized with deposition of IgG3 subclass heavy chains in glomeruli, it can rarely be recognized with deposition of other immunoglobulins like IgA and IgM as well as light chains. Treatment of this disease is based on clone directed therapy, which could lead to complete or partial remission in these patients. Our case is one of the rarer cases as it involved uncommon monocolonal IgA lambda chain deposition and it is also associated with diffuse large B-Cell lymphoma.

SA-PO205

Cryoglobulinemic Thrombotic Microangiopathy: A Subtype of Monocolonal Gammopathy of Renal Significance

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Introduction: Monocolonal gammopathy of renal significance (MGRS) encompasses a set of disorders in which a cell clone secretes immunoglobulin that causes kidney damage without meeting criteria for a malignant plasma cell dyscrasia. These conditions often involve damage mediated by direct monocolonal Ig deposition, though less commonly include processes like thrombotic microangiopathy (TMA) without direct

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antibody deposition in the kidney. Here, we present a case of kidney injury secondary to a cryoglobulin-mediated inflammation to steroids and clone-directed therapy.

**Case Description:** A 45-year-old African American woman with recent COVID-19 infection presented with weakness. Vital signs and exam were unremarkable. Labs were notable for creatinine of 8.3 mg/dL, hemoglobin 7.6 g/dL, platelet count 121 K/µL, and LDH 439 IU/L. Urinalysis revealed 4+ blood and 4+ protein with birefringent results in a muddy brown casts. PLASMC score was 4. ADAMTS13 activity and functional TMA panel were normal. SPEP/UEP showed monoclonal IgG lambda. Renal biopsy revealed chronic thrombotic microangiopathy. With a cryocrit of 2.5%, biopsy findings were most consistent with a cryoglobulinemia TMA with amyloid deposits. The patient was discharged with a prolonged course of corticosteroids with clinical improvement. Six months later, she re-presented with recurrent AKI (creatinine 3.1 mg/dL), anemia, and thrombocytopenia. Renal function continued to worsen with repeat pulse-dose corticosteroids. Plasmapheresis and clone-directed therapy with bortezomib resulted in dramatic improvement in renal function (creatinine 1.1 mg/dL).

**Discussion:** Thrombotic microangiopathy is a less common manifestation of monoclonal gamopathy of renal significance and even more rarely associated with Type I cryoglobulinemia. This case demonstrates a paraprotein-mediated process causing disordered complement activation leading to a TMA. To our knowledge this is only the second reported case of severe acute kidney injury caused by a cryoglobulinemia-thrombotic microangiopathy that was successfully treated with plasma exchange and clone-directed therapy. The role of these therapies in cryoglobulinemic TMA as well as consideration of eculizumab as a subsequent line of therapy in refractory cases merits ongoing discussion.

**SA-PO206**

**Primary Scleroderma with Monoclonal Gammopathy of Undetermined Significance (MGUS): A Case Report**

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**Introduction:** Scleroderma is characterized by proteinuria, edema, hyperalbuninemia, and hyperlipidemia. A diverse range of disorders has been associated with Scleroderma. Causes of the nephrotic syndrome vary and it can show a vigorous expression of medical conditions. Therefore, it is necessary to establish and treat the etiology of the nephrotic syndrome. Differential diagnosis for nephrotic syndrome is challenging due to possibility of nephrotic-range proteinuria by monoclonal gamopathy of undetermined significance (MGUS). Following is a case of a 60-year-old male diagnosed with MGUS concomitant with nephrotic syndrome.

**Case Description:** A 60-old male was hospitalized in the nephrology division due to proteinuria, microscopic hematuria, edema in his both ankles and decreased renal function. To rule out glomerulonephritis, blood tests, urinalysis, kidney biopsy, serum protein electrophoresis (EP), random urine protein EP and immune fixation EP were performed. The results revealed hyperalbuninemia and dyslipidemia. Initial urinary protein-to-creatinine ratio was 12.5 g/gCr. In the serum protein EP, the M protein was 0.2g/dL, and in the urine protein EP, Bence-Jones proteinuria was detected. The kidney biopsy revealed positive staining for IgA-C6 in intraglomerular histiocytes; a high possibility of histiocytic glomerulopathy. As this condition has been reported to be associated with underlying hematologic diseases, we requested a consultation with the hematology department for further evaluation. The hematologist performed a bone marrow examination to differentiate between MGUS and myeloma, and to determine the presence of plasma cells. On bone marrow examination, plasma cells constituted 4.7% of the nucleated cells on aspirate smears. Additionally, a PET scan did not reveal any evidence of primary malignancy or distant metastasis. The patient was diagnosed with MGUS as M protein level was less than 3g/dL, plasma cell ratio was less than 10%, and there were no accompanying myeloma symptoms. Furthermore, it was confirmed that there were no treatable diseases associated with histiocytic-related malignancy or plasma cell disorders.

**Discussion:** This case showed that MGUS might be a rare cause of nephrotic syndrome and thorough differential diagnosis for myeloma could be necessary to ensure not to miss the optimal treatment timing.

**SA-PO207**

**Membranous Nephropathy Masquerading as Amyloid Nephropathy in a Multiple Myeloma Patient**

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University of South Florida, Tampa, FL

**Introduction:** Renal dysfunction is a common presentation in many plasma cell dyscrasias, including multiple myeloma. In these disorders, malignant plasma cells proliferate and produce monoclonal immunoglobulins (Ig). These Iggs can result in myeloma cast nephropathy, light chain deposition disease, and most commonly, amyloid light chain (AL) amyloidosis. In AL amyloidosis, Ig light chains deposit into renal parenchymal tissue and cause proteinuria and progressive chronic renal failure. Therefore, dysproteinemia-associated kidney disease should be suspected in any patient with plasma cell dyscrasia and renal dysfunction.

**Case Description:** The patient was a 73-year-old Caucasian female first diagnosed with primary amyloidoma, Durie-Salmon Stage IIIA, in 2014. She underwent chemotherapy and autologous stem cell transplant (SCT) in 2015, with complete remission. After SCT she continued on maintenance immunomodulatory agents with a good hematological response. In 2022 she developed progressive lower extremity edema, worsening pain, and increased urinary protein. A serum protein electrophoresis revealed an M-protein of 3.5g/dL and multiple M-splkes. Given clinical suspicion for dysproteinemia-associated kidney disease, the patient underwent a repeat bone marrow and kidney biopsy. The bone marrow biopsy revealed myeloma plasma cells occupying only 5% of marrow. Kidney biopsy revealed immune complex deposits involving capillary loops in a subepithelial distribution, a finding consistent with membranous nephropathy (MN). Notably, Congo red staining was negative and ruled out amyloid deposits. Anti-phospholipase A2 Receptor (PLA-2R) immunostaining was negative, and nerve epidermal growth factor-like 1 (NELL-1) immunostaining was positive. Age-based cancer screening was initiated, and NSAIDS were discontinued.

**Discussion:** Herein, we present a case of NELL-1 positive MN in a patient with multiple myeloma. Membranous nephropathy is the second leading cause of nephrotic syndrome. MN can be idiopathic, related to infection, medication use (NSAIDS), or autoimmune diseases. Notably, NELL-1 positive MN has been linked to solid organ malignancies. Management of these patients should emphasize discontinuing possible causative agents and a thorough cancer screening. This case represents the importance of a thorough workup of nephrotic syndrome, even in patients with a high pretest probability of AL amyloidosis.

**SA-PO208**

**The Meaningful Medulla: Apolipoprotein A-IV Amyloidosis**

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**Introduction:** Apolipoprotein A-IV (ApoAIV) amyloidosis is a rare disease affecting the kidney. The few existing case reports cite limited proteinuria with renal decline. We report a case of ApoAIV amyloidosis presenting with acute renal failure and nephrotic range proteinuria.

**Case Description:** A 67-year-old man with a history of gout presented with 3 months of fatigue and leg swelling after mildly symptomatic COVID-19. Labs revealed a serum creatinine of 11.5 mg/dL, increased from 1.3 mg/dL at baseline. He had no diabetes or significant nonsteroidal use and no family history of renal disease. Urine protein-creatinine ratio was 4.7 g/g. Ultrasound showed increased renal echocytosis without obstruction. Renal biopsy sampled only medulla and revealed interstitial Congo red positive amyloid deposits without light chain clonality (Fig. a-c). He received a short steroid taper and started hemodialysis. Subsequent workup was notable for normal serum kappa/lambda light chain ratio, serum and urine electrophoresis, bone marrow biopsy, and PET/CT. A second renal biopsy sampled only cortex and showed focal and segmental glomerulosclerosis (FSGS) with incomplete podocyte effacement, 70% interstitial fibrosis and tubular atrophy (IFTA), moderate arterio- and arteriolosclerosis, and no amyloid deposits (Fig. d-i). Mass spectrometry of the medullary deposits showed ApoAIV amyloid. He remains on dialysis and has been listed for transplant.

**Discussion:** ApoAIV amyloidosis is a rare cause of renal amyloidosis, often presenting as progressive kidney failure with minimal proteinuria. Renal pathology is notable for amyloid deposits restricted to the medulla with cortical sparing. This patient additionally showed no pathological changes and proteinuria here is presumed to be due secondary FSGS. This case highlights an unusual presentation with nephrotic syndrome and the importance of mass spectrometry for amyloid subtyping.
a baseline of 0.9 mg/dL to 3.5 mg/dL. Upon chart review, 6 months prior his creatinine was already increased at 1.6 mg/dL. His work up was significant for a random urine microalbumin to creatinine ratio of 95 mg/dl and urine protein to creatinine ratio of 742 mg/g. Serum kappa was 237 mg/L, serum Lambda 11.5 mg/L and Kappa/Lambda ration 20.6. Serum immunofixation showed IgG Kappa monoclonal protein 673 mg/dL. Urine immunofixation showed monoclonal free Kappa light chains 75 mg/24hrs. Because of the degree of renal failure in the setting of non-nephrotic proteinuria and AL amyloidosis, he underwent renal biopsy. Renal biopsy confirmed AL kappa amyloid deposition in the vascular wall with little to no deposition in the glomeruli with 60% of cortex showing interstitial fibrosis and tubular atrophy.

**Discussion:** Immunoglobulin light chain amyloidosis can be deposited in diffuse pattern or vascular limited pattern. Our patient demonstrates a rare case of AL amyloidosis in a vascular limited pattern. He also had evidence of vascular involvement outside of the kidney as well. Further studies are needed to recognize this pattern of amyloid deposition.

Renal biopsy under Light microscopy shows amorphous hypoconophilic deposits in the vascular wall(a), which is positive by Congo red stain and shows bright apple-green birefringence under the polarized light (b).

**SA-PO211**

A Case of Membranous Nephropathy Secondary to Chronic Lymphocytic Leukemia in Association with a Novel Antigen

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**Introduction:** Membranous nephropathy (MN) is an uncommon presentation in patients with chronic lymphocytic leukemia (CLL). A novel target antigen has not been detected in MN associated with CLL. We describe a case of MN in association with CLL successfully treated with acalabrutinib and propose a novel antigen EGF-containing fibrillin-like extracellular matrix protein (EFEMP2) as a possible target antigen in this disease.

**Case Description:** A 72-year-old male presented with bilateral lower extremity edema. His serum creatinine (Scr) was 1.7 mg/dL, serum albumin (SA) was 2.2 g/dL with 24-hour urine protein (24hUP) of 9g. Kidney biopsy revealed a PLA2R antibody negative and thrombospondin7A domain antibody negative MN with 1% of lymphocytic interstitial infiltrate consistent with CLL. He received rituximab (RTX) 1 g over 2 doses 2 weeks apart. He went into partial remission with a 24hUP 1000 mg. He relapsed with reconstitution of B-cells due to which 2 additional RTX 1 g doses were given. However, he remained nephrotic despite RTX and a CD20+ B cell of 0. Subsequently, tacrolimus (TAC) 2 mg twice a day was initiated. He went into complete remission 1 year after TAC initiation but relapsed despite therapeutic levels of TAC. His 24hUP at the time of relapse was 13g with SA of 2.1 and Scr of 3.0. He received 2 doses of obinutuzumab 1 g 2 weeks apart for refractory MN. Despite that, he remained nephrotic over the next 4 months. He underwent a repeat kidney biopsy which demonstrated MN with 20% interstitial infiltrate that was PAX5, CD21, CD20 and CDS positive consistent with clonal B-cell lymphoproliferation with features of CLL. Bone marrow (BM) biopsy showed CLL with 5-10% of the BM cellularity. CT chest and abdomen demonstrated widespread lymphadenopathy. Mass spectrometry of the first kidney biopsy showed moderate spectral count for EFEMP2 as the potential antigen. Acalabrutinib 100 mg twice a day was monotherapy. At last FU (12-month) he was in complete remission with Scr 2.4, 24hUP 370 mg and SA 4.5 without other therapies.

**Discussion:** Acalabrutinib monotherapy led to complete remission of MN with CLL. EFEMP2 is a possible target antigen in MN associated with CLL. Further studies are needed to confirm the presence of this antigen, disease association and outcomes in this patient cohort with MN and CLL.

**SA-PO212**

Clinical and Pathological Analysis of Five Cases of Immune Checkpoint Inhibitor (ICI)-Associated Membranous Nephropathy

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**Introduction:** Since ICIs have become a promising approach and have shaped a paradigm shift in tumor therapies, clinicians are increasingly confronting immune-related adverse events (irAEs). Acute interstitial nephritis (AIN) is the most common renal irAE, and the treatment of ICI-AIN is based on ICI discontinuation and corticosteroids, which, in most cases, leads to recovery. On the other hand, ICI-associated membranous nephropathy (MN) is relatively rare, and its clinical and histological features and treatment remain unclear.

**Case Description:** We conducted a multicenter study on renal irAEs by the nationwide Onconephrology Consortium in Japan and analyzed five patients with ICI-associated MN. Patients received Nivolumab for NET, lung adenocarcinoma (two patients), ovarian cancer, and renal cell carcinoma. All patients presented with proteinuria after ICI initiation. Three patients responded to ICI discontinuation and immunosuppressive treatment, including corticosteroids and cyclosporine, and finally achieved remission, whereas two patients did not. The time from ICI administration to disease onset was longer (17.6 months) in treatment responders, whereas it was shorter (6 weeks) in patients with persistent proteinuria. Histologically, in all patients, immunofluorescence microscopy showed granular staining in the capillary walls for IgG (IgG1>4) and C3, and negative PLA2R staining, suggesting secondary MN. Two of the three remission cases showed granular staining for nerve epidermal growth factor-like 1 (NELL-1), which is frequently reported in malignancy-associated MN. The remaining remission case showed a lupus-like deposition pattern with high electron dense deposits in the subepithelial, intramembranous, and subendothelial areas. Two patients with persistent massive proteinuria showed negative NELL-1 staining and no dense deposit in subendothelial area.

**Discussion:** We revealed that the ICI-MN population is clinically and pathologically heterogeneous, and some patients showed proteinuria remission with treatment. The characteristics of slow-onset and NELL-1-potentiality might be predictors of proteinuria remission. Our results speculated that ICI may induce underlying antibodies against tumor antigens such as NELL-1, leading to malignancy-associated MN, or may trigger immune responses, causing lupus-like MN.
SA-PO213

Bevacizumab-Associated Glomerular Microangiopathy: It’s Not Always Thrombotic

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Introduction: Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). It has been associated with thrombotic microangiopathy (TMA) classically with fibrin thrombi on histology. Recent cases suggest a separate glomerular microangiopathy (GMA) with distinct histopathologic findings, including pseudothrombom, subendothelial dense materials, and full house pattern on immunofluorescence (IF). Herein, we describe a case of anti-VEGF therapy-induced GMA.

Case Description: A 52-year-old female with metastatic lung cancer for six years was referred for proteinuria. She was initially started on carboplatin, pemetrexed, and bevacizumab, then transitioned to bevacizumab monotherapy the past year. Other medical history includes undifferentiated mixed connective tissue disease. Urinary findings showed new-onset proteinuria with urine protein/Cr 5.1 g/g with last urinalysis with no proteinuria four years ago. She had stable renal function creatinine 1.3-1.4 mg/dl for the past two years, no thrombocytopenia, with normal haptoglobin and lactate dehydrogenase. Proteinuria workup was negative for complement abnormalities and monoclonal gammopathy. She had a positive ANA titer 1:320, with normal cryoglobulin and anti-double stranded DNA. Kidney biopsy showed (Figure) PAS-positive circulating materials and duplication of glomerular basement membrane on light microscopy. IF showed IgM and C3 staining. Electron microscopy showed subendothelial electron dense material. These findings were most consistent with bevacizumab-associated GMA and bevacizumab was held. Proteinuria improved to 1.3 g/g on follow up.

Discussion: As anti-VEGF therapy is commonly used, it is essential to recognize the glomerular findings of PAS-positive pseudothrombom that occur outside of previously reported fibrin thrombi. Pseudothrombom are thought to form as a result of VEGF inhibition, endothelial cell permeability and protein accumulation in the subendothelium. Differentiating this diagnosis from other causes of proteinuria is especially important in patients with history of autoimmune disease to avoid unnecessary use of immunosuppressants.

SA-PO214

Calyceal Rupture of Horseshoe Kidney Following Chemotherapy

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Introduction: Horseshoe kidney (HSK) is the most common congenital renal fusion anomaly. During embryogenesis, fusion of the kidneys prevents independent rotation and ascent. Vascular supply to HSK involves small arteries branching from aorta or renal arteries. Complications of HSK are pulvrieteric junction obstruction, renal stones, infarct, and infections. Rupture of HSK has been reported in few case series and mainly due to trauma. Herein we describe a case of calyceal rupture of HSK in the setting of thrombocytopenia following chemotherapy.

Case Description: 40-year-old male with HSK was diagnosed with acute myeloid leukemia. Baseline imaging showed left renal atrophy with hydronephrosis. Labs showed normal renal function, creatinine 0.8 mg/dl. He was started on induction chemotherapy with cytarabine and daunorubicin. Ten days later, he developed abdominal pain, distension, and hematuria. He was hypotensive, platelet count 25 K/μl, hemoglobin 6.9 g/dl. CT scan showed increased severe left hydronephrosis, large volume hemorrhagic fluid with dilated calyces and large perinephric/retroperitoneal hemorrhagic fluid consistent with calyceal rupture. (Figure A) He received 2 units of blood and platelets and underwent emergent interventional radiology (IR) embolization to multiple arterial branches of the kidney. Future cycles of cytarabine were carefully planned with heme, renal, urology, and blood bank.

Discussion: Bleeding and calyceal rupture was an unexpected potentially life threatening complication in this patient with known HSK. In patients planned for chemotherapy that can be complicated by thrombocytopenia, we recommend a) obtaining baseline renal imaging of HSK, b) involving nephrology or urology early in the patient care and c) close monitoring and considering platelet transfusion with a higher platelet count threshold of 50K rather than 20K in collaboration with the blood bank given complicated arterial blood supply. In the event of hematuria and thrombocytopenia, we recommend early IR involvement for consideration of embolization.

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SA-PO215

Frequency and Characteristics of Chemotherapy-Associated Thrombosis and Thrombotic Microangiopathy: Analysis from a Large Pharmacovigilance Database

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Background: Thrombotic microangiopathy (TMA) is a rare but detrimental complication of chemotherapy. We examined the frequency and characteristics of chemotherapy-associated TMA using a large pharmacovigilance database.

Methods: We utilized Vigibase, a global drug monitoring database containing over 30 million adverse reports, to examine the frequency of TMA after each of these drug classes: immune checkpoint inhibitors (ICI), proteasome inhibitors (PI), platinum, tyrosine kinase inhibitors (TKI)/vascular endothelial growth factors inhibitors (VEGFi), conventional chemotherapy (gemcitabine and mitomycin) and other conventional chemotherapy (bleomycin, doxetaxel, pentostatin and doxorubicin). The strength of association was determined using information component (IC), a measure of disproportionality between the observed and expected number of reports for a drug-event combination. A positive IC indicates that the number of observed reports exceeds the number of expected reports. We also analyzed characteristics of individual cases who had TMA.

Results: Between 2010 and 2023, there were 4703 reports of chemotherapy-associated TMA in 1099 individuals. The drugs with the highest IC were carfilzomib (5.92), gemcitabine (5.52), mitomycin (4.22), bevacizumab (3.87) and bortezomib (3.69) (Figure 1). Among cases where only a single agent was used, TMA was most common with conventional chemotherapy (n=379, 41.2%) followed by PI (n=228, 24.8%), TKI/VEGFi (n=185, 20.1%), and platinum. Time to TMA onset was shortest in patients receiving other chemotherapy (31 days, IQR 30-34) and PI (35 days, IQR 8-178) and longest for conventional chemotherapy (156 days, IQR 91-245). Though uncommon, ICPI-associated TMA was associated with the highest mortality rate (41%).

Conclusions: The drugs most commonly associated with TMA were PI, TKI/VEGFi and conventional chemotherapy. Time to onset was shortest for patients receiving other conventional chemotherapy, while ICPI-TMA was associated with the highest mortality.

SA-PO216

Rechallenging Gemcitabine with Eculizumab in a Patient with Gemicitabine-Induced Thrombotic Microangiopathy


Introduction: Thrombotic microangiopathy (TMA) secondary to gemcitabine therapy (GTMa) is a rare pathology that carries a poor prognosis, with nearly half of the cases progressing to end stage kidney disease. The mainstay of management is withdrawal of the offending drug and supportive care. Furthermore, a C5 inhibitor, eculizumab, has been successfully used in the treatment of GTMA.
Case Description: A 78-year-old lady with a history of ovarian adenocarcinoma stage 4 on gemcitabine was referred for abnormal kidney function. She had CKD with a baseline serum creatinine (Scr) of 1.6-1.8 mg/dl. On this presentation, she had new onset hypertension and Scr was elevated to 2.8 mg/dl. Hemoglobin was 8.7 mg/dl with elevated serum lactate dehydrogenase (539 U/L) and low haptoglobin (<20 mg/dl). Urine analysis showed moderate proteinuria and hematuria with 30RBCs/HPF. Her spot urine protein-creatinine ratio (UPCR) was elevated at 1.5. A kidney biopsy was pursued which showed chronic thrombotic microangiopathy with severe glomerular capillary wall remodeling, 20% global glomerulosclerosis. Work up for causes of TMA was done including ADAMTS-13 level, antinuclear antibody level, HIV, direct antiphospholipid levels, serum complement 3, serum complement 4, anti-neutrophilic cytoplasmic antibody levels and atypical HUS panel which came back unremarkable. Gemcitabine was thought to be the culprit medication and was withheld. Scr did not improve and the patient was initiated on eculizumab with an improvement in Scr to 2 mg/dl. After a multidisciplinary discussion on oncology and the family, and based on the premise that gemcitabine was the only drug working for adenocarcinoma, it was decided to re-challenge Gemcitabine concurrently with eculizumab therapy. 3 months follow up showed Scr stable at 1.8 mg/dl, normal LDH, Haptoglobin and a UPCR at 0.1.

Discussion: Eculizumab therapy is a rare condition. Physicians should have a high index of suspicion to diagnose GTMA early in the course of the disease. Mainstay of management is discontinuation of gemcitabine and supportive care. Eculizumab has been tried in GTMA with great success in improving hematologic and kidney parameters. However, continuation of Gemcitabine along with Eculizumab therapy is a novel strategy that has limited data. Further research is needed to validate this strategy.

SA-PO217

Gemcitabine-Induced Thrombotic Microangiopathy Treated with Eculizumab in a Patient with Pancreatic Cancer: A Case Report
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Introduction: Thrombotic microangiopathies (TMA) are characterized clinically by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ injury. Drug-induced thrombotic microangiopathy (DITMA) is often under-reported and under-recognized. The incidence of gemcitabine-induced TMA (GTMA) has been reported to be 0.02% and 2.2%

Case Description: 67-year-old female with history of DM, Hypertension, CKD (B/L creat 1.8-2.0), Ca Pancreas s/p Whipple’s on neoadjuvant chemotherapy (FOLFOXIRINOX followed by Gemcitabine/Abxanaxane) was admitted with history of frequent falls and worsening left upper and lower limb weakness for 3 days. She had received gemcitabine with cumulative dose of 15,000 mg/m2 for the preceding 1 year, with last dose 2 months prior to her presentation. On admission, her BP was 170/90 mm Hg, serum creatinine 3.5 mg/dl, serum albumin 3.1 g/dl, worsening anemia (hemoglobin 7.1 g/dl), thrombocytopenia (platelet count 89,000/mm3), LDH 447 IU/L, with schistocytes on blood film. Urinalysis revealed RBC casts with urine microalbumin-creatinine 2400 mg/gm. ANA, ANCA, hepatitis B and C serologies were negative and complements normal. A diagnosis of GTMA was considered and she was stabilized with conservative measures. She was started on treatment with Eculizumab with which her renal functions improved with stable Hb.

Discussion: TMA occurring in a patient with a malignancy can be either malignant or drug-induced. Mechanisms of drug-induced TMA can be direct endothelial damage (type 1, dose dependent) or immune-mediated through the development of drug-dependent autoantibodies (type 2, none-dose dependent). Treatment of drug-induced TMA includes supportive therapy and withdrawal of the drug. Eculizumab has shown promise as an effective therapy for GTMA.

SA-PO218

Renal-Limited Thrombotic Microangiopathy from Bleomycin-Etopo-side-Cisplatin Chemotherapy in a Young Male with Testicular Cancer
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Introduction: Thrombotic microangiopathy (TMA) is a systemic illness stemming from endothelial dysfunction. However some patients present with only renal-limited. In this case, a 29-year-old male with a history of stage 3A testicular cancer was started on cyclophosphamide, bleomycin, etoposide and cisplatin (CBEC) therapy. On initial presentation, he had stage 4 on gemcitabine with proteinuria and a UPCR of 10g/g. His CKD had become stage 4 with a baseline serum creatinine (Scr) of 1.6-1.8 mg/dl. On this presentation, he had new onset hypertension and Scr was elevated to 2.8 mg/dl. Hemoglobin was 8.7 mg/dl with elevated serum lactate dehydrogenase (539 U/L) and low haptoglobin (<20 mg/dl). Urine analysis showed moderate proteinuria and hematuria with 30RBCs/HPF. Her spot urine protein-creatinine ratio (UPCR) was elevated at 1.5. A kidney biopsy was pursued which showed chronic thrombotic microangiopathy with severe glomerular capillary wall remodeling, 20% global glomerulosclerosis. Work up for causes of TMA was done including ADAMTS-13 level, antinuclear antibody level, HIV, direct antiphospholipid levels, serum complement 3, serum complement 4, anti-neutrophilic cytoplasmic antibody levels and atypical HUS panel which came back unremarkable. Gemcitabine was thought to be the culprit medication and was withheld. Scr did not improve and the patient was initiated on eculizumab with an improvement in Scr to 2 mg/dl. After a multidisciplinary discussion on oncology and the family, and based on the premise that gemcitabine was the only drug working for adenocarcinoma, it was decided to re-challenge Gemcitabine concurrently with eculizumab therapy. 3 months follow up showed Scr stable at 1.8 mg/dl, normal LDH, Haptoglobin and a UPCR at 0.1.

Discussion: Eculizumab has been tried in GiTMA with great success in improving hematologic and kidney functions. Mainstay of management is discontinuation of gemcitabine and supportive care. Eculizumab has been tried in GiTMA with great success in improving hematologic and kidney functions. Mainstay of management is discontinuation of gemcitabine and supportive care.

SA-PO219

Renal-Limited Thrombotic Microangiopathy due to Anti-VEGF/ Tyrosine Kinase Inhibitor (TKI) Immunotherapy for Metastatic Renal Cell Carcinoma Presenting as Nephrotic Syndrome
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Introduction: Vascular endothelial growth factor (VEGF) inhibition may result in proteinuria, worsening hypertension, chronic kidney injury or glomerular disease. Recently, systemic VEGF inhibition has been reported to cause nephrotic disorders and thrombotic microangiopathy (TMA). We present a unique case of renal-limited TMA presenting as nephrotic syndrome in a patient on anti-VEGF/TKI immunotherapy for metastatic renal cell carcinoma.

Case Description: A 73-year-old male with history of metastatic renal cell carcinoma, managed with combination immunotherapy with axitinib and pembrolizumab, was presented with generalized swelling, increasing weight gain up to 30 lbs, heavy proteinuria, hypoalbuminemia and nephrotic syndrome. Workup showed urine protein creatinine ratio of 14. Renal biopsy revealed renal-limited thrombotic microangiopathy, most likely attributed to anti-VEGF/TKI therapy. He had no evidence of immune complex deposition on electron microscopy, however, noted to have extensive foot process effacement which accounted for heavy proteinuria. His anti-VEGF/TKI therapy was discontinued and he is maintained on losartan and dapaglifozin with improvement in urine protein creatinine ratio to 7g upon followup.

Discussion: Our case suggests that renal involvement in patients on anti-VEGF/TKI therapies may manifest as nephrotic-range proteinuria and clinically nephrotic syndrome with renal-limited histological TMA and cessation of anti-VEGF/TKI therapy results in significant improvement in proteinuria with possibility of re-challenge with immunotherapy. In such cases, other differentials may include minimal change disease or collapsing focal segmental glomerulosclerosis (FGS). Cessation of anti-VEGF/TKI therapy results in significant improvement in proteinuria with possibility of immunotherapy re-challenge in the future. In case of concerns for renal sequelae with anti-VEGF/TKI involvement, prompt referral to nephrology for further evaluation is necessary for appropriate and timely management.

SA-PO220

Renal Limited Thrombotic Microangiopathy (TMA) Secondary to Chronic Lymphocytic Leukemia (CLL): A Case Report
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Introduction: Chronic lymphocytic leukemia (CLL) is a monoclonal B cell lymphophty that produces a neoplastic monoclonal immunoglobulin (Mg). Compement-TMA and C3 Glomerulonephritis with systematic manifestations have been rarely reported associated to CLL. We report the first case of renal limited TMA secondary to CLL.

Case Description: 70-year-old female with a history of type 2 diabetes exceeding 10 years, hypertension (HTN), and CLL diagnosed nine years prior presented with massive proteinuria with a UPCR a 10g/g, increased from 1.9 g/g six months prior along with lower extremity edema. The creatinine level was 0.84 mg/dl (eGFR around 74 ml/min/m²) and at baseline. Her CLL had never been treated as she had been considered asymptomatic despite having a WBC count above 200000. Her UA showed pyuria and microscopic hematuria. The serological work-up was unrevealing except for trace cryoglobulin IgG lambda with a kappa lambda ratio at 0.34. A total body CT scan done 5 months prior to presentation revealed a stable mild retroperitoneal lymphadenopathy and no new and mild splenomegaly. A kidney biopsy showed early nodular sclerosis likely from diabetes along with minimal change disease.
with endocardial injury with glomerular basement membrane duplication and endothelial swelling suggestive of TMA on electron microscopy. Pronase immunohistochemistry studies were negative for immune deposits. There was no evidence of peripheral TMA with stable hemoglobin and platelet counts and normal LDH and reticulocyte count. Complement studies revealed unregulated activity at the C3 and C5 convertase level with depressed C3 and C5 levels. The patient’s HTN and proteinuria were initially managed with losartan 50 mg daily, enalapril 10 mg daily and furosemide 40 mg daily, however as her UPCR increased to 17g/g, her nephrotic syndrome was deemed to be secondary to her CCL and she was initiated on irbutinib. The proteinuria improved and is now 4.82 g/g three months later. In addition, her WBC count went down to 92.8K.

**Discussion:** The significant improvement in proteinuria after initiation of irbutinib and the unregulated activity at the C3 and C5 convertase level suggests renal endotheial injury secondary to activation of the complement pathway by the Mf. Clinicians need to be aware of this potential complication of CLL to initiate treatment promptly.

**SA-PO221**

Renal TMA Presenting After Eight Years of Sunitinib Therapy

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**Introduction:** Thrombotic microangiopathy (TMA) is a rare side effect of Tyrosine Kinase Inhibitor (TKI) therapy that has almost always been reported as occurring within the first year of TKI initiation, with very few cases reported between two-three years. We report a case of renal-TMA occurring after eight years of TKI therapy.

**Case Description:** A 70-year-old male was seen for worsening renal function and edema in early 2022. He had a history of metastatic renal clear cell carcinoma treated with left nephrectomy in 2013. TKI was started on Sunitinib (TKIs) in 2014 and in 2015, the serum creatinine was 151 umol/L and peaked to 260 umol/L with urine protein: creatinine ratio (UPCR) of 857 mg/mmol at the time of referral. Physical exam revealed hypertension and bilateral lower extremity pitting edema. Rheumatologic work up, complement levels, and proteinuria panel were unremarkable. Renal biopsy revealed hyaline occlusive glomerular microangiopathy. Sunitinib was discontinued and within one week, his serum creatinine decreased from 260 umol/L to 182 umol/L. He was switched to Nivolumab in late 2022. After a year of discontinuation of Sunitinib, his serum creatinine and UPCR decreased from 260 umol/l and 857 mg/mmol respectively at referral, to 135 umol/l and 50 mg/mmol. The only other treatment that was leveraged was the optimization of his renin-angiotensin block using Irbesartan. No recurrence of renal dysfunction was noted after a year of follow-up and his hypertension and edema had resolved.

**Discussion:** To the best of our knowledge, our case is the first to highlight renal TMA occurring after three years TKI therapy. In previous case reports, renal recovery was seen with simply discontinuing the medication and supportive care such as renin-angiotensin inhibition, as was seen with our case. Some reports have used steroid therapy however these cases have almost always included stopping the offending agent as well. Mixed results have been reported with re-introducing TKI therapy. Take-away points from this case include: (1) Renal TMA can occur even after many years of TKI therapy, and should be monitored for as a possible long term side effect (2) Management involves obtaining renal biopsy, stopping the TKI, and supportive care to optimize hypertension and edema. It is essential to understand if steroid treatment is effective and if re-introducing TKI therapy is safe.

**SA-PO222**

Nirmatrelvir Plus Ritonavir-Induced Acute Interstitial Nephritis

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**Introduction:** Drug induced acute interstitial nephritis is an idiosyncratic delayed type IV hypersensitivity reaction that manifests 7-10 days after exposure to the culprit drug. We present a case of biopsy-proven drug-induced acute interstitial nephritis in a patient who received oral antiviral therapy for the treatment of COVID-19.

**Case Description:** 73y woman with CKD stage II and resected HER 2+ Stage II A Lung Adenocarcinoma actively treated with fam-trastuzumab and deruxtecan since December 2021, referred to our nephrology clinic for AKI noted on routine testing. One-year prior referral, baseline renal function was at 1.0-1.2 mg/dl. During initial encounter, patient reported traveling outside the US where she contracted COVID-19 and was given Paxlovid for treatment. Initial referral labs revealed WBC 8500cells/mm³ and 1.9% eosinophils, SCr 1.8mg/dl, BUN 38mg/dl and renal ultrasound with normal echogenicity of both kidneys. Follow up labs after initial encounter showed SCr of 2.3mg/dl, BUN 36 and UA with moderate leukocyte esterase, negative nitrite, 4-6 RBC per hpf, >50 WBC cells/hpf and negative urine culture. Treatment with prednisone 60mg daily was started with plan to taper based on initial response. Over the next 3 months her SCr returned to 1.4mg/dl and urinary sediment returned to normal.

**Discussion:** Nirmatrelvir plus Ritonavir (Paxlovid™) was developed for the treatment and post exposure prophylaxis of COVID-19. While the exact mechanism for its association with acute interstitial nephritis is unknown, there is a distinctly dysregulated inflammatory response primarily a T cell–driven process. The withdrawal of the causative drug is fundamental as an initial step in management however in some cases corticosteroid therapy is initiated due to moderate to severe renal injury based on their potent anti-inflammatory effects and prevention of irreversible structural changes resulting in renal fibrosis.

**SA-PO223**

An Unusual Case of Kidney Infiltration by Heavy Chain Disease with Lamellar Inclusion Bodies

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**Introduction:** Heavy chain diseases (HCDs) are rare B-cell proliferative disorders characterized by the production of a monoclonal protein composed of incomplete immunoglobulin heavy chains. To the best of our knowledge, we report the first case of renal HCD infiltrated by plasmacytic cells exhibiting distinctive lamellar inclusion bodies.

**Case Description:** A 65-year-old woman with systemic lupus erythematosus in remission with hydroxychloroquine and low-dose prednisone presented with fatigue, weakness, weight loss, and shortness of breath. Examination revealed pallor, hepatosplenomegaly, and inguinal lymphadenopathy. Laboratory tests showed anemia (Hb 5.2 g/dL), elevated creatinine (3.9 mg/dL, baseline 0.6), nephrotic-range proteinuria (857 mg/mmol, baseline 3 mg/mmol) at the time of referral, to 135 umol/l and 50 mg/mmol. The only other treatment that was leveraged was the optimization of his renin-angiotensin block using Irbesartan. No recurrence of renal dysfunction was noted after a year of follow-up and his hypertension and edema had resolved.

**Discussion:** To the best of our knowledge, our case is the first to highlight renal TMA occurring after three years TKI therapy. In previous case reports, renal recovery was seen with simply discontinuing the medication and supportive care such as renin-angiotensin inhibition, as was seen with our case. Some reports have used steroid therapy however these cases have almost always included stopping the offending agent as well. Mixed results have been reported with re-introducing TKI therapy. Take-away points from this case include: (1) Renal TMA can occur even after many years of TKI therapy, and should be monitored for as a possible long term side effect (2) Management involves obtaining renal biopsy, stopping the TKI, and supportive care to optimize hypertension and edema. It is essential to understand if steroid treatment is effective and if re-introducing TKI therapy is safe.

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

**Underline represents presenting author.**

**784**
SA-PO224

Atypical Hemolytic Uremic Syndrome (aHUS)/TMA in Genetically Predisposed Patients Treated with a Novel Agent for Relapsed/Refractory Multiple Myeloma

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Introduction: A number of therapies are being studied to treat relapsed/refractory multiple myeloma (RRMM). Modakafusp alfa (TAK-573) is a novel candidate for treating RRMM. It is a first-in-class immunocytokine that delivers interferon-alpha-2b (IFNα-2b) to CD38+ cells, showing promising anti-myeloma activity.

Case Description: Here we present two adult males, ages 46 (Patient 1) & 56 (Patient 2) seen at MD Anderson Cancer Center, both with history of RRMM & enrolled in clinical study 2022-0497 G2A4 carfilzomib and modakafusp alfa. Both presented with oliguric AKI requiring RRT, new-onset thrombocytopenia, schistocytosis & transaminitis with elevated LDH. Both had genetic testing & kidney biopsy while admitted. Patient 1 is heterozygous for the extended CFH-H3 risk haplotype, consistent with increased risk for development/progression of atypical hemolytic uremic syndrome (aHUS). The kidney biopsy showed acute/active thrombotic microangiopathy (TMA)-like changes. Patient 2 is heterozygous for a CFHR1-3 deletion (strongly suggesting a large contiguous deletion of both CFHR1 and 3 genes). Patient 2’s kidney biopsy also showed findings consistent with TMA features. Both patients had hemodialysis & eculizumab while inpatient & are continuing on hemodialysis on an outpatient basis.

Discussion: Both patients were recently started on carfilzomib & modakafusp alfa, a relatively new phase III clinical trial. Preliminary results from 2021 show modakafusp alfa caused side effects such as neutropenia, thrombocytopenia & mild reactions post-infusion. aHUS/TMA with AKI from modakafusp alfa has not previously been reported to our knowledge. Case reports of aHUS/TMA from carfilzomib do exist, however. We conclude that it is reasonable to perform genetic testing prior to initiating treatment with modakafusp alfa +/- carfilzomib, to mitigate the risk of aHUS/TMA as seen in our two patients.

SA-PO225

Digital Necrosis: Presenting Feature of Type 1 Cryocrystalglobulinemia

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Introduction: Type I cryoglobulinemia involves cryoprecipitable monoclonal IgGs associated with multiple myeloma, Waldenstrom macroglobulinemia, or chronic lymphocytic leukemia (CLL). Some cryoglobulins can “crystallize,” causing vaso-occlusive gangrene in addition to a glomerulopathy with a specific pattern of injury.

Case Description: A 64-ya-old man presented with a purpuric ankle rash, and bluish discoloration of his fingers and toes (Fig. 1). Labs revealed AKI with pancytopenia, microscopic hematuria, and a urine Alb/Creat ratio of 500 mg/g. He had negative or normal testing for hepatitis B and C, HIV, Protein C and S activity, ANA, Anti-DS-DNA, anti-scleroderma and anti-centromere antibodies, C3 and C4 levels, RF, antiphospholipid Abs, and testing for hepatitis B and C, HIV, Protein C and S activity, ANA, Anti-DS-DNA, anti-scleroderma and anti-centromere antibodies, C3 and C4 levels, RF, antiphospholipid Abs, and ANCA. Serum immunofixation showed a monoclonal IgG kappa paraprotein. Cryoglobulin (CG) testing was negative X2. A renal bx demonstrated an MPGN pattern of injury with vascular thrombi, both with IgG kappa restricted staining on immunofluorescence. Electron micrographs revealed subendothelial and intraluminal electron-dense deposits with crystalline lattice-like substructures c/w cryoglobulinemia (Fig. 1). Repeat CG testing showed a cryocrit of 5% that was also IgG kappa restricted on immunofixation. He received plasmapheresis and steroids. He developed AKI and required HD for a week after which his AKI resolved. He was eventually diagnosed with CLL and received clone-directed therapy with α+-carfilzomib, to mitigate the risk of aHUS/TMA as seen in our two patients.

Discussion: AKI requiring RRT, new-onset thrombocytopenia, schistocytosis & transaminitis with elevated LDH. Both had genetic testing & kidney biopsy while admitted. Patient 1 is heterozygous for the extended CFH-H3 risk haplotype, consistent with increased risk for development/progression of atypical hemolytic uremic syndrome (aHUS). The kidney biopsy showed acute/active thrombotic microangiopathy (TMA)-like changes. Patient 2 is heterozygous for a CFHR1-3 deletion (strongly suggesting a large contiguous deletion of both CFHR1 and 3 genes). Patient 2’s kidney biopsy also showed findings consistent with TMA features. Both patients had hemodialysis & eculizumab while inpatient & are continuing on hemodialysis on an outpatient basis.

Discussion: Both patients were recently started on carfilzomib & modakafusp alfa, a relatively new phase III clinical trial. Preliminary results from 2021 show modakafusp alfa caused side effects such as neutropenia, thrombocytopenia & mild reactions post-infusion. aHUS/TMA with AKI from modakafusp alfa has not previously been reported to our knowledge. Case reports of aHUS/TMA from carfilzomib do exist, however. We conclude that it is reasonable to perform genetic testing prior to initiating treatment with modakafusp alfa +/- carfilzomib, to mitigate the risk of aHUS/TMA as seen in our two patients.
SA-PO228

Type I Cryoglobulinemic Glomerulonephritis in Solitary Kidney

A 68-year-old White man with CLL, chronic kidney disease and heart failure who presented with worsening edema and kidney function on outpatient labs. Urine microscopy showed proteinuria (3+), leukocyte cast, and dysmorphic RBCs. Creatinine increased from baseline of 1.0 mg/dl to 3.89 mg/dL due to pulmonary edema seen on imaging. Labs showed a rise in serum creatinine to 3.89 mg/dL from a baseline of 1.0 mg/dL. Urine dipstick showed 3+ hematuria and proteinuria (3+), IgG 1-2+, C3 1-2+, and lambda 1+. EM with membranoproliferative pattern, focal hylan thrombus, segmental fusion of foot processes, paired tubular structures identified in subendothelial spaces and pseudo-thrombus consistent with cryoglobulinemic GN. No subepithelial deposits. R-CHOP started for suspected lymphoma. Developed vasculitic lesions in mid-2021, C3 and C4 low, cryocrit positive for the first time. Transitioned to Obinutuzumab-based regimen.

Kidney biopsy showed a membranoproliferative glomerulonephritis pattern of injury with cellular crescents, possible cryoglobulins, and focal involvement by CLL cells (Fig 2). Obinutuzumab-based therapy in combination with steroids, cyclophosphamide, and vincristine resulted in an improvement of kidney function and complete remission of nephrotic syndrome and CLL.

Discussion: CLL-associated MPGN pattern of injury with cryoglobulinemia and leukemic cell infiltration of the kidneys is a rare complication of CLL, more common in White elderly men compared to others. Previously, chemotherapy with rituximab plus other agents was the standard of care. However, Obinutuzumab has shown better efficacy compared to rituximab in patients with untreated CLL. Obinutuzumab is a second-generation anti-CD20 monoclonal Ab with enhanced antibody-dependent cellular cytotoxicity and superior progression-free survival. Detection of proteinuria or declining kidney function in patients with CLL should trigger evaluation and consideration of kidney biopsy. Prompt treatment with Obinutuzumab regimen can result in kidney recovery and improved patient outcomes.

SA-PO230

Successful Obinutuzumab-Based Treatment of Chronic Lymphocytic Leukemia (CLL)-Associated Membranoproliferative Glomerulonephritis (MPGN) Lesion with Kidney Infiltration

Introduction: Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm characterized by the accumulation of monoclonal cells in the blood and bone marrow with an indolent course. Extraduillary CLL with kidney involvement is rare, and treatments are based on retrospective studies and expert opinion. We present a patient with CLL-associated kidney involvement and successful complete remission after treatment with an Obinutuzumab-based regimen.

Case Description: A 68-year-old White man with CLL, chronic kidney disease and heart failure who presented with worsening edema and kidney function on outpatient labs. Urine microscopy showed proteinuria (3+), leukocyte cast, and dysmorphic RBCs. Creatinine increased from baseline of 1.0 mg/dl to 3.89 mg/dL due to pulmonary edema seen on imaging. Labs showed a rise in serum creatinine to 3.89 mg/dL from a baseline of 1.0 mg/dL. Urine dipstick showed 3+ hematuria and proteinuria (3+), IgG 1-2+, C3 1-2+, and lambda 1+. EM with membranoproliferative pattern, focal hylan thrombus, segmental fusion of foot processes, paired tubular structures identified in subendothelial spaces and pseudo-thrombus consistent with cryoglobulinemic GN. No subepithelial deposits. R-CHOP started for suspected lymphoma. Developed vasculitic lesions in mid-2021, C3 and C4 low, cryocrit positive for the first time. Transitioned to Obinutuzumab-based regimen.

Kidney biopsy showed a membranoproliferative glomerulonephritis pattern of injury with cellular crescents, possible cryoglobulins, and focal involvement by CLL cells (Fig 2). Obinutuzumab-based therapy in combination with steroids, cyclophosphamide, and vincristine resulted in an improvement of kidney function and complete remission of nephrotic syndrome and CLL.

Discussion: CLL-associated MPGN pattern of injury with cryoglobulinemia and leukemic cell infiltration of the kidneys is a rare complication of CLL, more common in White elderly men compared to others. Previously, chemotherapy with rituximab plus other agents was the standard of care. However, Obinutuzumab has shown better efficacy compared to rituximab in patients with untreated CLL. Obinutuzumab is a second-generation anti-CD20 monoclonal Ab with enhanced antibody-dependent cellular cytotoxicity and superior progression-free survival. Detection of proteinuria or declining kidney function in patients with CLL should trigger evaluation and consideration of kidney biopsy. Prompt treatment with Obinutuzumab regimen can result in kidney recovery and improved patient outcomes.
SA-PO232

Preliminary Results from a Genome-Wide Association Study (GWAS) in Bladder Cancer: Toward a Multi-Omics Approach

Case Description:
A man in his fifties with bilateral renal cell carcinomas underwent left total nephrectomy and right partial nephrectomy. He was treated with neoadjuvant and adjuvant nivolumab. His pre-operative creatinine was 1.0 mg/dL. Two weeks post nephrectomy, he was hospitalized for anuric acute kidney injury. Urine microscopy revealed acute tubular necrosis (ATN). He had large-volume ascites, despite normal hepatic function, which was consistent with urine based on drained ascitic fluid creatinine level of 78.9 mg/dL. Serum creatinine peaked at 12.65 mg/dL and improved to 2.2 mg/dL after paracentesis and right ureteral stenting. Creatinine decreased to 1.9 mg/dL at discharge. He was readmitted two months later for Enterococcus faecalis bacteremia. CT IV pyelogram demonstrated active extravasation of contrast from the right renal pelvis and formation of a right perinephric urinoma which was 5.1 cm wide. Serum creatinine eventually settled at 1.9 mg/dL with a stable estimated glomerular filtration rate of 60 mL/min. The patient was discharged on day 14 post tocilizumab with marked improvement in renal function and edema, with weight back to baseline.

Methods:
We performed a retrospective chart review of patients treated with VEGF-I and underwent kidney biopsies from 2010 to 2022. Biopsy findings were reviewed by our pathologists.

Results:
Nineteen biopsies were performed during 2010-2022 for kidney dysfunction in patients treated with VEGF-I. Eleven/19 had complete data. The median age was 62 (IQR 58-66) years, and the most common malignancy was renal cell carcinoma. TMA was found on 8/11 biopsies. Proteinuria was the most common reason for biopsy in patients with TMA. Three patients presented with other lesions besides TMA. One had anti-phospholipase A2 receptor-negative membranous nephropathy and both VEGF-I and pembrolizumab were stopped. She received prednisone with improvement in proteinuria. Another patient had known cryoglobulinemia with nephrotic range proteinuria exacerbated by VEGF-I peaking at 11g/day. Despite stopping VEGF-I and treating with prednisone+rituximab, he progressed to ESKD. Third patient had IgA nephropathy with diabetic changes, proteinuria progressed even after stopping VEGF-I (Table).

Conclusions:
In this review of patients treated with VEGF-I undergoing kidney biopsy, we described the histological characteristics, clinical course, and outcomes. Our review adds information to the sparse literature on patients with renal dysfunction after receiving VEGF-I.

SA-PO234

Bilateral Resection of Renal Cell Carcinoma with Postoperative Urinary Ascites

Matthew F. Baker, Maura A. Watson. Walter Reed National Military Medical Center, Bethesda, MD.

Introduction:
Urinary ascites is a rare complication of nephrectomy in the absence of bladder or ureteral injury.

Case Description:
A man in his fifties with bilateral renal cell carcinomas underwent left total nephrectomy and right partial nephrectomy. He was treated with neoadjuvant and adjuvant nivolumab. His pre-operative creatinine was 1.0 mg/dL. Two weeks post nephrectomy, he was hospitalized for anuric acute kidney injury. Urine microscopy revealed acute tubular necrosis (ATN). He had large-volume ascites, despite normal hepatic function, which was consistent with urine based on drained ascitic fluid creatinine level of 78.9 mg/dL. Serum creatinine peaked at 12.65 mg/dL and improved to 2.2 mg/dL after paracentesis and right ureteral stenting. Creatinine decreased to 1.9 mg/dL at discharge. He was readmitted two months later for Enterococcus faecalis bacteremia. CT IV pyelogram demonstrated active extravasation of contrast from the right renal pelvis and formation of a right perinephric urinoma which was 5.1 cm wide. Serum creatinine increased from 2.2 mg/dL on admission to 3.25 mg/dL by the time of hospital discharge. Follow-up imaging one month later demonstrated decrease in size of the right perinephric urinoma but with persistent extravasation of contrast from the right renal collecting system. Four months after right ureteral stent placement, the stent was removed and intraoperative retrograde pyleoureterogram showed no renal collecting system extravasation. His serum creatinine eventually settled at 1.9 mg/dL with a stable estimated glomerular filtration rate of 49 mL/min.

Discussion:
Urinary ascites directly from the renal collecting system, as shown on imaging in this case demonstrates an unusual complication of bilateral nephrectomies. Loss of nephron mass, bacteremia, and post-operative ATN contributed to chronic kidney disease development, but estimation of renal function was likely clouded by reabsorption of creatinine from extravasated urine. The urinoma eventually became walled off and collecting system defects in the remaining kidney healed. Urinary leak leading to large volume ascites may occur post nephrectomy and should be considered in patients without hepatic injury. The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.
A Case of Possible Malignancy-Related Polyangiitis Overlap Syndrome with Henoch-Schönlein Purpura and ANCA-Negative Pauci-Immunoglobulin Glomerulonephritis as a Manifestation of Neuroendocrine Cancer
Muhammad Ali,1 Natasha Ghalib,2 Fadila Noor,3 Susan E. Collins.1 *Nivance Health, Poughkeepsie, NY; 1Montefiore Medical Center, Jack D Weiler Hospital, New York, NY.

Introduction: Henoch-Schönlein purpura (HSP) is an immunoglobulin A (IgA) mediated vasculitis affecting small arterioles and venules involving the skin, gastrointestinal tract, kidneys, and joints. It is often precipitated by infections but has also been reported with malignancies. Pauci immune crescentic glomerulonephritis (PICGN) is a cause of rapidly progressive glomerulonephritis (RPGN) and is usually ANCA positive with a paucity of immune complexes on renal biopsy. It is associated with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), or renal limited vasculitis. Polyangiitis overlap syndrome with features of more than one vasculitis has also been reported. We report a unique case of HSP and ANCA-negative PICGN in association with metastatic neuroendocrine cancer.

Case Description: A 54-year-old male with no medical history presented with fatigue, colicky abdominal pain, and dark urine for 2 weeks. He denied recent respiratory or gastrointestinal infection. He had new-onset hypertension (BP 163/96 mmHg), a purpuric rash on the buttocks and lower extremities, and acute kidney injury (AKI).

Urinalysis showed hematuria, pyuria, and proteinuria. Skin biopsy showed IgA vasculitis consistent with HSP. Prednisone was started but he required hospitalization due to worsening AKI (BUN 36 mg/dL & creatinine 3.11 mg/dL). Workup showed anemia (Hb 12.8 g/dL), normal platelet count and coagulation profile, proteinuria of 1g/day, positive ANA (titer 1:100), negative anti-MPO, PR3, ANCA, anti-glom antibodies. CT abdomen showed multiple liver masses and biopsy showed metastatic neuroendocrine cancer. Renal biopsy showed acute pauci immune necrotizing crescentic glomerulonephritis. Chemotherapy (carboplatin & etoposide) was initiated with steroids leading to the resolution of AKI.

Discussion: We report a unique case of HSP and ANCA-negative PICGN in association with metastatic neuroendocrine cancer. The difference in skin and renal biopsies indicates possible malignancy-related polyangiitis overlap syndrome. HSP and PICGN can be manifestations of occult malignancy, especially in adult males. Diagnosis of malignancy is crucial as remission of vasculitis may require both treatment of cancer and immunosuppressants.

SA-PO235

Diversity Outbred Mouse Model for Investigating Genetic Determinants of Cisplatin Nephrotoxicity
Yves T. Wang, Thu H. Le. University of Rochester Medical Center, Rochester, NY.

Background: Cisplatin is a commonly used chemotherapy agent that is highly effective against several cancers. However, it has significant toxicity to several organs including the kidney. This has a significant impact on patient outcomes, as 50% of patients have to reduce dosages or discontinue use of cisplatin and up to 30% suffer from acute kidney injury (AKI). The causes of inter-individual variability in cisplatin nephrotoxicity are unknown, but evidence points to the involvement of genetic factors. We propose to use a mouse model with high genetic variability to identify potential gene candidates involved with modifying cisplatin nephrotoxicity. Here, we demonstrate the feasibility of using the Diversity Outbred mouse model, which was designed to mimic genetic heterogeneity in humans, in a small pilot study that demonstrates highly variable nephrotoxic response to chronic cisplatin administration.

Methods: Male and female Diversity Outbred mice (The Jackson Laboratory) were exposed to 9 mg/kg cisplatin subcutaneously weekly for 4 weeks (n = 8/sex) or vehicle control (n = 4/sex). Three days after the last dose, plasma was collected and creatinine was measured by mass spectrometry and BUN was measured by a colorimetric assay at UAB/SD O’Brian Center for Acute Kidney Injury Research.

Results: Control mice had plasma creatinine levels of 0.06±0.02 mg/dL [range: 0.04-0.08] in males and 0.07±0.02 mg/dL [0.06-0.11] in females. Compared to controls, cisplatin treated mice had significantly elevated plasma creatinine levels of 0.21±0.10 in males and 0.24±0.17 mg/dL [0.21-0.70] in females. Similarly, BUN was elevated in treated males (77.3±26.4 mg/dL [21.1-104.1] vs 26.5±8.4 mg/dL [18.1-36.5], p=0.00073) and females (65.7±27.5 mg/dL [21.9-92.0] vs 23.5±7.6 mg/dL [12.4-29.6], p=0.0030).

Conclusions: This study demonstrated significant differences in kidney function between mice treated with and without cisplatin, indicating the diversity of the mouse strain. In addition, these unique mouse models may enable pharmacogenetic application to tailor chemotherapy and enable development of adjunct therapies to limit cisplatin-induced AKI.

SA-PO236

BK Virus Nephropathy (BKVN) in a Native Kidney of an Immunosuppressed Patient
Omar A. Ayah,1 Gabriela Dande,1 Akwe Nyabera,1 Evan A. Farkash,1 Tareq I. Nassar.1 *The University of Texas Health Science Center at San Antonio, San Antonio, TX; 1University of Michigan Medical School, Ann Arbor, MI.

Introduction: BK virus nephropathy (BKVN) is common in kidney allografts but in native kidneys, BK reactivation is typically transient. However, there are a growing number of reports of BKVN fulminating acute interstitial nephritis in immunosuppressed patients.

Case Presentation: We present a case of a native BKVN mimicking an ifosfamide-related karyomyelopathic-like nephritis.

Case Description: A 53-year-old male with a past medical history of marginal zone lymphoma with transformation to diffuse B-cell lymphoma presented with worsening kidney function and albuminuria.

During a median follow-up of 3.7 years (IQR, 2.7-3.8 years), 5,126 subjects were included. ACR changes were quantified by albuminuria changes (ACR tests up to 2 years apart). Albuminuria changes were counted if the fold change in ACR over 2 years, and stratified into the absence of clinically elevated albuminuria; albuminuria that remained constant; and albuminuria that increased; or decreased. The primary outcome was overall cancer incidence. Secondary outcomes were site-specific cancer incidences.

Background: A single albuminuria measurement is reported to be an independent predictor of future cancer risk. Whether progressive albuminuria (i.e. albuminuria changes) adds further prognostic information is not known.

Methods: We included 64,303 subjects of the Stockholm Creatinine Measurements (SCREAM) project without a history of cancer and with at least 2 urine albumin-to-creatinine ratio (ACR) tests up to 2 years apart. Albuminuria changes were quantified by the fold change in ACR over 2 years, and stratified into the absence of clinically elevated albuminuria; albuminuria that remained constant; and albuminuria that increased; or decreased. Increases in albuminuria over a 2-year period are associated with a higher risk of developing overall, urinary tract, and lung cancer. No other associations between 2-year ACR changes and site-specific cancers were found.

Conclusions: Increases in albuminuria over a 2-year period are associated with a higher risk of developing overall, urinary tract, and lung cancer, independent of baseline kidney function and albuminuria.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO239

Dripping Clues: Unveiling Diabetes Insipidus (DI), a Sneaky Presentation of Acute Myeloid Leukemia (AML)

Naveen Rathi, Isaac I. Kim, Prakash S. Gudsoorkar. University of Cincinnati College of Medicine, Cincinnati, OH.

Introduction: DI is a rare complication of AML seen with cytogenetic defects especially monosomy 7 & inversion 3. It can occur before or after diagnosis of AML, with or without brain imaging abnormalities. Here, we report a case of hyponatraemia from DI in a patient with AML.

Case Description: A 68-year-old male with no medical history presented to ICU with altered mental status & polyuria (urine output > 5L/day), noted to have hyponatraemia 6.8 g/dL. Led to AML diagnosis based on bone and blood marrow tests (Fig1). Karyotyping revealed inversion 3 [inv(3)(q21q26)] & monosomy 7. His serum sodium (SNa) was high on admission at 168 mEq/L. Over the past 3-4 weeks, he had increased urination. Further evaluations, including an MRI of the brain, showed no abnormalities. Urine osmolality was 168 mOsm/kg/L (other metabolic tests were normal). Treatment with diuretics (2-4 mg/day) & free water boluses improved SNa and urine volume (Fig2).

Discussion: DI is a rare complication seen in AML, especially monosomy 7 & inversion 3. It can occur before or after diagnosis of AML, with or without brain imaging abnormalities. Here, we report a case of hyponatraemia from DI in a patient with AML. Further studies are needed to prove an association between DI & AML. Our patient had features of CDI based on the evaluation & treatment response.

SA-PO241

Single-Cell Sequencing Analysis of Paired Peripheral Blood Mononuclear Cell (PBMC) and Bone Marrow Mononuclear Cell (BMMC) Samples from Amyloidosis (AL) Patients

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Background: Systemic light chain amyloidosis (AL) is the most common type of systemic amyloidosis. It has a variety of clinical manifestations and can involve multiple organs, kidney and heart are the most commonly affected organs. The diagnosis of AL depends on the presence of amyloid deposition of immunoglobulin light chain or heavy chain. For a second opinion. She was recently admitted for severe acute kidney injury (AKI) attributed to clinicians with partial recovery upon therapy cessation. On exam, the patient appeared hypervolemic, with labs notable for acute kidney injury. Urinalysis with hematuria and 3+ proteinuria; urine protein: creatinine ratio of 1.9 gm/24h. A secondary workup showed low C3, M protein < 0.1 g/dL, and SIFE/IFE showed a small protein peak in the gamma region (IgG2 kappa). The renal biopsy showed Membranoproliferative glomerulonephritis with a monoclonal IgG deposit (IgG2 Kappa). PET scan significant for hypermetabolic soft tissue lesion in the oropharynx with tonsil biopsy confirming the transformation of CLL to DLBCL. The patient received R-CHOP with subsequent improvement in renal function and proteinuria.

Discussion: PGNMID has previously been reported to be associated with hematological malignancies, including CLL and lymphomas, solid malignancies, and infections, in addition to Monoclonal gammopathy of renal significance (MGSR). Effective treatment requires differentiating between these associated conditions as treatment is directed toward that disease. Our patient had confirmed hematologic malignancy at the time of PGNMID, the diagnosis for which paraneoplastic PGNMID is more reasonable than MGSR. The observed paraproteinemia is likely evolved as a part of an underlying immunoproliferative disorders. Increased free light chain level has been considered an adverse prognostic factor and early chemotherapy is emphasized for patients with PGNMID-associated hematological malignancies.

SA-PO242

SA-PO240

Paraneoplastic Membranoproliferative Glomerulonephritis Associated with Neoplasm Transformation

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Introduction: Paraneoplastic glomerulonephritis is a rare complication of malignancy and early recognition could prevent ineffective and potentially harmful therapy. The mechanism is unclear and doesn’t appear to be correlated with the tumor burden, invasion, or metastasis but possibly with the by-products of tumor cells. We present an interesting and rarely reported case of paraneoplastic proliferative glomerulonephritis associated with monoclonal IgG deposits (PGNMD) associated with diffuse large B-cell Lymphoma (DLBCL) that responded to Cyclophosphamide/doxorubicin/ vincristine/rituximab (R-CHOP).

Discussion: A 63-year-old woman with a history of hypertension, and chronic lymphocytic leukemia (CLL) failed two lines of therapy admitted to the hospital for a second opinion. She was recently admitted for severe acute kidney injury (AKI) attributed to clinicians with partial recovery upon therapy cessation. On exam, the patient appeared hypervolemic, with labs notable for acute kidney injury. Urinalysis with hematuria and 3+ proteinuria; urine protein: creatinine ratio of 1.9 gm/24h. A secondary workup showed low C3, M protein < 0.1 g/dL, and SIFE/IFE showed a small protein peak in the gamma region (IgG2 kappa). The renal biopsy showed Membranoproliferative glomerulonephritis with a monoclonal IgG deposit (IgG2 Kappa). PET scan significant for hypermetabolic soft tissue lesion in the oropharynx with tonsil biopsy confirming the transformation of CLL to DLBCL. The patient received R-CHOP with subsequent improvement in renal function and proteinuria.

Discussion: PGNMID has previously been reported to be associated with hematological malignancies, including CLL and lymphomas, solid malignancies, and infections, in addition to Monoclonal gammopathy of renal significance (MGSR). Effective treatment requires differentiating between these associated conditions as treatment is directed toward that disease. Our patient had confirmed hematologic malignancy at the time of PGNMID, the diagnosis for which paraneoplastic PGNMID is more reasonable than MGSR. The observed paraproteinemia is likely evolved as a part of an underlying immunoproliferative disorders. Increased free light chain level has been considered an adverse prognostic factor and early chemotherapy is emphasized for patients with PGNMID-associated hematological malignancies.
SA-PO243
A Novel In Vivo Model of Renal Cell Carcinoma (RCC) Angiogenesis
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Background: Renal cell carcinoma (RCC) is the most common tumor in the kidney and currently lacks effective treatments. Remarkably, although RCC is an extremely angiogenic tumor, existing drugs aimed at inhibiting angiogenesis have shown disappointing results in patients. One potential reason for this discrepancy is the fact that most models used to dissect the molecular mechanisms of RCC angiogenesis involve transplantation of human tumor cells into mice, which results in development of host-derived vasculature, putting into question their clinical relevance. We have previously shown that combined transplantation of human kidney cells alongside human vessel forming cells into immunodeficient mice allows the generation of vascularized renal-vascular units. Herein, we aimed to develop a novel in vivo model that will include RCC cells and vessels that are both human-derived.

Methods: We inoculated immunodeficient NOD-SCID mice with a combination of 10^6 fresh RCC cells and two types of human cells: (1) 5X10^5 Endothelial Colony Forming Cells (ECFC); (2) 5X10^5 Multipotent Stromal Cells (MSC), and analyzed the grafts following 3 weeks using immunostaining.

Results: Remarkably, the grafts developed into vascularized tumor units consisting of both RCC-like tissue, expressing classical markers of the tumor (e.g., PAX2 and PAX8), as well as human, HLA-positive blood vessels, containing CD31+ endothelium, which were seen to feed the tumor tissue.

Conclusions: Taken together, this model represents a new purely-human in vivo model that allows studying the process of RCC angiogenesis, which could facilitate the uncovering of new mechanisms governing this critical process.

Funding: Private Foundation Support

SA-PO244
Elevated 1,25-Dihydroxy-Vitamin D Level: A Perplexing Case of Renal Sarcoma with Osteoclast-Like Giant Cells
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Introduction: Elevated 1,25 Dihydroxy vitamin D (DHVD) level is commonly attributed to increased macrophage activity in chronic granulomatous conditions such as sarcoidosis. There are no reports yet of DHVD elevation in renal tumors. Renal sarcoma is very rare accounting for 0.8-2.7% of malignant kidney tumors and coexistence with Extra-skeletal Osteoclast-like giant cell tumors (OOGC) is not yet reported.

Case Description: Our patient is 74 years old Caucasian female with history of HTN. She came to ER with complaints of right sided abdominal pain, also reported 18 lb weight loss and poor appetite. CT abdomen with contrast revealed Interval enlargement of the very large, heterogeneous right renal mass compatible with renal cell carcinoma now measuring up to 15.2 x 16.1 x 17.9 cm which directly invades the right hepatic lobe (hepatic invasion has increased) and possibly the posterior abdominal/chest wall. Laboratory data significant for total serum calcium level 15.0 mg/dl, 25 Hydroxy vitamin D level 33.6ng/ml, 1, 25 hydroxypyridinol D level 133 pg/ml, iPTH level 6.4 pg/ml and PTH related peptide level 1.7 pmol/L. She underwent radical nephrectomy with histopathology showing High grade dedifferentiated sarcoma, with multinucleated giant cells involving kidney and extending into liver segment 6 and 7 (19.2 cm), with lympho-vascular and perinephric adipose tissue involvement. Cytogenetics significant for CD 10 positive, RCC markers negative, MDM2 focally positive, High positive for PD-L1. One week postoperative, laboratory data significant for normalization of 1,25 DHVD level 9.6ng/ml, and serum calcium 8.7 mg/dl.

Discussion: Resolution of hypercalcemia and normalization of DHVD levels after Sarcoma resection in our patient is very unique. The most effective therapy for renal and metastasized sarcomas is the gross total resection of the tumor. Increased rates of necrosis, poor differentiation, mitotic activity and increased histological grade are associated with a poor prognosis.

SA-PO245
A Case of Paraneoplastic ANCA-Associated Glomerulonephritis in a Patient with Non-Small-Cell Lung Carcinoma
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Introduction: Paraneoplastic glomerular diseases are rare immune-mediated disorders temporally correlated with the detection of an underlying malignancy. The association between malignancies and glomerular diseases has been most commonly described with solid tumors and membranous nephropathy. In contrast, Anti-Neutrophil Cytoplasmic Antibody (ANCA) vasculitis in patients with solid carcinomas is a rare occurrence.

Case Description: A 76-year-old female former smoker with a medical history of Sjogren’s syndrome presented to our nephrology clinic to evaluate worsening kidney function. Two months prior, she was diagnosed with metastatic squamous cell carcinoma of the lung and received 1 dose of pembrolizumab 1 week prior to nephrology evaluation. She reported decreased appetite, weight loss, and fatigue. Physical examination was remarkable only for blood pressure of 152/68 mmHg. Laboratory findings showed worsening serum creatinine from a baseline of 1.6 mg/dl (two months prior) to a peak of 4.1mg/dl. Urinalysis showed positive blood with >20 RBCs per HPF and a urine protein and creatinine ratio of 5g/g. Serological workup showed positive anti- SSA, positive anti-MPO, and negative anti-PR-3 titers. She underwent a kidney biopsy which revealed a focal pauci-immune crescentic and sclerosis glomerulonephritis. The decision was to temporally hold the immunotherapy and to start treatment with corticosteroids and Rituximab. A 2-month clinical follow-up showed a serum creatinine stable to 2.4mg/dl.

Discussion: In the last decade, there has been increased awareness of the association between malignancies, cancer treatment, and glomerular diseases. A paraneoplastic glomerular disease can be challenging to distinguish from a drug-induced or a primary glomerular disease in the setting of illness and treatment of underlying malignancy. Moreover, it poses an essential dilemma regarding management decisions concerning treatment for underlying cancer versus treating the glomerular disorder if the therapies cannot be given concurrently. In our case, we attributed the AAV to a paraneoplastic glomerular disease; the subacute rise in the creatinine coincided with the newly diagnosed lung cancer. One dose of immune checkpoint inhibitor was less likely the culprit. This case adds to the literature on this rare manifestation of AAV presenting as a paraneoplastic disease.
after a COVID-19 infection.

Case Description: 56-year-old male with spastic paraparesis secondary to cerebral myelopathy due to severe cervical stenosis (C4-C5) with a history of chronic longstanding nasal congestion and obstruction. Started to have hyporexia, anosmia, weight loss, fatigue, rash and xerostomia for approximately 4 months. Accompanied by renal failure which was first detected 2 months prior to the onset of his symptoms. Urinalysis was positive for IgG monoclonal protein with kappa light chain. Due to concern for myelodysplastic disorder, the patient underwent bone marrow biopsy which showed plasma cells that comprised 8-10 % of the nucleated hematopoietic bone marrow well-differentiated cells. There was no detectable clonal plasma cell population on flow cytometry prompting a diagnosis of MGUS for which he underwent kidney biopsy that revealed acute on chronic interstitial nephritis with many IgG4-positive plasma cells, suspicious for IgG4-RD. Currently receiving treatment with Rituximab and renal function has remained stable.

Discussion: This patient presented with xerostomia, constitutional symptoms, and dermatologic abnormalities, with light chain workup was diagnostic of MGUS. However, a kidney biopsy was performed and showed acute on chronic interstitial nephritis with IgG4-positive plasma cells, which leads to a diagnosis of IgG4-RD. An increased free light chain concentration has been reported in a variety of inflammatory and autoimmune diseases and reflects the polyclonal B lymphocyte activation in these pathologies. This presentation is fairly unusual and the intervention in this context is to make physicians aware of this for the future and warrant further investigation.

SA-PO247

Proximal Tubulopathy Secondary to Chronic Lymphocytic Leukemia After COVID-19 Infection

William M. Paredes, Marjorie Mailing Flores Chang, Bessy Suyn Flores Chang. SBH Health System, Bronx, NY.

Introduction: Light chain proximal tubulopathy is a rare kidney disorder that occurs when free light chains are filtered by the kidneys and then accumulate in the tubules, leading to kidney damage and dysfunction. This condition is often associated with multiple myeloma. While chronic lymphocytic leukemia (CLL) is not typically associated with light chain proximal tubulopathy, there have been rare cases reported in the medical literature. However, to our knowledge, no reports have been found of developing both conditions after a COVID-19 infection.

Case Description: A 60-year-old male with pre-DM presented were decreased appetite, and during his physical examination was unremarkable. Initial workup was significant for COVID-19 infection, serum creatinine of 3.2 mg/dL, GFR: 20 cc/min, however, was discharged for outpatient follow-up. Urinalysis showed proteinuria and hematuria (33 RBC per hpf), serum creatinine stable to 3.3 mg/dL, GFR: 20 cc/min, spot protein-creatinine ratio of 1.8 g, ANCA profile, hepatitis B and C serologies were non-reactive. Complement C3 slightly decreased 73 mg/dL (82-167 mg/dL), serum-free light chains ratio of 146. Prior serum creatinine was 0.9 mg/dL –4 years prior. Kidney biopsy demonstrated focal endocapillary and extra capillary proliferative glomerulonephritis with apparent IgG1 kappa deposits (light chain proximal tubulopathy), supporting the diagnosis of monoclonal gammapathy of renal significance (MGRS). Hemato-oncology evaluation noted worsening weight loss since the COVID-19 infection and left supraclavicular and bilateral inguinal lymphadenopathy with palpable hepatosplenomegaly. He underwent a bone marrow biopsy showing atypical lymphocytes, trisomy 12 in 45.5% of cells, and flow cytometry findings of the clonal B-cell population (60-65% of total), immunophenotypically represents (CLL). Treatment was started with Venetoclax, febuxostat, and obinutuzumab. His CML was referred to our clinic for abnormal renal function. At the time of CML diagnosis, his serum creatinine was 1.94 mg/dL and white blood cell count (WBC) was 203,000/μl. He was treated with the tyrosine kinase inhibitor dasatinib and after six months his WBC normalized and creatinine improved to 1.6. His exam in renal clinic was notable for no hypertension or edema. Labs were significant for urine protein-creatinine ratio (UPCR) 0.2 g/g, kappa-lambda ratio mildly elevated to 1.85, and no evidence of Fanconi syndrome. Kidney biopsy revealed tubular injury with positive lysozyme staining in the proximal tubules and 2+ mesangial IgA staining with minimal interstitial fibrosis with a MEST-C score of 0. Since his CML was adequately treated, we concluded his lysozyme levels were likely improving. He continued dasatinib, and three months later creatinine improved further to 1.43 and UPCR was undetectable.

Discussion: Lysozyme is a cationic protein mainly produced by monocyes and macrophages. It is freely filtered at the glomerulus and reabsorbed in the proximal tubule back into the bloodstream. Excessive lysozyme production causes proximal tubulopathy and can result in AKI, Fanconi syndrome, and proteinuria. LyN is an undiagnosed entity that often resolves with cytoreductive therapy. Interestingly, our patient had minimal proteinuria and no evidence of Fanconi syndrome, and we concluded his LyN had already responded to dasatinib by the time he was seen in renal clinic.
Identification of Pathological Micro-Domains in Renal Carcinoma Biopsies Using High-Resolution Spatial Transcriptomics Signatures

Background: Kidney cancer globally ranks 14th in men, 9th in women, with most prevalent in North America and Europe. Clear cell renal cell carcinoma (ccRCC) arises in the proximal tubular epithelial cells (pTECs) and is currently treated with antiangiogenic molecules and immune checkpoint inhibitors, leading to increased survival rates in responders. However, not all patients respond to these treatments. Here, we applied high-resolution spatial transcriptomics to biopsies of ccRCC patients, identified known markers of progression and gained novel insights into the micro-environments (ME) of affected kidney tissues.

Methods: FFPE tumor and healthy adjacent tissue biopsies from 2 ccRCC patients (ICD-O-2: C644.5:1) were used to characterize the decellularized matrices (dECM). Expression of various immuno-markers, including transforming growth factor beta (TGFb), alpha SMA, collagen I, elastin, von Willebrand factor and matrix metalloproteinases (MMP1, MMP2) were measured. In parallel, proteomic analysis with a sCRNaSeq reference and CosMx further revealed rare populations of immune cells along the tumor edge within healthy adjacent tissue.

Results: Initial analysis of Visium data revealed distinct differences between the two ccRCC patient tumors: while both patients showed a clear T cell response, we noted an extensive B cell response exclusively in patient A, whereas patient B showed a high number of proliferating tumor cells with angiogenesis. Within tumor A, we observed a striking correlation of the tissue ME to tumor PTEC function. While immune ME preserved normal PTEC metabolism, stromal ME comprised of fully transformed PTECs, high TGFb and TGFb susceptibility of tumor cells, showed a strong predisposition of immune cells to function poorly.

Conclusions: Overall, the high-resolution spatial transcriptomics data revealed patient-specific disease micro-domains and characterized molecular pathways in kidney cancer progression, paving the way for further analysis on distinct disease progression and unraveling potential therapeutic targets at the individual level.

Characterization of Extracellular Matrix Composition in Wilms Tumor and Its Impact on Cellular Behavior
Laura Perin,1,2 David S. Koos,2 Matthew E. Thornton,3 Brendan Grubb,3 Stefano Da Sacco,4,5 Astgik ieziers,6 Menglin Zheng,7,8,9 Carinie Seip,8,9 Evotec SE, Evotec SE, University of Southern California Keck School of Medicine, Los Angeles, CA, Children’s Hospital Los Angeles, Los Angeles, CA.

Background: Wilms Tumor (WT) is a pediatric renal cancer that arises from abnormal kidney development. The extracellular matrix (ECM) in the tumor microenvironment plays a critical role in supporting normal and cancerous cells and is essential for tumor growth and development. This study aims to understand the differences in ECM composition between normal kidneys and WT samples and how these variations affect cellular behavior.

Methods: We decellularized normal kidneys and WT patient samples using an optimized decellularization technique. Second-harmonic generation (SHG) microscopy and two-photon excited fluorescence (TPEF), combined with immunohistochemistry, were used to characterize the decellularized matrices (dECM). Expression of various cancer-related proteins such as matrix metalloproteinases (MMPs) and αSMA in ECM samples was assessed using immunofluorescence microscopy. Changes in gene expression of seeded S12X-CITED1 WT and human fetal kidney (hFK) progenitor cells on different dECM scaffolds were analyzed by RNAseq.

Results: Our study found differences in ECM fiber expression in WT dECM, with the outer layer comprising dense and elongated fibers, followed by pocketed and mesh-like structures. WT dECM exhibited elevated levels of oncoprotein ERBB2/3, SERPIN1 and MMP2 compared to normal kidney dECM. The ECM supported the long-term survival, migration, and proliferation of WT and hFK cells. When seeded on different dECM scaffolds, WT and hFK cells showed altered transcriptional profiles and changes in cellular behavior. WT and hFK cells on WT dECM exhibited variations in ECM binding proteins (integrins) and increased expression of EMT and cancer stem cell markers like vimentin and SOX9 compared to normal kidney dECM.

Conclusions: This study provides valuable insights into the role of the ECM in regulating cancer cell behavior. The findings have significant implications for developing physiologically relevant in vitro tumor models and identifying novel therapeutic targets and mechanisms.

Funding: Private Foundation Support

Spontaneous Tumor Lysis Syndrome
Saced Saleman,1 Charles Russell,2 Navyen Punachial Narayanankutty,2 Kartikeya Srivastava,3 Purith C. Chirumamilla,4 Al Balqa Applied University, Jordan; 2University of South Florida, Tampa, FL; 3Guntur Medical College, Guntur, India; 4Srivastava Orthopaedic and Fracture Care Centre, Agra, India.

Introduction: Tumor lysis syndrome is a life-threatening oncological emergency characterized by metabolic abnormalities including hyperuricemia, hyperphosphatasemia, hyperkalemia and hypeocalemia. These metabolic complications predispose the cancer patient to clinical toxicities including renal insufficiency, cardiac arrhythmias, neurological complications and potentially sudden death. TLS is typically associated with the start of chemotherapy; however, in some instances, spontaneous TLS may occur without prior exposure to chemotherapy. STLS is typically seen in high-grade hematological malignancies such as B-cell non-Hodgkin lymphoma.

Case Description: A 68-year-old male with a history of hypertension presented with fatigue, poor appetite, and generalized weakness. He had been previously admitted to another hospital for hematemesis and was diagnosed with high-grade B-cell lymphoma found in a gastric ulcer biopsy. He developed acute kidney injury and urinary obstruction during that hospitalization. On presentation to our hospital, he denied other symptoms and had no further episodes of hematemesis. Initial lab results showed a low bicarbonate (<33.1 mg/dl), abnormal values for phosphorus, calcium, and creatinine. The patient was diagnosed with AKI secondary to acute spontaneous TLS. Standard treatment was initiated with Rasburicase, the patient needed hemodialysis. Chemotherapy was initiated for high-grade lymphoma. After five cycles of chemotherapy lab values improved, and he remained stable, transitioning to continuous renal replacement therapy.

Discussion: In conclusion, this case report underscores the importance of recognizing and promptly treating STLS in patients with high-grade hematological malignancies. Even in the absence of chemotherapy, STLS can occur and lead to severe metabolic abnormalities and renal dysfunction. Early intervention with appropriate pharmacological and supportive measures is crucial to prevent complications and improve patient outcomes. Further research and awareness are needed to better understand the pathophysiology and optimal management of STLS.

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SA-PO253

Chronic Myelomonocytic Leukemia (CMLM)-Related Glomerulopathy Without Lysozyme Nephropathy
Bharathi Koirala, Raad B. Chowdhury, Nelson Leung. Mayo Clinic Minnesota, Rochester, MN.

Introduction: Myeloproliferative neoplasms (MPN) are chronic hematopoietic cell disorders characterized by expansion of the myeloid lineages. We are increasingly recognizing myeloid disorders causing glomerular disease. Chronic Myelomonocytic Leukemia (CMLM) is a unique MPN overlap which has a few glomerular presentations. We present a rare case of myeloproliferative glomerulopathy secondary to CMLM and review the renal course as the neoplasm progressed.

Case Description: A 85-year-old male with past medical history of heart failure and CMLM was admitted for acute kidney injury and proteinuria. Initial labs were significant for creatinine of 2.18 (baseline function of 1.1-1.3) mg/dl, 2.6/g/day of total proteinuria, and microhematuria. Urinary sediment showed less than 3 red cells, 1-3 white cells, with occasional granular casts and free fat. Serological evaluation and infectious workup were unrevealing. Kidney biopsy was consistent with MPN-associated glomerulopathy. There was no evidence of lysozyme nephropathy even though serum lysozyme levels were elevated >10.8 mg/ml. Post hospital, he was seen in clinic and started on a course prednisone with improvement of pr/cr to 0.3 mg/mg and creatinine improved to 1.4 mg/dl. After completing steroids, his renal function and proteinuria began to worsen to >3 mg/dl and 1.48 g/mg, respectively. Additionally, he continued to have worsening microhematuria (1200/103/m). There were increasing peripheral blasts and serum lysozyme levels worsened to >19.3 mg/ml. It was apparent that the patient’s CMLM progressed to AML with coinciding worsening renal parameters.

Discussion: Renal manifestations secondary to MPNs are rare. When it is present, those elevated lysozyme levels are presumed to have lysozyme nephropathy, a sign of advanced hematological disease. In this case, the patient’s proteinuria and renal function improved with steroids. Once stopped, his hematological parameters worsened, with laboratory evidence of peripheral blasts, indicative of progression to AML. This coincided with worsening lysozyme levels and precipitous decline in renal function. In conclusion, renal disorders in the context of myeloid neoplasms warrant thorough investigation as it may be a sign of worsening hematological disease and the potential role of steroids for nephroprotection should be explored.

Piperacillin/Tazobactam Dosing Recommendation in Critically Ill Patients Receiving Tablo Kidney Replacement Therapy
Susan J. Lewis,1 Bruce A. Mueller,2 1University of Findlay, Findlay, OH; 2Mercy Health St. Anne hospital, Toledo, OH; 3University of Michigan, Ann Arbor, MI.

Background: Tablo kidney replacement therapy (KRT) machines provide flexibility in treatment duration, frequency, and effluent rates to treat ICU patients with AKI. These KRT options may clear piperacillin/tazobactam (PIP/TAZ) differently than conventional KRTs. This study’s purpose was to predict PIP/TAZ doses likely to attain the efficacy targets used were 1) free plasma concentrations above the MIC for S. aureus, Enterococcus faecalis, and E. coli. We analyzed pharmacokinetic models were developed using pertinent demographic & pharmacokinetic parameters to predict PIP/TAZ exposure in 5,000 virtual, anemic patients receiving 5 different KRT regimens (Table 1). PIP/TAZ doses with 0.5 or 4 hour infusions were simulated to assess the probability of target attainment (PTA). The 3 PIP efficacy targets used were 1) free plasma concentrations above the MIC for ≥50% of the dosing.
SA-PO255
Drug-Drug Interaction Between Phosphate Binders and Daprodustat in ASCEND-D
Nicole S. Stanko,1 Amy M. Meadowcroft,2 Nisha Bhatt,3 Angela R. Jones-Leone,2 Purav R. Bhatt,4 Jennifer Shannon,4 Ajay K. Singh.3 1University of Chicago, Chicago, IL; 2GSK; Collegeville, PA; 3Brigham and Women’s Hospital and Harvard Medical School, Boston, MA.

Background: Daprodustat (Dap), a hypoxia-inducible factor–prollyl hydroxylase inhibitor (HIF-PHI), is an oral alternative to erythropoiesis-stimulating agent (ESA) therapy and is indicated in the USA for the treatment of anemia of chronic kidney disease (CKD) in adults receiving dialysis for at least four months. Phosphate binders (PB) are widely prescribed for hemodialysis (HD) or peritoneal dialysis (PD) patients (pts) in the USA. This study aimed to determine if Dap dose modification (DOEM) is required in PB users.

Methods: In ASCEND-D, 2964 pts with CKD undergoing dialysis and receiving ESA pts were randomized in a 1:1 ratio to receive Dap or injectable ESAs (epoetin alfa in HD pts or darbepoetin alfa in PD pts). Change in Hb and median doses from Weks 1 to 52 was reported by baseline PB use and dialysis modality.

Results: 656 (22%) pts reported no PB use at baseline. In HD pts, the Hb profile in baseline PB users was generally indistinguishable from that in non-users, and the median Daprodustat dose was approximately one dose step higher than for pts with no PB (Fig. A). While similar results were observed in PD pts, the number of pts reporting no PB use at baseline was too small to draw definitive conclusions (Fig. B). At Week 52, the majority of PB users and non-users had Hb within 10–11.5 g/dl, irrespective of treatment randomization.

Conclusions: This analysis demonstrated that baseline PB use had no major impact on the effect of Daprodustat on Hb levels in HD and PD pts.

Funding: Commercial Support - Outset Medical

SA-PO256
Exploring the Potential of Renal Dopaminergic System-Meditated Enhancement in Sodium Excretion by Canagliflozin
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Background: We have found that the renal dopaminergic system starts to activate along with the onset of diabetes/diabetic nephropathy, leading to sodium excretion before the occurrence of polyuria using spontaneously diabetic SD rats. We raised the question of whether the SGLT2 inhibitors exert the natriuretic effects via the renal dopaminergic system in non-diabetic SD rats.

Methods: Sprague-Dawley (SD) rats (9-11 weeks old, N = 8 for non-treated rats, N= 7 for canagliflozin-treated rats) were fed a commercial rodent diet. Canagliflozin (1.5–2 mg/kg/day) dissolved with 200–250 mL of drinking water was orally administered every morning, from 14 to 25 weeks of age. Blood samples were collected from the tail vein every week from the ages of 13 to 25 weeks, after which the body weight and the glucose levels. Each rat was individually housed in a metabolic cage for 24 h every week from the ages of 13 to 25 weeks and collected urine samples. At 26 weeks of age, rats were euthanized, perfused intracardially with saline containing heparin (20 IU/mL) and paraformaldehyde (PFA) for histological analyses. Results: The plasma sodium concentration and blood glucose levels were similar across groups. But significant differences were observed in urinary sodium excretion, urinary sodium excretion, demonstrating the efficacy of canagliflozin. In mass spectrometry imaging analyses, mean values of cortical ionized L-DOPA intensity in canagliflozin-treated SD rats were significantly higher than the L-DOPA in non-treated SD rats. Also, we have observed that canagliflozin-treated SD rats exhibit higher levels of reduced glutathione compared to control SD rats, suggesting a potential contribution to the reduction of renal oxidative stress.

Conclusions: Although further study needs to be conducted, we speculate that each mechanism, the activation of renal dopaminergic system and the suppression of oxidative stress, is another possible mechanism for kidney protection brought about by SGLT2 inhibitors. Possibly, the increased cortical reduction of oxidative stress may contribute to the detoxification caused by excess amounts of L-DOPA and DA.

SA-PO257
One Drug, Different Mechanisms of Side Effects: Linezolid-Induced Thrombocytopenia and Type B Lactic Acidosis
Brock Manley, Ayman M. Alghamdi, Tushar Chopra. University of Virginia, Charlottesville, VA.

Introduction: As the burden of antibiotic-resistant bacteria grows, we must understand the pathophysiology and management of rare side effects of Linezolid.

Case Description: 73 yo male with a history of HTN, CKD 3 [basal serum creatinine(Scr) of 1 mg/dl], and lumbar radiculopathy status post lumbar fusion complicated by infections from Enterobacter cloacae, vancomycin-resistant Enterococci, and methicillin-resistant Staphylococcus aureus (MRSA) treated with- ciprofloxacin 500 mg twice daily for 60 days before admission. 30 days of tedizolid 200 mg daily, and Linezolid 600 mg twice daily for 9 days, leading to this admission. On admission, the patient had a Scr of 1.6 mg/dl, platelets of 93 K/UL, and lactate of 3.35 mmol/L. Lactate increased to 3.9 mmol/L on hospital day (HD) 1 and returned to normal limits by HD 2 mmol/L. He had a platelet nadir of 43 K/UL on HD 5, along with improvement in Scr to 1.1 mg/dl. Platelet count recovered to 570 K/UL 12 days after admission.

Discussion: Linezolid induced lactic acidosis and thrombocytopenia is diagnosed after excluding other conditions such as hypoxemia, anemia or low cardiac output. Approximately 30% of linezolid is eliminated via the renal route, with an elimination half-life of 7-8 h with the therapeutic trough concentration being 2-8 µg/ml. In patients with impaired renal function, elimination half-life increases from 6.1 to 8.4 hours. Mitochondrial toxicity of linezolid causes severe lactic acidosis usually related to its toxic trough serum levels. Two mechanisms of LIT have been proposed; decreased platelet production via bone marrow suppression, and immune-mediated platelet destruction. Pharmacokinetic modeling of the two mechanisms found that suppression of platelet formation was the significantly more prominent mechanism of LIT. Immune-mediated platelet destruction typically develops within 7-14 days and recovers rapidly, whilst bone marrow suppression-associated thrombocytopenia develops gradually over multiple weeks and recovers gradually. The latter was observed in this case; a gradual decline and recovery of platelet counts. One has to consider reducing linezolid dose in patients with renal insufficiency on prolonged treatment to reduce toxicity amongst patients at low risk for treatment failure while being guided by therapeutic drug monitoring.
SA-PO258
Linezolid Adsorption During In Vitro Model of Hemoperfusion with Mini-Module of HA380 Cartridge
Anna Lorenzin, Massimo de Cal, Claudio Ronco, Monica Zanella. San Bartolo Hospital and IRRI, Vicenza, Italy.

Background: AKI due to sepsis is the result of a dysregulated host immune response to infection, with the production of inflammatory mediators and cytokines. Jaftron HA380 cartridge has been specifically designed for cytokine storm in sepsis. Given the growing application of these hemoperfusion device, an unsolved problem is whether these polymers absorb drugs, including antibiotics. In vitro experiments were conducted to determine its adsorption capacity towards Linezolid (LZD) antibiotic.

Methods: In vitro circulation was performed using a dedicated testing platform Galileo. A customized cartridge was built assembling mini-module components scaled in dimension towards HA380 and filled with 75g of HA380 beads (25% of the regular size). Blood pump was set at 250ml/min. Saline and human blood solutions enriched with 600µg of LZD have been tested for 2hrs. Samples were collected after the first passage (FP) through the cartridge and every 5 or 10min. LZD concentrations were measured. Adsorption was assessed considering the Remaining Ratio (RR)=100%×C0/Ct,

Results: Experiment with saline solution was performed in duplicate. In vitro circulation confirms the affinity of beads material in binding LZD. The kinetics shows a rapid adsorption in the very first part of the experiments, after that the adsorption rate decreased due to the decrease of antibiotic available in the solution. After FP of the solution through the cartridge, a RR higher than 80% has been achieved. At the end of the experiments the adsorption reached about the 100% of RR. Blood circulation reinforced these results: the RR of FP was higher than 80%, and at the end the mass injected in the solution was almost entirely adsorbed (see table).

Conclusions: HA380 adsorbs significant amounts of LZD. Further investigation using a higher quantity of LZD is necessary to reach the saturation of the cartridge and understand the sorbent material capacity. These preliminary results highlight that there is an interaction that could affect the clinical outcome.

SA-PO259
Use of Antiplatelet Drugs Targeting Platelet P2Y12 Receptor Is Associated with Reduced Risk for Infectious Death in Veterans with CKD
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Background: Platelets modulate thrombosis and inflammation, a hallmark of CKD pathophysiology. As a result, antiplatelet drugs are commonly used to reduce the risk of thrombosis in patients with CKD. Recent studies also demonstrated that platelet P2Y12 receptor inhibitors (P2Y12I) reduce inflammatory burden in patients with CKD, but their clinical impact on inflammation-related outcomes in CKD is not established. We investigated whether treatment with P2Y12I is associated with reduction in infection related deaths in patients with CKD.

Methods: We examined a national cohort of 90,701 US Veterans with incident CKD using a higher quantity of LZD is necessary to reach the saturation of the cartridge and understand the sorbent material capacity. These preliminary results highlight that there is an interaction that could affect the clinical outcome.

Conclusions: HA380 adsorbs significant amounts of LZD. Further investigation using a higher quantity of LZD is necessary to reach the saturation of the cartridge and understand the sorbent material capacity. These preliminary results highlight that there is an interaction that could affect the clinical outcome.

SA-PO260
Torsades De Pointes Decreases Kynurenine Acid Production in Rat Kidney In Vitro
Izabela Zakuć, Wojciech T. Zaluzka. Uniwersytet Medyczny w Lublinie, Lublin, Poland.

Background: Loop diuretics are one of the most widely used agents in the treatment of congestive heart failure or arterial hypertension and related edemas. Torsades is known to have longer time of action compared to other class representatives and thus more often chosen to stimulate diuretics. It was speculated that torsades by volume depletion can be responsible for impaired kidney function, however direct nephrotoxic effect cannot be excluded. Tryptophan metabolites are well described uremic toxins. Among them kynurenic acid (KYNA) presents ambivalent effects. KYNA is a broad spectrum glutamatergic receptors antagonist, an agonist of cholinergic alpha-7-nicotinic receptors and a ligand of aryl hydrocarbon receptors. Direct precursor of KYNA, kynurenine (KYN) is metabolized through kynurenine aminotransferases (KATs). In animal models of hypertension KYNA was reported to cause natriuresis and lower the heart rate. On the other hand, it was observed that KYNA accumulated in the body proportionally to kidney function decline in animal and human studies. The aim of our study was to examine the influence of torsades on KYNA synthesis and KATs isoenzymes activity, KAT I and KAT II in rat kidney in vitro.

Methods: KYNA production and enzymes activity was analyzed in kidney homogenates and on purified enzymes after 2 hours incubation in the presence of L-KYN and torsades in 6 different concentrations (1 µM, 10 µM, 50 µM, 100 µM, 500 µM, 1 mM). Due to the limited drug’s solubility torsades was tested in kidney homogenates up to 500 µM concentration, whereas enzymes activity was analyzed up to 1 mM concentration. The amount of formed KYNA was quantified by high-performance liquid chromatography.

Results: Torsades at 500 µM concentration decreased KYNA production to 68 % (p < 0.05) of control value. At 500 µM and 1 mM concentration torsades inhibited KAT I activity to 78 % (p < 0.05) and 43 % (p < 0.05) of control value, respectively. Only at 1 mM concentration torsades lowered KAT II activity to 17 % (p < 0.01) of control value.

Conclusions: We show for the first time that torsades inhibits KYNA production and KATs activity in rat kidney in vitro. Further studies are warranted to investigate the impact of presented results on kidney function.

SA-PO261
Lack of Consistency in Loop Diuretic Strategies of Acute Heart Failure
Amer A. Belal, Alejandro J. Ruiz Toledo, Amir Kazory. University of Florida College of Medicine, Gainesville, FL.

Background: Symptoms and signs of fluid overload are the primary reason for hospitalization of patients with acute heart failure (AHF). Intravenous loop diuretics (LD) remain the mainstay of therapy in this setting, with a significant subset of patients showing suboptimal response. The efficacy of combination diuretic therapy (CDT), a widely recommended strategy to counter renal sodium avidity, is compared against LD-based regimens that are considered the standard of care. We sought to explore the consistency of LD use in contemporary trials of CDT in AHF.

Methods: Articles cited in the PubMed database using keywords “acute heart failure”, “diuretic”, and “congestion” were searched. Available data from clinical trials performed between January 2005 and December May 2023 were included. The studies were selected if 1) they were randomized controlled trials that explored the role of CDT in management of AHF, and 2) included loop diuretics as their control arm. Perfusion data on clinical and laboratory parameters (e.g. diuresis, weight change, and renal function) were extracted and reviewed.

Results: A total of 13 studies with 7,826 participants were included with a mean age of 72 years. They consisted of a variety of HF populations with a mean ejection fraction of 25%. At 24 hours after enrollment, 55% received CDT and 15% of samples were extracted and reviewed.

Conclusions: While the current guidelines of AHF recommend intensifying LD therapy prior to CDT to enhance the decongestion process, there is no consensus on an optimal diuretic strategy. This study shows that 1) the LD regimens used in contemporary trials of CDT are highly variable, 2) the inconsistency in these regimens results in a highly variable diuresis as a marker of decongestion, and 3) a reliable comparison of the efficacy of add-on agents is challenging due to lack of consistency in the control arm. These results call for the development of an optimal LD strategy for AHF to help improve the decongestion process.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
SA-PO262

Accelerating Drug Discovery for CKD Through Mendelian Randomization Analyses of Druggable Proteins
Jefferson L. Triozzi,1 Guanchao Wang,1 Adriana Hung,1,2 Million Veteran Program.1 Vanderbilt University Medical Center, Nashville, TN; 1VA Tennessee Valley Healthcare System, Nashville, TN.

Background: Drug repurposing can accelerate the discovery of treatments for chronic kidney disease. To identify potential therapeutic targets, we conducted Mendelian randomization analyses using genetic instruments for proteins targeted by approved drugs or drugs in clinical development.

Methods: Genetic instruments for 879 druggable proteins were derived from the Genotype-Tissue Expression (GTEX) project. Kidney outcomes included estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD), and end-stage kidney disease (ESKD) derived from genome-wide association study statistics of European ancestry individuals in the Million Veteran Program (MVP). A drug target was considered significant if it fit study-wide Bonferroni significance in the inverse variance weighted analysis for all three kidney outcomes stratified by diabetes status. Significant findings in MVP were replicated in the Chronic Kidney Disease Genetics Consortium (CKDGen). Analysis was performed using the TwoSampleMR package in R version 3.3.3 using the Vanderbilt Advanced Computing Center for Research and Education.

Results: Our study identified 69 independent drug targets within MVP ($p < 9.48\times10^{-6}$). Shared targets in non-diabetic patients were Myosin Heavy Chain 7B ($p_{\text{MVP}} = 8.70E-08$, $p_{\text{CKD}} = 5.95E-17$, $p_{\text{ESKD}} = 7.90E-12$) and GSNOTD Releasing Hormone Receptor ($p_{\text{MVP}} = 3.61E-14$, $p_{\text{CKD}} = 1.94E-15$, $p_{\text{ESKD}} = 2.07E-09$, $3.24E-17$). Shared targets in diabetic patients were HLA-DRB1 ($p_{\text{MVP}} = 3.31E-54$, $p_{\text{CKD}} = 1.05E-53$, $p_{\text{ESKD}} = 1.72E-14$), Glycoprotein Nmb ($p_{\text{MVP}} = 1.52E-14$, $p_{\text{CKD}} = 5.37E-16$, $p_{\text{ESKD}} = 2.31E-10$), and GSNOTD Releasing Hormone Receptor ($p_{\text{MVP}} = 2.50E-15$, $p_{\text{CKD}} = 5.45E-08$, $p_{\text{ESKD}} = 1.42E-08$). All findings in MVP were replicated in CKDGen. The direction of effect was consistent across all findings, except for GSNOTD Releasing Hormone Receptor which exhibited a positive effect in diabetic patients and a negative effect in non-diabetic patients.

Conclusions: Our findings highlight potential targets for therapeutic intervention in CKD. Pathway enrichment analyses are underway to explore underlying mechanisms. Further studies should confirm the causal relationship between druggable proteins and kidney outcomes.

Funding: Veterans Affairs Support

SA-PO263

Health Effects (Renal) Of Extra Strength Avmacol (HEROES) Study: Results from the Pharmacokinetic Phase of a Randomized Double-Blind Placebo-Controlled Trial

Background: Increased oxidative stress is a major molecular underpinning of chronic kidney disease (CKD) progression. Decreases in the antioxidant enzyme glutathione-S-transferase μ-1 (GSTM1) due to a very common null gene variant have been shown to elevate oxidative stress and increase disease progression in animal and clinical studies. GSTM1 and many other antioxidant enzymes are regulated by the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. This pathway can be upregulated by sulforaphane (SFN), which can be obtained naturally from cruciferous vegetables such as broccoli. Commercially available SFN supplements provide much greater consistency in dosage compared to dietary availability. Further, SFN supplements provide much greater consistency in dosage compared to dietary availability. SFN can elevate oxidative stress and increase disease progression in animal and clinical studies.

Methods: A pharmacokinetic (PK) study was first performed to establish an optimal dose of Avmacol ES for CKD patients with eGFR of 25 – 45 mL/min/1.73m² to achieve similar peak concentrations and area under the curve (AUC) of plasma SFN observed in non-CKD patients. Subjects were given 2, 4, or 6 tablets once daily for 7 days. Plasma was collected at 0-8 h after the last dose. SFN levels were measured by LC/MS/MS.

Results: Peak plasma concentration ($C_{\text{max}}$) was reached between 2-4 h ($t_{\text{max}}$) in subjects taking 4 tablets (average $C_{\text{max}}$: 120 nM, AUC: 824 nmol h/L, n = 4) and those taking 2 tablets (average $C_{\text{max}}$: 85.1 nM, AUC: 581.4 nmol h/L, n=4). No $C_{\text{max}}$ was observed in those taking 6 tablets during 8h, and gastrointestinal (GI) side effects (SE) were significant. Both 2 and 4 tablets daily were well tolerated with minimal GI SE.

Conclusions: In CKD Stages 3-4, SFN $t_{\text{max}}$ is delayed compared to the 1-2 h $t_{\text{max}}$ reported in non-CKD subjects. Avmacol ES 4 tablets daily is well-tolerated with greater and more consistent $C_{\text{max}}$ and AUC than 2 tablets daily and is being used in the on-going randomized phase.

Funding: NIDDK Support, Commercial Support - Nutramax (providing drug and placebo)

SA-PO264

Magnetic Resonance Imaging Contrast Agent Safety: Prodigiosin Phosphorus in Renal Gadolinium-Rich Nanoparticles
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Background: Magnetic resonance imaging (MRI) contrast agent complications include fibrosis, kidney injury, and fatal gadolinium encephalopathy. Routine diagnostic imaging leads to the formation of gadolinium-rich nanoparticles in human kidneys. The mechanism is unclear.

Methods: Mice were treated with a MRI contrast agent. After four weeks of treatment and a washout period of 0.5 weeks, the kidneys were harvested. Flash-frozen kidney samples were homogenized in radioimmunoprecipitation assay buffer. Gadolinium-rich nanoparticles were purified from homogenate ultracentrifuged through sucrose gradients of different concentrations. We localized the nanoparticles using transmission electron microscopy (TEM). The elemental characterization of the nanoparticles was obtained using X-ray energy-dispersive spectroscopy (aberration-corrected scanning TEM, JEOL NEOAROM). We compared quantities between core and coronal areas using a two-tailed t-test. We adjusted the p-values using the Benjamini-Hochberg (B-H) method to account for false discoveries.

Results: Electron-dense intracellular debris peppered the proximal tubular epithelium. The dendritic cores and coronas contained high levels of gadolinium. Among the elements, phosphorus was 9.5-fold higher in the cores ($p = 1.2 \times 10^{-9}$).

Conclusions: There is more than one side to the argument concerning the safety of MRI contrast agents. Our findings suggest that nanoparticulate dendritic cores exhibit high phosphorus levels, which does not support the formation of GdPO4 precipitate. These results contribute to understanding the mechanism of gadolinium-induced complications.

Funding: NIDDK Support, Other NIH Support - UL1TR001449, Veterans Affairs Support, Private Foundation Support
SA-PO265
Hydralazine Adduct Formation on Myeloperoxidase Contributes to Development of Drug-Associated ANCA Vasculitis
Gang Xi,1 Elizabeth A. McNinns,2 Olivier Lardininos,1 John S. Poulton,1 Dhruvi P. Chen,1 Evan Zeitzer,1 Vimal K. Denebali,1 Ronald Falk,1 1The University of North Carolina at Chapel Hill Kidney Center; Chapel Hill, NC; 2National Institute of Environmental Health Sciences, Research Triangle Park, NC.

Background: Hydralazine exposure, an anti-hypertensive agent and a carbonyl scavenger, is associated with the development of ANCA vasculitis. We propose a pathogenic mechanism for hydralazine associated ANCA vasculitis hinging on formation of hydralazine adducts on myeloperoxidase (MPO), the primary immunogen for MPO ANCA.

Methods: In vitro hydralazine studies were performed using horse metmyoglobin (Mb) and human MPO. Hydralazine labeled Mb was digested by trypsin and peptides were analyzed with reverse phase HPLC and electrospray mass spectrometry. In addition, hydralazine labeled MPO was separated using PAGE gels and the hydralazine adduct was detected using an anti-hydralazine antibody. Commercially anti-MPO antibodies recognizing different portions of MPO were used to investigate the conformational change of the MPO heavy chain after hydralazine adducts formation. In addition, an immunoprecipitation assay was performed to detect hydralazine adducts on circulating MPO from patients. Furthermore, anti-MPO IgM and IgG antibodies were measured using ELISAs. Purified IgM and IgG from patients and healthy controls’ plasma were investigated their ability to recognize control MPO or hydralazine labeled MPO.

Results: In vitro studies showed that carbonyl groups formation on primary amines of a protein in the presence of aldehydic products, such as acrolein, is required for hydralazine to bind a protein. Mass spectrometry data showed that hydralazine bound to a carbonyl group of Mb. Under similar conditions, hydralazine adducts were formed on MPO. Importantly, the hydralazine adducts on MPO could be detected in plasma from hydralazine associated ANCA patients but not from patients with non-hydralazine associated ANCA or healthy subjects. Using commercially anti-MPO antibodies, we demonstrated that hydralazine adducts formation on MPO resulted in conformational changes. In addition, purified IgM and IgG autoantibodies from hydralazine associated ANCA patients were reactive against hydralazine labeled MPO.

Conclusions: Under appropriate reactive conditions, hydralazine adducts were able to be formed on MPO in some subjects who were exposed to hydralazine. Hydralazine adducts induced MPO conformational changes which may facilitate autoantibody development, leading to hydralazine associated ANCA vasculitis.

Funding: NIDDK Support

SA-PO266
Dapagliflozin Ameliorates Cisplatin-Induced Nephrotoxicity by Upregulating Nuclear Factor Erythroid 2-Related Factor 2/Heme Oxygenase-1 Signaling Pathway: A Pre-Clinical Molecular Approach
Anuradha A. Nair, Mohamed Farook, Nirmal N. Binu, Sofiya Khan, Mohamed Elyha Mohamed Mustafa, Mohammed M. Khan, Shakti Mani Satyam, Laxminarayana K. Bairy, Abdul Rehman, Dr. Satyam’s Lab - DAPA CKD Team. Ras Al Khaimah Medical and Health Sciences University College of Medical Sciences, Ras Al Khaimah, United Arab Emirates.

Background: A dose-limiting side effect of cisplatin administration is nephrotoxicity which impairs a patient’s quality of life. No potent nephroprotective agent is available to combat cisplatin-induced nephrotoxicity. This study aimed to explore the nephroprotective potential of dapagliflozin and silmyrin alone and in combination against cisplatin-induced nephrotoxicity in Wistar rats.

Methods: 30 adult Wistar rats were randomly divided into five groups (n=6/group): Group I- Normal control, Group II- Negative control, Group III- Silmyrin, Group IV- Dapagliflozin and Group V- Dapagliflozin + Silmyrin. Nephrotoxicity was induced in Group II to Group V by administering cisplatin weekly for seven weeks. Biomarkers for kidney injury, inflammation, and oxidative stress were estimated following a histopathological examination of the kidney.

Results: Chronic kidney disease was significantly (p<0.05) demonstrated in cisplatin-intoxicated (negative) control compared to normal control rats. Dapagliflozin alone and in combination with silmyrin significantly (p<0.05) reduced serum urea, creatinine, inflammatory cytokines, and oxidative stress markers compared to negative control.

Conclusions: The present study revealed that dapagliflozin alone and in combination with silmyrin ameliorates cisplatin-induced nephrotoxicity in Wistar rats via stimulating Nrf2/HO-1 signaling pathway.

SA-PO267
Pharmaceutical Inhibition of Lysine-Specific Histone Demethylase 1 Protects Against AKI
Baihai Jiao,1 Hao Du,1 Melanie Tran,1 Bo Song,1 Yanlin Wang,1 2UConn Health, Farmington, CT; 1VA Connecticut Healthcare System, West Haven, CT.

Background: Acute kidney injury (AKI) is a common clinical condition associated with increased mortality and morbidity. Current therapeutic options for this serious disorder are often limited and ineffective. Therefore, new therapeutic strategies are urgently needed to prevent or treat AKI. Macrophages play a critical role in the pathogenesis of cisplatin-induced AKI. However, the molecular mechanisms underlying macrophage activation in AKI are not fully elucidated. In this study, we investigated the role of lysine-specific histone demethylase 1 (LSD1) in the regulation of macrophage activation in the development of cisplatin-induced AKI.

Methods: To examine the role of LSD1 in cisplatin-induced AKI in vivo, wild-type C57BL6/J mice were administered intraperitoneally with a single dose of 20 mg/kg cisplatin to induce AKI and treated with GSK-LSD1, a selective LSD1 inhibitor, at 1 mg/kg or vehicle daily by intraperitoneal injection for 3 days. Cultured bone marrow-derived macrophages were used to examine the role and mechanisms of LSD1 in the regulation of macrophage activation in vitro. The expression of LSD1 was increased in macrophages in the kidney following cisplatin-induced AKI. Pharmaceutical inhibition of LSD1 with GSK-LSD1 protected the kidney from cisplatin-induced AKI and preserved kidney function in vivo. Furthermore, pharmaceutical inhibition of LSD1 with GSK-LSD1 suppressed macrophage activation, attenuated the NLRP3 expression, and inhibited inflammasome activation, resulting in reduced cleaved caspase 1 and IL-1β levels in the kidneys of cisplatin-induced AKI. In bone marrow-derived macrophages, pharmacological inhibition of LSD1 with GSK-LSD1 abolished macrophage activation and suppressed proinflammatory cytokine production. Moreover, GSK-LSD1 blocks NLRP3 expression and inflammasome activation in bone marrow-derived macrophages.

Conclusions: Our study identifies LSD1 as a critical regulator of NLRP3 expression and inflammasome activation in macrophages, leading to proinflammatory molecule production and development of cisplatin-induced AKI. Therefore, targeting LSD1 may represent a novel therapeutic strategy for AKI.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support
Human Primary Renal Proximal Tubule 3D Spheroid Model for Kidney Injury and Drug Discovery

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Background: Renal proximal tubular epithelial cells (RPTECs) have a prominent role in maintaining kidney function by reabsorbing filtered nutritional substances, while allowing selective permeation of substances secreted in the urine. RPTEC injury, cell death, and differentiation are mechanisms involved in kidney diseases including acute kidney injury (AKI). Human primary RPTECs isolated from normal human kidney tissue maintain the original phenotype in vitro for several passages and provide a translational advantage for studying nephron function and pathology. Conventionally two-dimensional culture methods frequently result in loss of tissue-specific RPTEC phenotypes partially due to changes of cell-cell communications and microenvironment. Hence, 3D models of RPTECs are being developed and used for drug discovery.

Methods: Primary hRPTECs were cultured in ULA spheroid plates for 4 days to form spheroids. Cellular injury was then induced by treatment with cisplatin or incubation in hypoxic chambers. Cytokine concentration, cell viability and apoptosis were measured by using commercial kits. RNA-seq were carried out, and pathway enrichment were analyzed by using Ingenuity Pathway Analysis software.

Results: Here we found that compared to 2D cultured cells, the hRPTEC 3D spheroid increased cisplatin induced injury responses and sensitivity with higher apoptosis and lower cell viability. Hypoxic condition induced significant increase of cell apoptosis and decrease of cell viability in hRPTEC spheroid. Transcriptomic analysis on the 3D hRPTEC hypoxia injury model identified similar pathway changes that found in in vivo ischemic AKI models. Pathway analysis in this model supports a role of IL-17A in promoting hRPTEC inflammation and injury. In contrast, SIRT3 activator treatment protected hRPTEC from hypoxia injury likely by improving energy metabolism and mitochondria function.

Conclusions: 3D injury models in primary hRPTEC spheroid are more sensitive to cisplatin injury than 2D cultures and pathway analysis revealed pathway changes consistent with the role of IL-17A in physiological and pathological injury. Therefore, we have developed a novel 3D spheroid injury model to evaluate the function and pathology of the kidney with higher translational relevance and can be leverage for fast screening and evaluation of potential therapeutic targets for kidney diseases.

Funding: Commercial Support - INJ

Distinct Pharmacokinetics of AA V9 and AA VKP1 Enable Context-Dependent Efficient Renal Transduction

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Background: Recent progress in capsid engineering led to generation of numerous adeno-associated virus (AAV) vectors with novel phenotypes. However, they have not been evaluated in the context of renal gene transfer. Increased permeability of glomerular and peritubular capillary (PTC) is a common feature of CKD, but renal transduction in CKD kidney is yet to be characterized.

Methods: Renal transduction of 47 different AAV vectors following IV and renal vein (RV) administration was evaluated in C57BL/6j mice using NGS-based high-throughput method called AAV Barcode-Seq. Effect of CKD on renal transduction was assessed in X-linked Alport syndrome model mice. Select AAV vectors were individually vectorized and relationship between renal transduction and pharmacokinetics was evaluated.

Results: AAV Barcode-Seq followed by individual characterization revealed that proximal tubule (PT) and podocyte transduction is not attainable by IV administration of AAV vectors. On the other hand, AAVKPI but not AAV9 transduced PT following RV administration. Assessment of injection path using fluorescent microspheres showed accumulation in the cortical interstitial space following RV administration. Interestingly, >10 times more AAVKPI vectors were detected in the injected kidney ten minutes post RV administration compared to AAV9. These observations suggest that RV administration bypasses PTC and efficient interstitial retention of AAVKPI enables PT transduction from basolateral side. In contrast to minimal urinary excretion of AAV vectors in healthy mice, excretion of AAV9 but not AAVKPI was significantly increased in CKD mice by about 10 times following IV administration. Difference between AAV9 and AAVKPI is explained by rapid blood clearance of AAVKPI that shows >1000 times less blood concentration than AAV9 over eight hours post injection. Consistent with this observation, IV administration of AAV9 but not AAVKPI achieved efficient podocyte and PT transduction in CKD kidney, suggesting that higher blood concentration of AAV9 facilitates access to podocytes and PT across leaky glomerular filtration barrier and PTC in CKD.

Conclusions: Our study underscores the important role of AAV pharmacokinetics in renal gene transfer. Appropriate selection of AAV vector depending on administration route and host condition is vital for successful gene therapy.

A Novel and Unique Fe-C Fusion Protein i-Body AD-214 Ameliorates Kidney Fibrosis Through Inhibition of Leukocyte Migration

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Background: Tissue fibrosis is the common pathological pathway in progressive chronic kidney disease (CKD). Current clinical practices are ineffective in limiting renal fibrosis. CXCR4 has been demonstrated to be central to the development of fibrosis. The usage of neural cell adhesion molecules as scaffolds by incorporating binding loops, mimicking the shape of shark antibody, allows construction of fully humanized single-domain antibody-like scaffold, designated as i-bodies. The i-body AD-214, which bind CXCR4 with high affinity, has been shown to be effective in limiting lung fibrosis. However, the role of AD-214 in renal fibrosis has not been investigated.

Methods: Renal proximal tubular cells (PTC) were incubated with TGFIβ1 with/without AD-214 for 48 hours. Supernatant was collected and collagen-3 (Col-3) and collagen-4 (Col-4) were measured by Western blot. Mice with unilateral ureteral obstruction (UUO) were administrated AD-214 every two days from one day after UUO for 14 days. Changes in renal morphology were examined by H&E and PAS staining, mRNA analyzed by qRT-PCR, extracellular matrix (ECM) and highlight striking differences with rodent.

Results: AD-214 suppressed TGFIβ1-induced overexpression of Col-3 and Col-4 by RPTEC cells compared to negative control. In UUO model, mice treated with AD-214 markedly ameliorated collagen deposition (30.4% reduction) relative to negative control group. IHC staining revealed that administration of AD-214 significantly attenuated the Col-4 and fibronectin (FN) deposition by 74.4% and 34.6% respectively relative to negative i-body treatment group. Consistently, physiological parameters BUN and KIM-1 were markedly reduced in mice treated with AD-214. Mechanism studies revealed that AD-214 inhibited the migration of leucocytes including macrophages and neutrophils into UUO kidneys. In the in vitro scratch assay, AD-214 effectively inhibited the migration of macrophages induced by LPS.

Conclusions: Blocking CXCR4 using the i-body AD-214 is a promising therapeutic strategy to prevent the development of CKD.

Funding: Commercial Support - Adalta Ltd, Private Foundation Support

Optimized Normothermic Machine Perfusion of Kidney, Liver, and Combined Liver-Kidney to Predict Human Pharmacokinetics

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Background: Robust translational models are key to predict the intestinal absorption, hepatic extraction (metabolism and biliary excretion) and renal elimination of compounds. Ex vivo normothermic machine perfusion (NMP) of whole organs is a promising tool, especially

Funding: Commercial Support - Adalta Ltd, Private Foundation Support

RXFP1, the Relaxin Receptor, Is a Therapeutic Target Expressed in the Human Kidney, Not Rodent

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Background: RXFP1 is a G-protein coupled receptor (GPCR) potentially agonized by its candidate ligand, relaxin. Historically named the pregnancy hormone following its identification and physiological description in rodents, relaxin is broadly recognized as a circulating hormone possessing several potentially clinically relevant cardiovascular-modulating and anti-fibrotic properties. It has long been recognized that there is remarkable diversity amongst species with regard to tissue source, regulation of synthesis and secretion, and physiological effects of relaxin. On the other hand, there is limited and inadequate understanding of RXFP1’s tissue and cell expression across species, especially human.

Methods: Here, we describe the human target validation of RXFP1 in human kidney and highlight striking differences with rodent.

Results: As opposed to mouse and rat kidney, where RXFP1 is poorly expressed, RXFP1 is identified as one of the most highly expressed GPCRs in human glomeruli. Specifically, by single cell RNAseq, in situ hybridization and immunohistochemistry, we identify glomerular endothelial cells as the principal cell type expressing RXFP1. Through extensive analysis of human kidney expression data sets from patient biopsies, we find that RXFP1 expression correlates with kidney function and disease progression. We identified a 428 gene RXFP1 co-expression network (R=0.6, FDR<0.05) that was enriched for an endocell wall and extracellular matrix function.

Conclusions: These observations provide a vital foundation to building our pharmacologic understanding of relaxin/RXFP1 function in human and suggest that kidney-intrinsic target engagement may mechanically explain the renal hemodynamic adaptive responses to clinical trends with relaxin. Great care needs to be taken to avoid confounding of relaxin’s diverse physiological effects observed in species where RXFP1 cellular expression is not congruent with human.

Funding: Other NIH Support - NIH, Commercial Support - AstraZeneca

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

Underline represents presenting author.
SA-PO273

Metabolomics of Drug-Induced Mitochondrial Biogenesis in Aged Mice Kidneys

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Background: Mitochondrial dysfunction is important in the aging process of many organs. We have shown that MC16, a drug candidate, induces mitochondrial biogenesis (MB) in mouse renal cortices and improves renal function in response to acute kidney injury. Thus, we hypothesized that stimulation of MB in aged mouse kidneys would improve global metabolomics in the kidney cortex.

Methods: Aged 22-month-old male C57BL/6J mice were administered a 1.0mg/kg MC16 or saline i.p. for eleven consecutive days. Kidneys were harvested and snap frozen in liquid nitrogen. Cortical biopsies were analyzed by Metabolon via multi-mass spectrometry. After mass normalization, log-transformation, imputation, Welch’s two-sample t-test was used to identify metabolites that differed significantly between treatment groups. A p-value of p<0.05 and a false discovery rate of q<0.10 were used to identify global metabolite changes and correct for multiple comparisons.

Results: In total, the dataset of detected metabolites consisted of 1,010 biochemicals (BCs). Of these, 441 were statistically different in saline-treated old mice compared to young control mice, with 276 BCs increased and 165 BCs decreased. 140 BCs were statistically different in the MC16-treated old mice group compared to the saline-treated old mice group, with 72 BCs increased and 68 BCs decreased. Saline-treated old mice had reduced 1,5-anhydroglucitol and elevated glucose-6-phosphate, fructose-6-phosphate, and dihydroxyacetone phosphate compared to young control mice, indicative of enhanced glycolysis. Conversely, MC16-treated old mice had no statistical changes in glycolysis metabolites compared to young control mice. While both groups had elevated carnitine levels, MC16-treated old mice derived most of their carnitines from fatty acid metabolism, indicative of impaired fatty acid metabolism in the saline-treated old mice group.

Conclusions: These data reveal that global metabolomics can be utilized to identify various age-related kidney metabolic alterations within the renal cortices of mice. This approach will allow us to identify and monitor age- or disease- related metabolic changes in the renal cortex of mice to evaluate potential pharmacological agents that may alter/blunt the progression of renal dysfunction in future studies.

Funding: Other NIH Support - NIEHS T32 - University of Arizona Southwestern Environmental Health Sciences Center - Training Grant Award Number: T32 5T32ES00791-39, Veterans Affairs Support

SA-PO274

Development of Drug Efficacy Testing Platform for Glomerulonephritis

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Background: There was little evidence for the treatment of glomerulonephritis (GN), although the guideline of GN was published. Therefore, we developed drug efficacy testing platform for GN using a 3D glomerular tissue chip.

Methods: A gravity-driven glomerular-filtration-barrier (GFB) chip was designed with human podocytes and endothelial cells, allowing bi-directional flow in the bottom channel. Purumycin was used to induce glomerulonephritis (GN) models, and serum from membranous nephropathy (MN) patients was used to establish personalized models on the chip. The reproducibility of MN and the effects of tacrolimus were compared with clinical data. RFP-Gendo, WT1, and nephrin, representing the glomerular filtration barrier’s molecular structure, were examined. Functional aspects of the GFB, such as cell viability and albumin permeability, were also evaluated.

Results: In the PAN-induced GN model, podocytes exhibited reduced levels of WT1 and nephrin, resulting in decreased albumin permeability and cell viability compared to the standard GFB. However, after the administration of tacrolimus, WT1 expression increased while nephrin expression decreased in the PAN-induced GN model. Tacrolimus also led to a reduction in albumin permeability and restoration of cell viability in this model. MN patients (MN1, MN2, and MN5) who received tacrolimus showed significant improvement. MN1 and MN2 had the most severe pathological injury among the enrolled patients. In the serum-induced MN1 and MN2 models on the chip, there was a significant decrease in cell viability compared to other groups, which was restored after tacrolimus treatment. Additionally, albumin permeability decreased in the MN1, and MN5 models following tacrolimus treatment on the chip. WT1 and nephrin expression increased after tacrolimus treatment in the case of MN1 model, which had the most favorable response clinically.

Conclusions: The efficacy of tacrolimus was successfully evaluated using PAN-induced and serum-induced GN models on a chip that mimics the structure and function of the GFB. The GFB-mimicking chip holds promise as a personalized platform for assessing drug efficacy using patients’ serum samples.

Funding: Government Support - Non-U.S.

SA-PO275

Endothelin Receptor Antagonists (ERAs) May Protect Against Rapid Kidney Function Decline: A Drug-Target Mendelian Randomization Study

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Background: Currently, the efficacy of ERAs to treat kidney disease is being tested in randomized controlled trials, positive effect in reducing albuminuria, preserving eGFR, and lower blood pressure has been reported. However, evidence from large randomized controlled trials comprehensively comparing the long-term renal effects of ERAs is lacking.

Methods: We applied a two-sample Mendelian Randomization approach to evaluate the causal effect of genetically mimicked ERA-induced blood pressure lowering on a series of kidney outcomes. Endothelin receptor (EDNR) SNPs associated with blood pressure and EDNR expression level were selected using GWAS summary data from the International Consortium of Blood Pressure (ICBP) and GTeX. GWAS summary statistics on kidney outcomes, including eGFR, proteinuria, and rapid kidney function decline, were drawn from CKDOjen. We used fixed effects inverse variance weighted (IVW) meta-analysis of SNP-specific Wald estimates for primary analysis, the weighted median and MR-Egger methods for sensitivity analysis.

Results: Four EDNRA SNPs and no EDNRB SNPs met the inclusion criteria. Genetic mimicry of EDNRA blockage was associated with a lower risk of rapid kidney function decline (OR = 0.39, 95% CI = 0.20-0.79 for eGFR decline<25%, OR = 0.57, 95% CI = 0.36-0.92 for eGFR decline<3 unit per year) and a higher eGFR based on creatinine (β = 0.02, 95% CI = 0.01-0.04). Despite the significant proteinuria-lowering effect reported in clinical trials, we do not observe a causal effect for EDNRA inhibition on UCAR, in the general population or on the population with diabetes at baseline.

Conclusions: Mendelian randomization study suggests ERAs may protect against rapid kidney function decline through the blood pressure-lowering effect induced by EDNRA blockage.

Funding: Government Support - Non-U.S.
A: Study Design. B: The OR and 95% CI indicate the effect estimates of decrease in disease risk per 10 mmHg lowering of SBP via EDNRA inhibition.

SA-PO276
Sparsentan Receptor Occupancy Modeling, Clinical Actions, and Safety
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Background: In the PROTECT study, sparsentan, which targets both the endothelin type A (ETAR) and angiotensin type 1 (AT1R) receptors, reduced proteinuria vs active comparator in IgA nephropathy with minimal changes in fluid status. This contrasts with ETAR blockers may promote fluid excretion, continual high fluid balance. The pharmacokinetic (PK) properties of sparsentan were used to estimate diurnal changes in receptor occupancy (RO) at steady state in the PROTECT study.

Methods: Receptor affinities (Ki) were determined for sparsentan at ETAR, ETBR, ETBR, and AT1R using radioligand binding assays. PopPK modeling of sparsentan was used to derive 24-hour PK and RO profile of patients in PROTECT.

Results: Sparsentan receptor affinities and PK data of a typical IgAN patient in the PROTECT study are shown in Fig. 1A. The 24-hour plot of sparsentan RO for ETAR, ETAR, and AT1R using radioligand binding assays. POPPK modeling of sparsentan was used to derive 24-hour PK and RO profile of patients in PROTECT.

Conclusions: Sparsentan has a stable 24-hour relationship in relative RO of ETAR to AT1R in which AT1R RO always exceeds ETAR RO. In contrast, when a drug solely targets ETAR, on top of AT1R blockade, periods of relatively unaccompanied ETAR antagonism may occur, representing a risk for fluid retention. This could partly explain the fluid retention seen with ERA and the minimal changes in fluid status seen with sparsentan.

Funding: Commercial Support - Traveere Therapeutics, Inc.

SA-PO277
Targeted Mass Spectrometry to Detect and Quantify Circulating α-Klotho Isomers
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Background: Progress in α-Klotho research has been limited by the lack of reliable assays that can discriminate between various α-Klotho isoforms which potentially exert differential physiological roles. We designed a novel targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay to detect and quantify the known circulating α-Klotho isoforms: soluble full-length Klotho (sFL-K), secreted KL1 (secKL1), soluble KL1 (sKL1) and soluble KL2 (sKL2).

Methods: We developed a parallel reaction monitoring-based (PRM) LC-MS/MS method that exploits unique peptide sequences present at the α2/B-site and the C-terminus of secKL1. During assay design, we tested enzymatic digestions of recombinant human sFL-K and secKL1 with commercially available proteases: trypsin, Lys-C, Asp-N, or chymotrypsin. After determining that chymotrypsin successfully created unique peptides covering the various α-Klotho isoforms, 11 synthetic peptides were used to optimize LC-MS/MS parameters and to determine limit of detection and quantification (LLOD/LLOQ) in solvent matrix. These peptides included chymotrypsin missed cleavages and deamidated Asn residues which were observed in our preliminary studies. We then utilized recombinant sFL-K and secKL1 proteins spiked into Top14 depleted plasma for further optimization and assessment of the assay.

Results: Only chymotrypsin digestion produced peptide signatures that cover the α2/B-site and the C-terminus. Therefore, we used secKL1 C-terminus to identify secKL1 from sFL-K and sKL1. The LLOD/LLOQ for synthetic peptide signatures in solvent matrix ranged from 0.02/0.06 to 1.3/3.8 fmol. Synthetic peptides with an intact α2/B-site resulted in multiple peaks, most likely due to the high number of prolines in the peptide which can create distinct conformers that were resolved with application of a 60°C column heater. Deamidated peptides were detectable in depleted plasma matrix spiked-in with recombinant sFL-K and secKL1 proteins. sFL-K and sKL1 were detectable in human serum samples.

Conclusions: This is the first α-Klotho assay that can specifically detect and quantify different isoforms of circulating α-Klotho and overcome limitations of antibody-based methods. Further optimization for robustness, reproducibility as well as validation studies are required to assess α-Klotho isoforms in other sample types.

Funding: Other NIH Support - NIH K23 DK115683

SA-PO278
Identification of RNAs in Urinary Extracellular Vesicles for Detecting Renal Nr2f Activation
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Background: NF-κB-related factor 2 (Nr2f), a master transcription factor, is known to be activated in response to oxidative stress, leading to producing antioxidant molecules. Renal oxidative stress condition can be estimated by measuring oxidative by-products and reactive oxygen species in urine. On the other hand, since activation of antioxidant molecules may mask renal oxidative stress condition, detecting renal Nr2f activation is likely helpful for early detection of renal oxidative stress. However, little is known about the non-invasive detection method. Urinary extracellular vesicles (uEVs) released from renal epithelial cells contain RNAs that may serve as biomarkers for renal diseases. Here, we examined RNAs in uEVs after administration of bardoxolone methyl (BARDO), an Nr2f activator, in rats.

Methods: Male SD rats were randomly divided into two groups: the BARD (10 mg/kg intraperitoneally) and vehicle (75% corn oil:25% DMSO) groups. The urine was collected for 6 hrs after the administration, and uEVs were isolated. Kidneys were also obtained at 6 hrs post-treatment. RNAs were extracted from uEVs and kidneys and analyzed by next-generation sequencing and microarray techniques.

Results: Based on the blood and urine tests, BARD administration did not impair renal function. Microarray analyses revealed that 19 genes in the kidney and 211 genes in uEVs were significantly altered after BARD administration. Next-generation sequencing identified 958 genes that were significantly changed by BARD treatment in the uEVs. Of these genes, only two genes, Pir and Ephx1 were commonly increased in the kidneys and uEVs (Pir: >3 fold, Ephx1: approximately 2-fold). Since the increase in Pir was higher than in Ephx1, we further investigated Pir as a potential biomarker for detecting Nr2f activation. In situ hybridization revealed that BARD-treatment increased Pir expression in the proximal and distal tubules of the renal cortex. Moreover, we established the pre-amplification method of RNAs in uEVs and successfully detected Pir in uEVs by PCR.

Conclusions: Theoretically, Nr2f is activated before the early onset of kidney diseases or under pre-oxidative stress condition. Thus, detecting Nr2f activation in the kidney by measuring Pir in uEVs could be a potential tool to detect early kidney diseases.
Conclusion: Serum creatinine shifts were comparable between ecu pts and pts who changed from ecu to crova or stayed on crova. Overall, the crova Phase 3 data show that the risk/benefit profile of crova is favorable in PNH and no new safety signals, including for kidney function, were observed. Crova is being evaluated for aHUS in the ongoing COMMUTE-a (NCT04861259) and COMMUTE-p (NCT04958265) studies.

Funding: Commercial Support - This study was funded by F. Hoffmann-La Roche, Basel, Switzerland.

**SA-PO281**

Long-Term Outcomes Comparing Belatacept vs. Tacrolimus in Older and Marginal Kidney Transplant Recipients: A UNOS Database Analysis

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**Background:** Studies have shown that kidney transplantation with even a marginal kidney provides a survival advantage in older patients when compared to dialysis. Older kidney transplant recipients (KTR) of marginal organs where KDPI ≥ 85% are more likely to be negatively impacted by the nephrotoxic effects of calcineurin inhibitors. Hence, the aim of the study was to compare long term patient and graft outcomes in older and high KDPI KTRs stratified by Tacrolimus (Tac) vs Belatacept (Bela) maintenance immunosuppression.

**Methods:** We identified adult, first-time kidney only transplant recipients from 2010 to 2022 who received induction therapy and were discharged on Tac or Bela based maintenance immunosuppression from the UNOS database. Multivariate Cox regression models adjusting for several donor, transplant and recipient factors were used to compare long term outcomes vs Bela maintenance in KTRs with age ≥65 yrs, KDPI ≥85%, and donation after cardiac death (DCD).

**Results:** The results comparing Tac vs Bela groups are detailed in Table 1. Bela use was associated with higher DCGF and death in KDPI ≥85% group (p=0.05). The rest of the long-term outcomes were similar between the groups.

**Conclusions:** The use of Bela in older KTRs recipients and DCD kidney recipients is associated with non-inferior outcomes, likely due to GFR advantage with Bela. Inferior outcomes in the Bela group among high KDPI KTRs could reflect selection bias. Other contributory factors could include higher risk for early rejections and opportunistic infections in the Bela group. These identified associations should be regarded as preliminary evidence, taking into account the retrospective nature of the study. They serve as a catalyst for future analysis.

**Comparison of long-term outcomes in older and marginal kidney transplant recipients based on maintenance immunosuppression.**
SA-PO282
Association Between Mycophenolic Acid (MPA) Pharmacokinetics and In Vitro MPA Glucuronide (MPAG) Turnover by Gut Microbiota of Kidney Transplant Recipients
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Background: Pharmacokinetic (PK) studies show enterohepatic recycling (EHR) of mycophenolic acid (MPA) due to MPA glucuronide (MPAG) hydrolysis by gut bacteria, which suggested that the relative abundances of MPAG producers would correlate with MPA EHR. We hypothesized that higher MPAG turnover would be associated with higher MPAG concentrations in vitro. Methods: 9 KTRs underwent simultaneous PK and stool collection at 30-60 days post-transplant. MPA % EHR was defined as MPA AUCl0-12h / AUCinf 100. Stool samples were anaerobically exposed to 100 mg/mL of MPAG in 5 mL of YCFA broth, with aliquots collected at 0, 30, 60, 90 and 120 mins post incubation (R = 0.85, 0.68, 0.58, 0.48, 0.43 respectively, p < 0.05 at 0 and 30 mins). We included 7 out of 31 previously known BGUS producers in our network analyses, which suggested that the positive correlations between MPAG concentrations and MPAG producers present in >10% of samples (Threshold R >0.3).

Results: After exposure to MPAG, we observed an increase in MPA with a concurrent decrease in MPAG concentrations across all in-vitro samples. Further comparison showed a positive correlation between MPA AUCl0-12h / AUCinf 100 and in-vitro MPAG concentrations assessed using mass spectrometry. Microbiota were characterized by 16S sequencing. We applied the Louvain Modularity Maximization algorithm to the correlation between in-vitro MPAG levels, MPA PK, and BGUS producers present in >10% of samples (Threshold R >0.3).

Conclusions: These data suggest that MPAG metabolism to MPA by the stool microbiome is correlated to the relative abundance of known BGUS producers. Further studies are needed to associate the extent of MPA PK with BGUS producers. Funding: NIDDK Support

SA-PO283
Take Drug Interactions Seriously: Paxlovid in Transplant Patients Taking Tacrolimus

Introduction: Kidney transplant recipients are highly susceptible to severe adverse respiratory syndrome coronavirus 2 (SARS-CoV-2) and are eligible candidates for Paxlovid™ (nirmatrelvir and ritonavir), an antiviral medication that reduces morbidity associated with COVID-19 infection. Ritonavir effectively maintains serum concentrations of nirmatrelvir by inhibiting CYP3A but can also elevate levels of other drugs metabolized by this enzyme, including immunosuppressive medications. We describe a kidney transplant recipient who received Paxlovid and subsequently developed supratherapeutic tacrolimus levels after dose titration upward.

Case Description: A 65-year-old man with history of ESKD due to type 1 diabetes mellitus and renal transplant on tacrolimus (dosed at 0.5mg BID) presented to our ED with symptomatic COVID-19 infection, for which Paxlovid was initiated. Tacrolimus was held. He was hospitalized for two days and discharged with instruction to continue Paxlovid and hold tacrolimus until outpatient follow-up. The next day, he presented again with anuria, leg edema, and AKI. Tacrolimus level was 2.0 mg/mL and creatinine had risen from baseline 1.8 mg/dL to 2.7 mg/dL. Due to a concern for acute rejection, Paxlovid treatment was stopped, and he was given two 2mg doses of tacrolimus 12 hours apart before lab work revealed a sudden rise in serum tacrolimus level to 54 ng/mL on hospital day 2. Tacrolimus was again held. Serum levels trended down to therapeutic range within four days. AKI steadily improved with supportive care.

Discussion: The introduction of tacrolimus has transformed the field of kidney transplantation. Maintaining therapeutic serum levels remains challenging due to its metabolism by CYP3A, resulting in potential drug interactions and high tacrolimus levels that can lead to irreversible nephrotoxicity. Transplant recipients frequently receive Paxlovid, and tacrolimus is often held during treatment. After Paxlovid is discontinued, 70-90% of CYP3A inhibition is relieved within 2-3 days, but may take longer with advancing age. Our case highlights the crucial need for cautious and conscientious resumption and dose titration of immunosuppression in the days after cessation of Paxlovid to avoid supratherapeutic and nephrotoxic serum levels of tacrolimus.

SA-PO284
Genistein Reduces Albuminuria by Inhibition of Caveolae-Mediated Endocytosis into Glomerular Endothelial and Epithelial Cells
Takahito Moriyama, Rie Suzuki, Yoshitaka Miyaoa, Yoshikiko Kanno. Tokyo Ika Daigaku, Shinjuku-ku, Japan.

Background: We previously reported the intracellular trafficking pathway of glomerular endothelial cells (GECs) and epithelial cells (podocytes) through caveolae as the new possibility of the easy etiology of albuminuria. The non-steroidal phytoestrogen belonged to potent soy isoalloflavone, genistein (Gen) inhibits Src kinase, which plays an important role of internalization of caveola coated pits into cytoplasm as caveola endocytosis. In this study, we analyzed the effect of Gen to reduce albuminuria by inhibiting albumin endocytosis through caveola into GECs and podocytes.

Methods: After 1 hour pre-treating cells with 50, 100, or 200 µM of Gen, cells were incubated with time course treatment of albumin (15, 30, and 60 min), and then the expression of caveolin-1 (Cav-1), albumin, and p-Src were measured by immunofluorescence (IF) and western blots (WB) analysis. It was also analyzed whether 14 days treatment of Gen reduced albuminuria in the streptozotocin induced diabetic nephropathy modeled mice (STZ mice).

Results: Albumin and caveolin-1 (Cav-1) expression levels were significantly decreased with dose dependent manner of Gen in IF and WB analysis (Figure). The expression of p-Src was also decreased in WB analysis. In vivo study, though body weight and blood glucose were not changed, Gen significantly decreased the urinary albumin/creatinine ratio in STZ mice (0.28 to 0.05, p=0.02) in comparison to non-treated STZ mice (0.21 to 0.14, p=0.37).

Conclusions: Gen inhibited albumin endocytosis through caveola by suppressing caveola expression according to inhibit Src kinase and resulted in reduced albuminuria in STZ mice. These results indicated the possibility of Src kinase inhibitor, Gen as the new therapeutic approach to reduce albuminuria in diabetic nephropathy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO285

Dexamethasone and Enalaprilat but Not SB525334 Exhibit Anti-Inflammatory Properties in Precision-Cut Kidney Slices (PCKSs) Obtained from Mice with Adriamycin-Induced Nephropathy Wioletta Pijacka,1 Giselle Linecupvics,1 Jessica Willis,2 Stephanie Butler,2 Steven Vickers,2 Sharon Cheetham,2 1Syngature Discovery Ltd, Newcastle, United Kingdom; 2University of Nottingham, Nottingham, United Kingdom.

Background: Precision cut kidney slices (PCKS) provide a valuable step between in vitro and in vivo testing. PCKS obtained from rodents exposed to adriamycin exhibit specific pathological features associated with glomerular and tubular injury, inflammation, and eventual fibrosis. In this study, we have evaluated the effects of dexamethasone, enalaprilat, and SB525334 on inflammation and fibrosis in PCKS from kidney slices from adriamycin-treated mice.

Methods: Male mice were dosed with adriamycin (11.25 mg/kg, iv) to induce nephropathy. On Day 7 mice were humanely sacrificed and kidneys were cut at 250μm on a vibratome. Slices were cultured in Williams Medium E media. Tissue viability was evaluated at 18h to 96h by LDH assay and ΔpEC (versus control). Independent slices were treated with SB525334 (1μM), Dexamethasone (1μM) and enalaprilat (10μM) for 24 or 96h. Pro-fibrotic (Fn, Col1a, Col3a, PAI1), pro-inflammatory genes (IL-6, TNFα, IL-1β, and CCL2) and C/EBPβ expression were significantly increased from 24h onwards, p<0.001. Nephrin, WT1 expression decreased, and KIM-1 increased at 24h and remained elevated, p<0.01. SB525334 decreased the expression of all pro-fibrotic genes, p<0.01 but not the pro-inflammatory mRNA and increased KIM-1 (p<0.05) but had no effect on WT1. Dexamethasone significantly reduced TNFα, IL-6, IL-1β, CCL2 (p<0.001) as well as Fn1, Col1a, Col3a and PAI1 (p<0.01). Dexamethasone increased WT1 and reduced KIM-1 (p<0.05, p<0.001) but unchanged nephron. Enalaprilat effects were limited, it reduced IL-1β (p<0.01) and increased WT1 (p<0.05).

Conclusions: Dexamethasone and enalaprilat produced a reduction in inflammation and fibrosis (dexamethasone only) leading to protection of the functional unit of the kidney. In contrast, SB525334 effects were limited to fibrosis but the effects on kidney function were intact. Taken together, inflammation plays a crucial role in adriamycin-induced nephropathy and PCKS present a reliable platform to test novel anti-inflammatory and anti-fibrotic therapies.

Funding: Commercial Support - Syngature Discovery

SA-PO286

Antifibrotic Effects of Tadalafil, a Phosphodiesterase 5 Inhibitor, with PAI1 Downregulation via eGMP in Rats and Fibroblasts Misuzu Noda,1 Yuji Hotta,1 Aya Nakato-Ito,1 Natsumi Tomita,1 Akimasa Sanagawa,2 Tomoya Katoaka,2 Yoko Hibi,1 Satoru Takahashi,1 Kazunori Kimura,3,4 1Department of Hospital Pharmacy, Faculty of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; 2Department of Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; 3Department of Clinical Pharmaceutics, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan; 4Department of Experimental Pathology and Tuberculosis, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan; 5Department of Pharmacology, Graduate School of Pharmaceutical Sciences, Chiba Institute of Science, Choshi, Japan.

Background: Renal fibrosis is common in cases of renal dysfunction, and the development of therapeutic agents for renal fibrosis is desired. It was recently reported that phosphodiesterase 5 (PDE5) inhibitors, used for the management of erectile dysfunction and pulmonary hypertension due to increased eGMP, have renoprotective effects. Thus, in this study, we investigated whether tadalafil, a PDE5 inhibitor, has antifibrotic effects via PAI1 downregulation in rats and renal fibroblasts.

Methods: Dahl salt-sensitive rats were used as a renal dysfunction model and divided into the following groups: normal salt (NS), high salt (HS), and HS plus tadalafil (HS+T). The NS group was fed a normal diet (0.5% NaCl), and the HS group and HS-T group were fed a high-salt diet (8% NaCl). Tadalafil (10 mg/kg/day) was orally given once into the following groups: normal salt (NS), high salt (HS), and HS plus tadalafil (HS+T). Tadalafil (10 mg/kg/day) was orally given once into the following groups: normal salt (NS), high salt (HS), and HS plus tadalafil (HS+T).

Results: Collagen-rich areas visualized by AZAN-staining obviously increased in the HS group compared with that in the HS group. On Day 7 mice were humanely sacrificed and kidneys were cut at 250μm on a vibratome. Slices were cultured in Williams Medium E media. Tissue viability was evaluated at 18h to 96h by LDH assay and ΔpEC (versus control). Independent slices were treated with SB525334 (1μM), Dexamethasone (1μM) and enalaprilat (10μM) for 24 or 96h. Pro-fibrotic (Fn, Col1a, Col3a, PAI1), pro-inflammatory genes (IL-6, TNFα, IL-1β, and CCL2) and C/EBPβ expression were significantly increased from 24h onwards, p<0.001. Nephrin, KIM-1 and WT1 were determined.

Conclusions: Tadalafil shows antifibrotic effects, which may be due to the prevention of active PAI1 expression due to increased eGMP in fibroblasts.

SA-PO287

When Hepatic Therapy Backfires: Unraveling the Intricacies of Rifaximin-Induced Rhabdomyolysis Post-Transplantation Salem Vilayet, Genta Uchra, Karim Soliman. Medical University of South Carolina, Charleston, SC.

Introduction: Rhabdomyolysis, a severe condition marked by muscle cell content leakage into circulation, manifests as weakness, pain, swelling, and myoglobinuria. It can result from diverse causes, leading to complications like acute kidney injury (AKI). We report a case of rifaximin-induced rhabdomyolysis.

Case Description: A 56-year-old male with a pancreas-kidney transplant, and cholestatic/drug-induced cirrhosis due to lacosamide (Stage 1 fibrosis on biopsy, now Stage IV). The initial presentation included weakness and altered mental state; labs revealed hyperammonemia (155 umol/L), elevated tacrolimus level (9.7 ng/mL), and creatinine (1.7mg/dL). He was started on intravenous fluids, rifaximin, lactulose, and continuation of his atorvastatin, resolved hepatic encephalopathy, and improved creatinine to 1.4 mg/dL. He returned three weeks later with increased weakness and leg pain. Labs showed elevated creatinine kinase (14614 U/L), creatinine peaking at 4.5 mg/dL, and a tacrolimus level of 8.9 mg/L. A renal biopsy suggested acute tubular injury, rhabdomyolysis-induced pigment nephropathy, and borderline acute rejection.

Management included pulse-dose solumedrol (500mg/3 days), followed by a taper, discontinuation of rifaximin, intravenous fluids, and dose reduction of tacrolimus, leading to resolution of rhabdomyolysis and improved kidney injury.

Discussion: In this case, rifaximin, a medication started during the patient’s initial presentation, likely caused the rhabdomyolysis. Despite its limited gut absorption, hepatic impairment may enhance absorption. The mechanism could involve rifampin-induced mitochondrial oxidative stress in muscle, promoting myofibrillar proteolysis, similar to statin-induced rhabdomyolysis. This case underscores rifaximin’s potential for inducing rhabdomyolysis, especially in patients with hepatic impairment.

Figure 1: Hematoxylin and eosin stain of renal tubules notable for brown pigment in cytoplasm and granular cast.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Discussion: Hypersensitivity reactions associated with the treatment of H. pylori infections were predominantly diagnosed as drug allergy. However, hypersensitivity against the eradicated H. pylori itself has recently been reported from Japan as a novel mechanism. To the best of our knowledge, this is the first case in which acute kidney injury manifested as complications. Recognition of this mechanism is crucial not only for dermatologist but also for nephrologist to prevent misdiagnosis.

SA-PO289
A Case of Drug-Induced Thrombotic Microangiopathy During Pulmonary Tuberculosis Treatment
Hyung Duk Kim,1 Yuanei Kim.2 Catholic University of Korea Eunjyeong St Mary’s Hospital, Eunjyeong-gu, Seoul, Republic of Korea; 1Seoul Saint Mary’s Hospital, Seocho-gu, Seoul, Republic of Korea.

Introduction: Drug-induced thrombotic microangiopathy is a rare, but serious complication. Here, we report a case of severe rifampin-associated TMA with acute kidney injury required renal replacement therapy during pulmonary tuberculosis treatment.

Case Description: A 67-year-old man diagnosed with pulmonary tuberculosis was referred to nephrology department for hematuria. The patient had a history of diabetes and hyperlipidemia. Isoniazid, rifampin, pyrazinamide and ethambutol were administered after the diagnosis of pulmonary tuberculosis. And on the 7th day of tuberculosis treatment, gross hematuria and purpura were developed. Laboratory tests showed a hemoglobin level of 8.4 g/dL, a leukocyte count of 9.01x10^9/L, a platelet count of 11x10^9/L, a urea nitrogen of 132.8 mg/dL and a creatinine level of 13.8 mg/dL.

Hemodialysis was initiated to control severe metabolic acidosis and uremic symptoms. Direct Coombs’ test was positive and schistocytes were observed on peripheral blood smear. Hemolytic anemia with thrombocytopenia and acute kidney injury were suspected to be related to rifampin. So, we discontinued the rifampin and start therapeutic plasma exchange. In vitro test for drug-induced immune complex proved that hemolytic anemia was induced by rifampin. After 4 sessions of plasma exchange, the patient’s renal function was gradually recovered and hemodialysis was stopped.

Discussion: It is known that hemolytic anemia occurs because rifampin binds to circulating antibodies to form immune complex and attaches to the surface of red blood cells, which activates the complement cascade. Thrombocytopenia also occurs by an immunological mechanism induced by rifampin. Hemolytic anemia and thrombocytopenia are usually known to appear on the 3rd day to 3rd week of rifampin administration. Here, we report a case of severe thrombotic microangiopathy with acute kidney injury in which the etiology was identified with an immune complex test and successfully treated with plasma exchange.

Results of the drug-induced immune complex test

<table>
<thead>
<tr>
<th>Patient’s screen + drug</th>
<th>O/RBC</th>
<th>I/RBC + anti-gludose</th>
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SA-PO290
Drug-Mediated Thrombotic Microangiopathy Associated with Eltrombopag
Mohammad Tinawi, Nephrology Specialists PC, Gary, IN.

Introduction: Eltrombopag is a thrombopoietin-receptor agonist indicated in the management of severe primary immune thrombocytopenia (SITP) and of chronic ITP. This is the first report of full-blow biopsy-proven thrombotic microangiopathy (TMA) with acute kidney injury (AKI) and the nephrotic syndrome (NS) in an ITP patient on eltrombopag.

Case Description: 65-year-old woman with steroids and immunoglobulins resistant ITP presented with confusion, worsening thrombocytopenia, fever, and AKI. Eltrombopag was started 4 days prior to admission. Three weeks earlier, creatinine was 0.84 mg/dl, and platelets 84,000/μL. On admission, Creatinine was 5.22 mg/dl, and platelets 50,000/μL with schistocytes. LDH was 1,935 U/L. Urine protein-to-creatinine ratio was 6510 mg/g creatinine with hyperlipidemia and hypoalbuminemia. Blood and urine cultures, and direct Coombs were negative. Anticardiolipin antibodies, hepatitis B and C, and connective tissue disorders serologies were unremarkable.

Pre-plasma exchange ADAMTS13 was normal. Eltrombopag was stopped, IV corticosteroids and hemodialysis (HD) were started. Renal biopsy showed focal cortical necrosis, ischaemic changes in the glomerular capillary loops, and focal arteriolar fibrin thrombi with red blood cell fragmentation. After 7 days plasma exchange sessions, platelets normalized and confusion resolved. Two months later she was taken off HD.

Discussion: There are four reports of eltrombopag-associated AKI, one was renal limited TMA, another in a patient with antiphospholipid syndrome, and two presented with AKI. In this case report, Naranjo adverse drug reaction probability scale showed a score of 7 or a probable relationship between eltrombopag and TMA. Eiltrombopag drug-mediated TMA is uncommon. Drug cessation, corticosteroids, plasma exchange and renal replacement therapy should be considered in the management of this disorder.

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

Ischemic glomerulus with fibrin thrombi

SA-PO291
Ophthalmological Safety of Hydroxychloroquine in CKD
Darín Pourn,1 Ashutosh M. Shukla,1,2 Malea Joyce,1 Kailyn Pearce,1 Selin Kavak,2 Wanda Martinez-Navarro,1 Mark S. Segal,1,2 Alfred K. Cheung,2 Sudhir V. Shah,1 1VA Medical Center Malcom Randall, Gainesville, FL; 2University of Florida, Gainesville, FL; 1University of Utah Health, Salt Lake City, UT; 2University of Arkansas for Medical Sciences College of Medicine, Little Rock, AR.

Background: Hydroxychloroquine (HCQ) is routinely used in advanced CKD for rheumatological disease, despite known concerns for its ophthalmological safety in older individuals and patients with CKD. Recently, HCQ has been implicated in therapeutically treating cardiovascular (CV) disease in patients with CKD.

Methods: We report the findings of the planned interim analysis examining the short-term ophthalmological safety of HCQ among all enrolled Veteran participants (n=100) in the Management of CV disease in CKd (MaCK) study, a phase 2b, randomized placebo-controlled trial aimed to examine the impact of HCQ on CV and renal outcomes. Blinded ophthalmological evaluations were done at baseline and at one-year after randomization by measuring visual acuity and evaluating macular health with autofluorescence(ASF), Humphrey’s visual field (HVF), and optical coherence tomography (OCT), when clinically needed.

Results: Across the 100 Veterans aged 71.2±5.92, 95%/male with eGFR of 48.0±4.72 and albuminuria of 438.0±784.4 mg/gm of creatinine, randomized in 1:1 proportion between placebo-HCQ, worsening of visual acuity was similar across both groups (16 vs. 18, p =0.87). Ophthalmological symptoms prompted repeat macular health evaluation in 22 participants on follow-up with no significant difference between abnormalities detected on AVF (2 in each group), HVF (2 vs. 1 participant), and OCT (2 in each group).

Conclusions: Use of HCQ is safe from short-term ophthalmological perspectives among elderly, predominantly male participants with significant CKD.

Funding: Veterans Affairs Support
Prevalence of Polypharmacy and Associated Adverse Outcomes in Kidney Transplant Recipients
Tai yeon Koo, Sangeyon Kim, Yookyoung Jang, Sang-Kyung Jo. Korea University Anam Hospital, Seoul, Republic of Korea.

Background: Polypharmacy (PP) continues to increase, and is associated with numerous adverse clinical outcomes and mortality. Although the burden of medication in kidney transplants (KTRs) is well-known, PP has not been characterized in detail in the KTRs. The aim of this study was to assess the prevalence of PP among KTRs and the association between PP and clinical outcomes in the KTRs.

Methods: A total of 972 KTRs from a prospective multicenter observational cohort study in Korea (KNOW-KT, KoreaN cohort study for Outcome in patients With Kidney Transplantation) between 2012 and 2016 were included in the study. We investigated the association between the number of prescribed medications and adverse outcomes such as graft failure, all-cause mortality and cardiovascular events. PP was defined as the use of more than 10 medications per day at 1 year after kidney transplantation.

Results: The patients with PP were noted in 478 (49.2%) patients. The PP prevalence at 1, 2, 3, 5, and 8 years after transplantation was 49.2%, 36.5%, 35.7%, 36.3% and 24.6%, respectively. The prevalence of diabetes, dyslipidemia and history of cardiovascular disease was significantly higher in the PP group than in the non-PP group (the use of fewer than 10 medications; n = 494). The mean follow-up period was 6.9 years, and there were 69 graft failures, 63 new-onset cardiovascular diseases, and 36 deaths. When the effect of PP was compared to 1-year post-transplant on clinical outcomes was analyzed, there was no difference in glomerular filtration rate between the non-PP and PP groups, and the hazard ratio of graft failure and death in the PP group was 1.07 (0.718 to 1.59) and 1.37 (0.71 to 2.64), respectively, compared to the non-PP group. However, multivariate analysis adjusted for classical risk factors showed that PP and medication counts independently increased the risk of new cardiovascular disease (adjusted HR 1.76 (1.051-2.950); p=0.032, adjusted HR 1.079 (1.00-1.164, p=0.049), respectively) after KT.

Conclusions: These results showed that PP is common in KTRs, and considering the adverse effects of PP on KT outcomes, physician’s attention and efforts are needed to systemize (by managing and reviewing). Long-term and large-scale research is needed to establish management guidelines for PP in the future.

SA-PO293
The Relationship of Polypharmacy with Increasing CKD Stage
Rie Suzuki, Takahito Moriyama, Yohsithaka Miyaoka, Yoshikihio Kanno. Tokyo Medical University. Tokyo Ika Daigaku, Shinjuku-ku, Japan.

Background: Previously, chronic kidney disease (CKD) and hemodialysis has been reported as the one of the factors of polypharmacy. However, it has been unclear the relationship of increasing CKD stage with the higher number of medications.

Methods: In this retrospective cohort analysis, 408 CKD patients (CKDG1 and 2 (n=23), CKDG3-5 (n=81) and CKDG (n=304) were included. We analyzed the background, the number and details of prescribed medications in January 2017, the number of patients who met STOPP (Screening Tool of Older Person’s Prescriptions) criteria, and the risk factors for polypharmacy (6-9 medications) and hyper-polypharmacy (≥10 medications) were also examined.

Results: The mean number of medications was significantly different among three groups and increased as the higher CKD stage (4.5±2.6 in CKDG1 and 2, 8.0±3.5 in CKDG3-5, and 9.7±3.5 in CKDG, p<0.001). The number of patients of polypharmacy and hyper-polypharmacy was increased as the CKD stage (polypharmacy: 26.1% in CKDG1 and 2, 72.8% in CKDG3-5, and 72.1% in CKDG, p<0.001, hyper-polypharmacy: 32.1% in CKDG1 and 2, 37.8% in CKDG3-5, and 22.6% in CKDG, p<0.001, and 0.001). The ratio of patients with ≥4 weeks was also significantly different among three groups and increased as CKD stage (4.35% in CKDG1 and 2, 14.8% in CKDG3-5, and 27.6% in CKDG, p<0.004), and patients who had benzodiazepines for > 4weeks were also significantly different (8.7% in CKDG1 and 2, 7.41% in CKDG3-5, and 24.7% in CKDG, p<0.001). Multivariate logistic analysis indicated that CKD stage and diabetes were independent risk factors for polypharmacy and hyper polypharmacy (polypharmacy: CKD stage; HR 1.62/ one stage increase, p<0.001, and diabetes; HR 2.23 (vs. without DM), p=0.007, hyper polypharmacy: CKD stage; HR 1.54, p=0.001, and diabetes; HR 1.64, p=0.017).

Conclusions: The number of medications, patients with polypharmacy, and the risk for polypharmacy were increased as higher CKD stage.

SA-PO294
Barriers and Facilitators of Pharmacist-led Programs: Insights from Survey Among Providers
Masasaki Yamada,1,2 Diana I. Jalal,1,2 *University of Iowa Hospitals and Clinics, Iowa City, IA; 1University of Iowa Medical Center, Iowa City, IA.

Background: Hypertension is a leading cause of cardiovascular death in the United States (US). Despite current guidelines emphasizing strict blood pressure control, over half of the US population fails to reach the recommended goal. Clinical pharmacists can play a crucial role in a team-based approach to overcome these challenges. However, our previous survey found that pharmacists are underutilized in certain positive attitudes among providers. To understand the barriers and facilitators of implementing pharmacist-led programs, we conducted a thematic analysis of survey data from providers.

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

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Poster/Saturday
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SA-PO296

Outcomes of Australian and New Zealand Dialysis and Transplant Patients with Kidney Failure Attribution to Kidney Stones

Hicham I. Cheikh Hassan,1,2 David J. Tunnicliffe,3,4 Lyn Lloyd,2 Adela Yip,5 Brydey Cashmore,2 Adam W. Mullan,6 Matthew D. Jose,7,8 Andrew J. Mallett.6,9,10 University of Wollongong Faculty of Science and Medicine, Wollongong, NSW, Australia; Ilawarra Shoalhaven Local Health District, Wollongong, NSW, Australia; The Children’s Hospital at Westmead, Westmead, NSW, Australia; The University of Sydney, Sydney, NSW, Australia; Auckland City Hospital, Auckland, New Zealand; The University of Auckland, Auckland, New Zealand; Te Whatu Ora Health New Zealand Te Tai Tokerau, Whangarei, New Zealand; Royal Hobart Hospital, Hobart, TAS, Australia; University of Tasmania, Hobart, TAS, Australia; Townsville Hospital and Health Service, Townsville, QLD, Australia; James Cook University College of Medicine and Dentistry, Townsville, QLD, Australia.

Background: Prevalence of kidney stones in the general population can reach 15% to 40% in adults and between 6% and 8% in children (p<0.001) vs 5% to 13% (p<0.001) in the intervention vs usual care groups, respectively. There was no between group difference in the change in ACEI/ARB (p=0.46), statin (p=0.12), or SGLT2i and/or GLP1RA (p=0.80) use.

Conclusions: A PHM approach did not improve use of guideline-recommended medication therapy in patients with high-risk CKD compared to usual care. This research supports a need to address barriers in the primary care setting, including therapeutic inertia and access to clear practice guidelines, and efforts to improve the delivery of CKD care.

Funding: NIDDK Support

SA-PO298

Characteristic Alterations of Bone and Mineral Metabolism in Children and Adults. Effects of Nephrocalcinosis (NC) on Bone and Mineral Metabolism: Stones, Calcifications, Case Reports

Elenice Henninges,1,2 Hicham I. Cheikh Hassan,1,2 David J. Tunnicliffe,3,4 Lyn Lloyd,2 Adela Yip,5 Brydey Cashmore,2 Adam W. Mullan,6 Matthew D. Jose,7,8 Andrew J. Mallett.6,9,10 University of Wollongong Faculty of Science and Medicine, Wollongong, NSW, Australia; Ilawarra Shoalhaven Local Health District, Wollongong, NSW, Australia; The Children’s Hospital at Westmead, Westmead, NSW, Australia; The University of Sydney, Sydney, NSW, Australia; Auckland City Hospital, Auckland, New Zealand; The University of Auckland, Auckland, New Zealand; Te Whatu Ora Health New Zealand Te Tai Tokerau, Whangarei, New Zealand; Royal Hobart Hospital, Hobart, TAS, Australia; University of Tasmania, Hobart, TAS, Australia; Townsville Hospital and Health Service, Townsville, QLD, Australia; James Cook University College of Medicine and Dentistry, Townsville, QLD, Australia.

Background: Prevalence of kidney stones in the general population can reach 15% to 40% in adults and between 6% and 8% in children (p<0.001) vs 5% to 13% (p<0.001) in the intervention vs usual care groups, respectively. There was no between group difference in the change in ACEI/ARB (p=0.46), statin (p=0.12), or SGLT2i and/or GLP1RA (p=0.80) use.

Conclusions: A PHM approach did not improve use of guideline-recommended medication therapy in patients with high-risk CKD compared to usual care. This research supports a need to address barriers in the primary care setting, including therapeutic inertia and access to clear practice guidelines, and efforts to improve the delivery of CKD care.

Funding: NIDDK Support

SA-PO299

Low Expression of Renal Claudin-2 Increases Medullary Pro-Inflammatory Macrophages and Calcification in Nephrectomy Patients with a History of Urinary Stone Disease

Muthuvel Jayachandran, Miles Delbousse, Loren P. Herrera Hernandez, Zajfa Haskic, Andrew D. Rule, Kevin Koo, John C. Lieske. Mayo Clinic College of Medicine and Science, Rochester, MN.

Background: The transmembrane protein claudin-2 (Cldn2) is highly expressed in the proximal tubule and descending thin limb which is key for ~70% of filtered Ca2+ reabsorption. Men with a rare missense mutation in Cldn2 manifest hypercalciuria and urinary stone disease (USD). However, the relationship of Cldn2 expression to renal calcification and interstitial cellular responses is not known. Thus, we examined Cldn2 (dRTA) and monogenic hypercalciuria were statistically more frequent in the pediatric group (40 vs 13 and 24 vs 11%, p< 0.001, respectively) and primary hyperparathyroidism (HPT) and use of drugs were seen only in adults (14 and 7%). Undetermined or still under investigation cases were more common among adults. Cases of familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC), medullary sponge kidney (MSK), Limb-Girdle Muscular Dystrophy, Hypoparathyroidism (HypoPT) did not differ.

Conclusions: Adults with nephrocalcinosis exhibited reduced renal function at presentation possibly due to delay on diagnosis, worse clinical outcome or previous urological procedures. Molecular analysis could help to further elucidate clinical causes of NC in this group.

Funding: Commercial Support - Chiest
SA-PO300

Controls but Not Patients with Calcium Nephrolithiasis Secrete Less Urinary Uromodulin After Salt Loading

Salar Bani Hani,1 Matthias T. Wolf,1 Khashayar Sakhaee.1,2 The University of Texas Southwestern Medical Center, Dallas, TX; 2NewYork-Presbyterian Brooklyn Methodist Hospital, Brooklyn, NY.

Background: Calcium is the most common constituent of kidney stones. Uromodulin (UMOD) enhances TRPV5 membrane abundance increasing renal Ca\textsuperscript{2+} absorption thus reducing hypercalciuria. UMOD stimulates Na\textsuperscript{+} absorption via NKCC2 causing hypertension. High salt intake is also risk factor for nephrolithiasis. We hypothesize that a higher urinary UMOD secretion with a high salt diet compensates for the higher stone risk by improving hypercalciuria.

Methods: This is a prospective, randomized, cross-over study. Stone-formers and controls were randomized to a control or a high salt diet for 2 days. After washout, the participants received the diet they were not exposed to previously. After each diet, we obtained 24-hour urine and fasting serum studies.

Results: At baseline, there was no significant difference for urinary UMOD secretion between stone-formers and controls. In contrast to our hypothesis, we found that urinary UMOD secretion was significantly reduced after the salt load in controls but not in stone-formers.

Conclusions: There was no lower baseline urine UMOD level in stone-formers. After salt loading, we show lower urinary UMOD secretion in controls but not in stone-formers. As UMOD enhances NKCC2 contributing to hypertension, acute downregulation of UMOD after a salt loading makes physiologically sense.

SA-PO301

CYP24A1 Activity Associates with Phenotypic Traits in Idiopathic Hypercalciuria

Daniel G. Fuster,1 Matteo Bargagli,1 Olivier Bonny.1,2 Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; 2Service of Nephrology, Lausanne University Hospital, Lausanne, Switzerland; 3Service of Nephrology, Department of Medicine, Fribourg State Hospital, and University of Fribourg, Fribourg, Switzerland.

Background: Hypercalciuria is the most frequent abnormality in kidney stone formers. The underlying mechanisms remain unknown in most cases, hence the designation "idiopathic hypercalciuria". We hypothesized that the Vitamin D-inactivating enzyme CYP24A1 contributes to the pathogenesis of hypercalciuria in kidney stone formers.

Methods: We conducted association analyses between CYP24A1 activity, estimated by the Vitamin D metabolite diagnostic ratio (25(OH)D/24,25(OH)\textsubscript{2}D), Vitamin D, ratio; VMDR), and the phenotype of participants in two observational cohorts of kidney stone formers, the Swiss Kidney Stone Cohort and the Bern Kidney Stone Registry. Linear and logistic regression models adjusted for multiple confounders, including plasma 25(OH)D\textsubscript{3}, were applied. Plasma 25(OH)D and 24,25(OH)D\textsubscript{2} were measured using an established, highly sensitive and specific LC-MS/MS assay.

Results: In total, 974 participants were included in the analysis. After multivariable adjustment, a higher VMDR (i.e. lower CYP24A1 activity) was associated with higher
Bone and Mineral Metabolism: Stones, Calcifications, Case Reports

Poster/Saturday

SA-PO302

Distinguishing Uric Acid Stone Formers from Type 2 Diabetics with Low Urine pH: The Role of Impaired Buffering

Seyed Ali Reza Zomorodi,1 John Poin Dexter, Khashayar Sakhaee, Naim M. Maalouf, Orson W. Moe. The University of Texas Southwest Medical Center, Dallas, TX.

Background: The prevalence of uric acid (UA) nephrolithiasis has increased in the past decades, particularly among patients with metabolic syndrome, and this lithogenicity is driven by acidic urine pH. Previous studies in these patients on random diets showed that this lower urine pH results from higher acid excretion and insufficient urinary buffering by ammonia. However, intrinsic vs. extrinsic contributors are hard to discern because diet was not controlled. In addition, patients with type 2 diabetes mellitus (T2DM) often exhibit an acidic urine, but only a minority develop UA stones. Here, we provide a comprehensive report of acid-base and stone risk parameters in UA stone formers (USAF) and non-stone forming controls with and without T2DM, who were equilibrated and studied under a fixed metabolic diet.

Methods: A total of 74 USAF, 13 T2DM patients without a history of kidney stones, and 51 normal subjects without stones or diabetes (Ctrl) were studied. All participants were equilibrated on metabolic diet for at least 5 days. Blood and urine samples were collected for analysis of acid-base and stone risk parameters. Statistical analyses were performed to compare the stone risk profiles among the three groups.

Results: Participants were comparable with respect to demographic characteristics, with age range of 48-60 years (aligning with peak incidence of UA stone). USAF had slightly higher BMI and Ctrl exhibited a lower body mass index. Under a fixed diet, USAF and T2DM exhibited lowered urinary pH, higher net acid excretion (NAE), and lower levels of citrate and bicarbonate compared to Ctrl. The proportion of NAE excreted as ammonium (ammonium/NAE) was significantly lower in USAF (0.50 [95% confidence intervals: 0.46-0.54]) compared to T2DM (0.64 [0.53-0.76]) and Ctrl (0.74 [0.68-0.81]).

Conclusions: This study contains the largest number of subjects evaluated on a controlled metabolic diet to date. We found a similarly high NAE in USAF and T2DM and non-stone formers; the parameter that sets aside USAF was the significantly lower ammonium/NAE and pH compared to T2DM and Ctrl. The latter demarcates the low urine pH driven by acidic urine pH. Previous studies in these patients on random diets showed that this lower urine pH results from higher acid excretion and insufficient urinary buffering by ammonia. However, intrinsic vs. extrinsic contributors are hard to discern because diet was not controlled. In addition, patients with type 2 diabetes mellitus (T2DM) often exhibit an acidic urine, but only a minority develop UA stones. Here, we provide a comprehensive report of acid-base and stone risk parameters in UA stone formers (USAF) and non-stone forming controls with and without T2DM, who were equilibrated and studied under a fixed metabolic diet.

SA-PO303

Adherence to Potassium Citrate and Changes in 24-Hour Urine Stone Risk Parameters

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Background: Patient adherence to potassium citrate therapy for urinary stone disease (USD) is low. We assessed associations of potassium citrate adherence with changes in 24-hour urine parameters.

Methods: We identified adults enrolled in Medicare with USD, a baseline 24-hour urine collection (Litholink, 2011-2017), hypocitraturia or low urine pH, a prescription for monotherapy with potassium citrate tablets within 3 months, and a follow-up urine collection 6-12 months after baseline. We defined two measures of adherence: (1) percentage of days covered (PDC) over 0-3 months based on pharmacy claims and (2) change in urinary potassium (ΔK) between baseline and follow-up. We assessed the association between PDC and ΔK using an independent t-test and the association of adherence with changes in urinary citrate and pH using ANCOVA. Finally, we compared the strength of association of PDC and ΔK with these changes using a Wald test.

Results: Among 432 patients, 366 (85%) had hypocitraturia and 266 (62%) had low urine pH. Patients adherent to medication based on pharmacy claims (PDC>80%) had a significantly higher mean ΔK compared to those not adherent to medication (+29.6 ± 217 mg/day vs. +17.9 ± 100 mg/day, P<0.001). The adjusted mean increase in urinary citrate and pH among patients adherent to medication significantly exceeded that of patients not adherent to medication (Figure). Compared to PDC, ΔK had a stronger association with change in urinary citrate (P<0.001) and pH (P<0.007), though the latter was not statistically significant.

Conclusions: Adherence to pharmacy claims, the increase in urinary potassium was generally more predictive of increased urinary citrate and pH, emphasizing the value of urinary potassium as a measure of adherence.

Funding: NIDDK Support

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

SA-PO304

Differential Effects of Thiazide, Alkali, or Both on Urine Determinants of Stone Risk in Calcium Oxalate (CaOx) and Calcium Phosphate (CaP) Stone Formers

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Background: Thiazide type diuretics, potassium citrate (K-Cit), and lifestyle changes are used to prevent calcium kidney stones. Thiazides decrease stone risk by decreasing urinary calcium (Ca). Citrate (Cit) is an inhibitor that decreases urine supersaturations (SS), however, it also increases urine pH and therefore Ca phosphate (CaP) SS. Thus, the effect of K-Cit on stone risk is complex.

Methods: To study the effects of common treatments for Ca stone risk we analyzed the 24-hour urinalysis of Calcium Oxalate (CaOx) and CaP stone formers (SF) by 4 different treatment types: lifestyle, K-Cit, thiazide, or both medications.

Results: Thiazides reduced urine Ca in both CaOx SF (-7.4±9.5 mg/day) and CaP SF (-102±100 mg/day). K-Cit alone and when combined with thiazide had no effect on urine Ca. K-Cit increased urine Cit in CaOx SF (252±306 mg/day), but not in CaP SF (26±53 mg/day). Thiazide decreased combined increased Cit in CaOx SF (118±264 mg/day), but not CaP SF (94±217 mg/day). Urine pH rose in all groups except CaOx SF on only lifestyle treatment. Among CaOx SF, pH increased in patients receiving K-Cit (0.6±0.6) and both (0.7±0.6) compared to patients receiving thiazide (0.1±0.5). There is a similar pattern among CaP SF receiving K-Cit (0.3±0.5), both (0.5±0.5), or thiazide (0.1±0.3). Thiazide decreased CaOx SS in both CaOx SF (-3.3±3.5) and CaP SF (-3.1±2.9). K-Cit did not lower CaOx SS in either CaOx or CaP SF. Thiazide decreased CaP SS in both CaOx SF (-0.5±0.9) and CaP SF (-0.8±0.9).

Conclusions: K-Cit had no significant effect on urine Ca and increased urine citrate levels in CaOx SF; however, increased urine pH lead to increased CaP SS for CaOx SF. The study raises questions about the best preventive treatment for patients with CaP stones and suggests that K-Cit may not confer the same benefits on CaP SF as it does on CaOx SF.

Funding: NIDDK Support

Figure 1. Boxplots of the change in urine CaOx and CaP SS by treatment group and stone type. Each includes t-tests comparing treatment groups.
SA-PO305
Effect of Hydrochlorothiazide on Bone Mineral Density in Patients with Kidney Stones: A Post Hoc Analysis of the NOSTONE Trial
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Background: Low bone mass and fractures are highly prevalent in patients with kidney stones. Thiazide diuretics lower urine calcium and hence may preserve bone mass. No placebo-controlled randomized trial (RCT) has been conducted to examine the impact of thiazide diuretics on bone mineral density (BMD) in patients with kidney stones.

Methods: We conducted a post-hoc analysis of the NOSTONE trial to assess a range of hydrochlorothiazide (HCT) doses or placebo on bone mineral density in patients with recurrent calcium-containing kidney stones. Computed tomography (CT) attenuation was measured at T12-L3 vertebrae in Hounsfield units (HU) at baseline and the end of the study, using a previously validated approach, with lower values corresponding to lower BMD. BMD measurements were performed by two independent readers blinded to the study intervention. Random-effects linear regression models were used to investigate treatment effects on changes from baseline.

Results: BMD measurements were available in 388 of 416 (93%) randomized patients. Median follow-up time was 2.92 years. At baseline, mean BMD was directly associated with eGFR (β: 0.934 HU, 95% confidence interval [CI] 0.680; 1.189, p < 0.001) and inversely with age (β: -2.208 HU, 95% CI -2.510; -1.907, p < 0.001). Mean BMD decreased by 6.4±15.7 HU in the placebo group, by 5.1±5.1 in the 12.5mg HCT group (β coefficient vs placebo, 0.368 HU, 95% CI 0.385; 2.472, p = 0.732), by 4.1±6.3 in the 25mg HCT group (β: 0.926 HU, 95% CI -1.335; 3.187, p = 0.422), and by 4.8±5.9 in the 50mg HCT group (β: 0.699 HU, 95% CI -1.145; 2.848, p = 0.524). No association was observed between HCT dose and change in BMD (p = 0.430). The results were confirmed in sensitivity analyses for eGFR, urinary calcium, body mass index, and in per-protocol analyses.

Conclusions: In patients with recurrent calcium-containing kidney stones, loss of bone mineral density was similar in patients receiving hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily.

SA-PO306
Vascular Calcification in Kidney Stone Formers: The Impact of Age and Stone Composition
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Background: Nephrolithiasis is a common condition, associated with increased cardiovascular morbidity. Previous observational studies have showed that kidney stone formers (KSF) have increased vascular calcifications (VC) and osteoporosis. However, data regarding the effect of age and stone component on VC in these patients is limited.

Methods: This is a retrospective, single center, matched case-control study. KSF with a pure stone analysis (uric acid stone or calcium oxalate) who were treated in the urology clinic of Shaare Zeedek Medical Center from 2015 to 2021 were identified. Fully matched controls without history of nephrolithiasis were drawn from patients hospitalized or admitted to the emergency room of the same hospital. Abdominal aortic calcification (AAC) and vertebral bone mineral density (BMD) were assessed using available computed tomography (CT) imaging. KSF and non-KSF were compared for prevalence and severity of AAC and BMD.

Results: A total of 335 patients were investigated, 134 with calcium oxalate stone, 67 with uric acid stone, and 134 fully matched controls. Overall, the severity of VC, measured by the AAC score, did not differ significantly between the groups. However, in patients aged <60 years, both prevalence and severity of aortic calcification were significantly higher in calcium oxalate and uric acid stone groups compared to control (55.1%, 37.8% and 21.8%, p = 0.001, for the prevalence of aortic calcification and 95±4.1±8.5; 8.8±16.6 and 16.3±8.6, p = 0.001, for ACC score, respectively). The prevalence of osteoporosis was similar between the groups.

Conclusions: In this study, the prevalence and severity of VC was higher in younger KSF. These findings may suggest premature vascular calcification among patients with nephrolithiasis, both in calcium oxalate and uric acid stone formers.

SA-PO307
SYNBB8802 Lowers Urinary Oxalate During a Diet-Controlled Study in Patients with Roux-en-Y Gastric Bypass
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Background: Patients with Roux-en-Y (RnY) gastric bypass surgery are at risk for development of intestinal malabsorption which can increase the absorption of dietary oxalate, resulting in enteric hyperoxaluria (EH). Hyperoxaluria may lead to kidney stone formation, kidney damage, and deposition of oxalate in other tissues and organs. SYNBB8802 is an engineered probiotic bacteria designed to consume oxalate in the GI tract and reduce urinary oxalate (UOx) absorption.

Methods: Study SYNBB802-CP-002 was a Phase 1b, randomized, placebo-controlled, single-center, open-label study in subjects with a history of RnY gastric bypass surgery. Subjects were placed on a 12-day diet-controlled study containing 300 mg of oxalate and 400 mg of calcium. A diet and placebo run-in period of 3 days was followed by oral administration of increasing dose levels of SYNBB8802 up to 3x10^7 lives cells or placebo for 12 days. 24-hour urine was collected daily from days -3 to 12 and analyzed for urine oxalate content as well as other analytes.

Results: SYNBB8802-CP-002 enrolled 11 subjects (median [SD] age 56 (8.6), 1.1M/0.9F) with a history of RnY gastric bypass, and no prior kidney stones. Seven subjects received SYNBB802 and 4 patients received placebo. Two placebo subjects were excluded from the efficacy analysis because of major protocol violations (antibiotic use and incomplete dosing). The oxalate diet resulted in a baseline mean (SD) UOx of 29.4 (2.3) mg/24h for the placebo and 32.5 (9.0) mg/24h for the SYNBB8802. SYNBB8802 lowered UOx by -41.0% (p<0.01) compared to -8.8% (p=0.73) for placebo but the change over placebo (-35.3%) did not achieve statistical significance (p=0.16). A post-hoc pharmacometrics model incorporating the effects of dose and frequency showed a significant UOx lowering of -37.3% [95% CI: 45.9, 28.3] relative to placebo (p<0.05). The most common adverse events were mild to moderate and GI related. There were no SAEs.

Conclusions: SYNBB8802 was well tolerated in patients with RnY gastric bypass and demonstrated the capacity to lower UOx. SYNBB8802 should be further evaluated in subjects afflicted with kidney stone disease and EH.

Funding: Commercial Support - Sylogic Therapeutics, Inc.
activities of daily life in our sample. Anxiety regarding recurrent stone events and future kidney failure was high among all 3 PH types. PH3 pts had recurrent or bilateral stones 9% had stone compositions that were high risk for recurrence 3% had co-morbidities that increase risk of recurrence as detailed above 9% under the age of 30 yrs. Patient demographics Treatment choice First stone vs recurrent Testing of basic biochemistry Presence of Risk factors Use of CT or ultrasound imaging to discern Long-term follow-up and noted resistance to treatment a diagnosis for spuriously pseudo hyperphosphatemia was made. This was attributed to analytic interference of elevated paraprotein level. Discussion: True Hyperparathyroidism with normal renal function is a rare reported condition. Clinicians should have a high suspicion for pseudo hyperparathyroidism/ spuriously hyperphosphatemia due to analytical limitations to avoid expensive diagnostic work up, treatment and prolonged hospital stay. SA-PO312 The Dangers of Vitamin D Powder Supplements, Found Over-the-Counter, Causing Vitamin D Toxicity Hiraa Tahir, Hubert Wang, Fatima Sheikh. Stony Brook University Hospital, Stony Brook, NY. Introduction: Vitamin D toxicity is a rare but serious condition, potentially leading to death if not treated in a timely manner. This case highlights risks of misusing vitamin D supplements marketed directly to consumers. Case Description: A 54-year-old female with no medical history presented with 4 days of headache, fatigue, nausea, vomiting, polyuria, polydipsia and constipation. She took no medications but had self-started vitamin D powder taking “a tablespoon daily in coffee for health and strong bones.” She learned vitamin D could decrease risk of COVID-19 infection as alternative to vaccination. Further investigation revealed this over-the-counter vitamin D powder was sold in 8 ounce bags with a 50 mg serving size equal to 5000 international units (IU) of Vitamin D3. Each bag contained 4,520 servings equaling 21,250,000 IU. “One tablespoon” of powder every morning equated to 1,328,125 IU, exceeding maximum recommended dose. Admission labs showed high Cr 1.76 mg/dL, calcium 14.4 mg/dL and ionized calcium 6.9 mg/dL but normal phosphorus 3.2 mg/dL, albumin 4.6 g/dL, PTH 26.3 pg/mL and TSH 1.21 uIU/mL. Renal US and CT imaging were unremarkable. EKG noted Osborn waves in leads II, III, aV1, V5, and V6, and QTc 412. 25-hydroxy vitamin D level was high at 650 ng/mL, 24-hour urine calcium was high at 410 mg/24 hr, 1,25-dihydroxy vitamin D was high at >600 pg/mL. PTHrP, SPEP and UPEP with immunofixation were negative. Vitamin D toxicity was diagnosed with counseling for powder vitamin D supplement cessation. With IV hydration, calcitomin and bowel regimen, symptoms and calcium levels improved and patient was discharged with follow up. Discussion: Vitamin D toxicity reported in literature recommends discontinuation of exogenous vitamin D. Previous case studies suggest glucocorticoids or bisphosphonates but clear guidelines for therapy are not identified. The most common cause of toxicity is excess exogenous intake greater than 10,000 IU/day causing 25-hydroxy vitamin D concentration >150ng/mL [1]. During COVID-19 pandemic, there was emphasis on supplementation including vitamin D thought to protect against respiratory viral infections [5]. Our case elucidates risks of misusing over-the-counter supplements in a generation of changing trends in nutrition. Further studies should be performed to find treatments given risks of unintentional overdose. | Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only | Underline represents presenting author. | 809 |
SA-P0313

I Am in a Crystal Bind! A Case that Gave Us Ulcers

Introduction: In patients with ESKD, hyperphosphatemia has been shown to increase mortality. Common complications include vascular and heart calcification, as well as perihypertrophic kidney. Managing hyperphosphatemia includes dietary modifications as well as phosphate binders. Sevelamer, a non-calcium phosphate binder, is commonly prescribed and usually well tolerated. Side effects of sevelamer are generally non-specific and limited to nausea and gastrointestinal discomfort.

Case Description: A 37-year-old man with ESKD on intermittent hemodialysis, hypertension, congestive heart failure, and recent mitral and aortic valve repair presented with hematocritia and fatigue. His hemoglobin level was 5.9mg/dl upon admission. He was transfused and underwent an urgent colonoscopy, which revealed ulcerative mucosal injuries in the colon. Biopsy showed mucosal ulcers with sevelamer crystals. The patient was taken off sevelamer, stabilized, and switched to sucralfate/lanthamum for hyperphosphatemia and is stable at follow-up.

Discussion: Hyperphosphatemia is a common complication of end-stage kidney disease (ESKD) due to decreased renal elimination and continued intestinal absorption of dietary phosphate. Sevelamer, a non-calcium phosphate binder, is commonly used to control hyperphosphatemia. We present a case of a patient with ESKD on sevelamer, with lower gastrointestinal bleeding and endoscopic finding of colonic mucosal injuries with sevelamer crystals. Though reported in laboratory literature, nephrology reports show a paucity of discussion around this increasingly common adverse effect and the need for vigilance in ESKD.

SA-P0314

Three Patients with Recurrent Nephrothiasis and Heterozygous ABCC6 Mutations
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Introduction: Pseudoxanthoma elasticum (PXE) is an autosomal recessive disease caused by mutations in the ABCC6 gene, which encodes an ATP efflux transporter. Loss-of-function results in low extracellular PPi levels, which results in progressive ectopic deposition of CaP leading to skin papules, ocular lesions, and arterial calcification. The association between PXE and nephrolithiasis (stones) is known, though this has not been implicative in those who are heterozygous. We present three cases of recurrent stones and fat necrosis consistent with calciphylaxis. Over the course of his hospitalization, the patient improved with antibiotics and fluids, and his AKI resolved. Blood cultures remained negative throughout his hospital stay, and antibiotics were adjusted accordingly by discharge. He was given clinic follow-ups with dermatology and rheumatology.

Discussion: To our knowledge, this is the first case of calciphylaxis reported in a patient with polymyositis and no underlying CKD. Clear treatment guidelines for polymyositis on prolonged prednisone course, bronchiolitis obliterans organizing pneumonia, atrial fibrillation, hypertension, diabetes, and systolic heart failure. Physiological examination revealed sinus tachycardia, coarse breath sounds with bilateral crackles. On his left leg, there were two tender-to-touch ulcers (~2x2 cm, clean-based, with dry yellow fibrinous exudate and surrounding hyperpigmentation). Laboratory data revealed a white blood cell count of 19.6 (81% neutrophils), blood urea nitrogen 52 mg/dl, creatinine 1.8 mg/dl, parathyroid hormone was 39 pg/ml, 1.25-(OH)2 vitamin D was 11 pg/ml (normal range 20-60 pg/ml), and urinary glucose was negative. The phosphate excretion rate was 44% and serum phosphate was 91 mg/dl (normal range <30 pg/ml). The whole-body bone scintigraphy revealed bone destruction in the tenth thoracic vertebra. Contrast-enhanced CT showed multiple enlarged lymph nodes. He was diagnosed as ABCC6-related hypophosphatemia due to WM. Sodium phosphate monobasic and tirabrutinib was initiated. Three months after treatment, serum IgM decreased to 423 mg/dl, and serum phosphate increased to 3.7 mg/dl.

Discussion: From the previous report, there are only three types of hematological malignancy that cause FGF23-related hypophosphatemia: diffuse large B-cell lymphoma, natural killer T-cell lymphoma and acute leukemia. We should also consider WM induce FGF23-related hypophosphatemia.

SA-P0315

Calciphylaxis in a Patient with Polymyositis and Absence of Renal Disease
Dorce Morisson, Sarah J. Lewis, Stella Radosta, Erin E. Boh, Flor Alvarado. Tulane University School of Medicine, New Orleans, LA.

Introduction: Calciphylaxis is a rare and life-threatening disease in which calcium accumulates in small arteries and can cause tissue necrosis, thrombosis, and painful, non-healing skin ulcers. It is most often seen in patients with advanced chronic kidney disease (CKD) but may occur when risk factors such as autoimmune or inflammatory conditions are present. We describe a case of calciphylaxis in a patient with polymyositis and acute kidney injury (AKI) without CKD.

Case Description: A 61-year-old man with polymyositis presented to the hospital with worsening dyspnea, and painful, lower leg wounds. He first noticed the leg wounds following a muscle biopsy for his polymyositis about 6 months prior to presentation; he reported the wounds increased in size since the biopsy. Medical history was significant for polymyositis on prolonged prednisone course, bronchiolitis obliterans organizing pneumonia, atrial fibrillation, hypertension, diabetes, and systolic heart failure.

Discussion: To our knowledge, this is the first case of calciphylaxis reported in a patient with polymyositis and no underlying CKD. Clear treatment guidelines.
for calciphylaxis are lacking and many physicians are not familiar with nonuremic presentation of calciphylaxis. We present this case to further advance awareness and knowledge of calciphylaxis occurring in the absence of advanced CKD.

SA-PO317
Bone Disease Related to Severe Vitamin D Deficiency, in an Adult
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Introduction: Severe vitamin D deficiency (VDD) as a cause of bone disease is seen very rarely. While VDD can cause osteomalacia, associated secondary hyperparathyroidism (HPT) can also produce significant histopathological changes in the bone.

Case Description: A 60-year-old post-menopausal Caucasian woman, was admitted with a left subtrochanteric femur fracture in 2021, following a ground-level fall and underwent ORIF. She has had prior vertebral fractures, stage 3A CKD, and 30 pack-year smoking history. Laboratory data revealed vitamin D (VD) <6.5 ng/mL, iPTH 492 pg/mL, calcium 7.9 mg/dL, ALP 602 U/L and BSAP >120 u/L. Albumin, phosphorus, creatinine, and eGFR were 42 mg/dL, 2.9 mg/dL, 1.0 mg/dL, and 50ml/min, respectively. Imaging indicated diffuse sclerosis of the spine. Whole-body bone scintigraphy showed diffuse increased uptake throughout the skeleton in a “super scan” pattern. Forearm bone density showed a T-score of -2.6. Undecalciﬁed bone biopsy of the iliac crest with double tetracycline labeling revealed a mixed pattern with high turnover, low mineralization and increased bone volume with areas of woven bone, with diffuse single labels on fluorescent microscopy (image). Malabsorption workup was inconclusive. Aggressive vitamin D replacement over a year, resulted in progressive normalization of VD, iPTH and BSAP levels and improvement in radiological sclerosis.

Discussion: This patient presented with severe VDD in the setting of multiple fractures, with severe secondary HPT, bony sclerosis and renal osteodystrophy. The severity of HPT was out of proportion to her CKD and caused by VDD. Aggressive treatment with vitamin D resulted in marked reversal of bone abnormalities. With a fourth of the US population estimated to have VDD (<20ng/mL), it is important to consider VDD as a treatable secondary cause of and contributor to bone disease and fracture.

Fig 1

(SA-PO318

The Pursuit of the Perfect Body: Need for Myocardial Revascularization and Dialysis After Polymethylmethacrylate Injection
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Introduction: Polymethylmethacrylate (PMMA) is a synthetic polymer, initially used to correct HIV-associated lipodystrophy. However, gluteal augmentation for aesthetic purposes are procedures that are increasingly performed all over the world, mainly in Latin America. PMMA can promote foreign body granulomas around its microspheres, leading to increased calcitriol synthesis and, consequently, hypercalcaemia.

Case Description: A 58-year-old female patient with a history of arterial hypertension, type 2 diabetes mellitus and sleeve gastrectomy 20x) undergoing agressive treatment with parathyroid-independent hypercalcaemia and hyperphosphatemia. In the following 4 months, the patient progressed to end-stage chronic kidney disease and required renal replacement therapy. Renal biopsy showed 60% of tubular atrophy and interstitial fibrosis, with intratubular calcific casts. Positron emission tomography showed irregular densifications in the gluteal muscular plane (fig 1). Despite the previous described findings, no specific treatment was prescribed, as the proper diagnosis of hypercalcaemia etiology was not done.

Discussion: PMMA injection promotes granulomatous reaction, with overexpression of 1α-hydroxylase. This leads to extrarenal production of calcitriol by macrophages, and subsequent hypercalcaemia, associated with vascular calcification and nephrocalcinosis. This environment favors the onset of acute kidney injury and the progression of vascular damage. If not identified and treated quickly, it may predispose to ischemic events and progression to chronic kidney disease. As some patients have an unfavorable evolution even after treatment, the use of PMMA in large quantities should be prohibited.

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

SA-PO319

When Woman Turns to Stone: Extraosseous Calcification in a Dialysis Patient
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Introduction: Extraosseous calcification (EC) involves vascular and soft tissue calcification, and is a serious complication of chronic kidney disease (CKD), associated with mortality. EC is an active process arising from the complex interaction between electrolyte levels, cell differentiation, and dysregulation of many biochemical pathways. We report the case of a patient with diffuse EC.

Case Description: A female, aged 43, CKD of unknown etiology, on hemodialysis for four years. One year ago, the patient felt pain in the lower limbs, muscle weakness and hard edema in the legs. Seven months ago, she stopped walking, with disabling muscle weakness. On examination, edema in the lower limbs, palpable diffusely hardened nodules, and increased volume and pain in the right clavicle. No calciphylaxis.

Admission exams (March 2023): intact parathyroid hormone (iPTH pg/dL) 4296, total alkaline phosphatase 706 U/L, calcium (mg/dL) 13, and phosphorus (mg/dL) 5.4. She was on paricalcitol 15 mg/kg and sevelamer 7.2 g/day. She has never tolerated cinacalcet. Previous exams confirmed a 2-year progressive increase in iPTH from 658 to 4296, monthly calcium average of 14 and phosphorus of 5.9. Paricalcitol was withdrawn. Radiology: extensive calcifications in the subcutaneous tissue of the legs and thighs, bilateral fracture of the femoral neck, brown tumor in the right clavicle, calcifications in the abdominal aorta and iliac arteries and calcifications in the mitral and aortic valves. Ophthalmology: calcifications in lower conjunctiva. Bone densitometry T score: lumbar spine -5.2 and femoral neck -4.2. Scintigraphy: capture in inferior parathyroids. The patient is awaiting parathyroidectomy.

Discussion: This is an unusual case of severe EC in a young, non-diabetic patient on dialysis for a short time. We confirmed the role of bone turnover disorders in the pathogenesis of EC, where the rapid progressional secondary hyperparathyroidism was a determinant of the patient’s clinical manifestations. We emphasize the interrelation of bone and vessel, demonstrated by the severe loss of bone mass and the intensity of the EC. Nephrologists must understand the consequences of the mineral and bone disorder of CKD, so that interventions are early, in order to avoid very serious cases such as the one reported herein.

SA-PO320

The Developing Kidney Actively Negotiates Geographic Packing Conflicts to Avoid Defects

Background: Ureteric bud (UB) tubules branch at the kidney’s surface, where their tips encounter sites of nephron induction through interactions with the surrounding cap mesenchyme. The extent of UB branching determines nephron endowment at birth (up to ~1 million in humans) and low nephron count poses a risk of hypertension and adult disease. Here, we examine physical and geometric factors involved in UB tip packing into a limited organ surface area and how UB morphology changes across developmental stages to accommodate branching.

Methods: We use confocal immunofluorescence of embryonic day (E)14-18 mouse kidneys and tissues to investigate the organization of UB and cap mesenchyme. Live imaging of E14-15 embryos revealed packing conflicts in the developing kidney, and tubule retraction was measured by confocal microscopy. We used a computational model to predict branching tubule structures and defects that occur as a function of packing density, repulsion between tips, and node depth. Models were compared to our acquired data and previously published imaging studies of genetic mouse models.

Results: Surface packing density of UB tips increases between E14-18, accompanied by morphological changes in the size and shape of cap mesenchyme clusters and interacting aerenchymal tissue boundaries. Branching tip morphologies change across this interval as well, with branching points progressively moving into deeper tissue layers. Physics-based computational modeling predicts these anatomical changes using geometric parameters. Consistent with model predictions, experimental measurements of tubule retraction following dispase treatment show that actomyosin-based forces are necessary for progressive restructuring of tubules. Our model also predicts conditions where ‘packing defects’ form, including colliding, or overlapping tubules (‘short circuits’) or tips being forced into deeper tissue layers (‘buried tips’). We successfully reproduce these predicted tips defect in mesodiscyted tubule kidneys and investigate published literature examples of mouse mutations that exhibit packing defects.

Conclusions: Our work indicates that the UB must actively restructure during development to avoid organizational defects. We suggest new classification criteria for branching morphogenesis-related congenital defects.

Funding: NIDDK Support, Other NIH Support - NIGMS, Other U.S. Government Support
SA-PO321

Probing Mechanical Regulation of Kidney Morphogenesis Through a Novel 3D Explant Culture Technique
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Background: Achieving proper tissue organization during kidney development plays a vital role in its subsequent functions. For example, congenital anomalies of the kidney and urinary tract can manifest as underdeveloped or disorganized tissue compartments that cause dysfunction or disease. While underlying genetic and molecular factors have been studied, there is little understanding of their interplay with tissue-level cell composition, geometry, and mechanics that together set the final organ structure. Here we address the limited capability to observe developing kidney tissues in a 3D context and seek to uncover the physical principles that set kidney architecture during embryonic development.

Methods: We incorporated a hydrogel droplet into a silicone ring device to encapsulate mouse embryonic day 13 (E13) kidneys for subsequent 3D culture. We tested different organotypic hydrogels (Matrigel, Collagen I) as embedding materials, and characterized their mechanical properties using microindentation. E13 kidneys grown in 3D gels and at in traditional air-liquid interface cultures were imaged every hour and fixed after 4 days.

Results: Our data showed that kidney morphogenesis proceeded in ECM-derived gel droplets, not just in air-liquid interface cultures. Both methods yielded similar numbers of ureteric bud branches and nephrons, as confirmed by immunofluorescence. Notably, our live branch tracking analysis revealed dynamic growth and rearrangement of ureteric tubules in unfallen kidneys for the first time. The mechanical properties of the embedding gel also impacted overall explant morphology. Low concentration Collagen I (0.3-1mg/ml, E<2kPa) best mimicked in vivo development. Matrigel (E>1kPa) failed to maintain the 3D integrity of the explant, resulting in partially flattened tissue. High concentration Collagen I (3mg/ml, E>4kPa) impeded development and led to enlarged ureters in some samples, resembling certain congenital defects.

Conclusions: We present a 3D culture technique that not only supports ex vivo morphogenesis but also enables live imaging of mouse embryonic kidneys. Our data suggest organ ex vivo development is influenced by its mechanical environment. This work aims to transform long-term explant culture techniques and clarify the role of the mechanical environment in kidney development.

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Intracellular Acetyl-CoA Levels Are Pivotal for Nephron Progenitor Cell Fate Decisions
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Background: Low nephron endowment at birth correlates with the development of hypertension in later life. Nephron endowment at birth is governed by a delicate balance between nephron progenitor cells (NPC) self-renewal and differentiation. Previous studies showed that inhibition of glycolysis pushes NPC to differentiation and causes progenitor pool depletion.

Methods: Organ culture experiments: E12.5 embryonic kidneys cultured for 24h-48h in the presence of a vehicle or several pharmacological agents: the glycolysis inhibitor drug, 2-NPy, the mitochondrial pyruvate carrier blocker, UK5099; sodium acetate or canonical Wnt signaling activator (CHIR90021). Immunofluorescence was performed to characterize the observed phenotypes. Bulk RNA seq. and Proteomics: NPCs were extracted by MACS (passage 0), cultured for 24h with the vehicle, CHIR, and YN1, and then processed for proteomics and bulk RNA sequencing. Data Analysis. Differential gene expression, pathway analysis, and GO enrichment analysis were performed in R.

Results: Here, we showed a direct relationship between glucose metabolism and NPC fate decisions. First, E12.5 embryonic kidneys cultured in the presence of 2-NPy showed reduced extracellular acidification rate (ECAR), and increased differentiation rate. Second, E12.5 embryonic kidneys stimulated with UK5099 showed an increased ECAR, reduced ATP production from oxidative phosphorylation, augmented NPC pool, and reduced differentiation. We compared the proteome and transcriptome of E13.5 NPC stimulated with either CHIR or YN1 to dissect the molecular mechanism underlying these phenomena. Decreased cholesterol biosynthesis emerged as a top pathway targeted by both drugs. Inhibition of cholesterol synthesis stimulated NPC differentiation at the cost of cap mesenchyme depletion, which, in turn, phosphorycated YN1 treatment. Acetyl-CoA links cholesterol production and glucose metabolism. Sodium-acetate is an alternative source of acetyl-CoA. Sodium-acetate supplementation increased cytosolic acetyl-CoA levels and cap mesenchyme size, without hindering NPC differentiation. Co-treatment with exogenous sodium-acetate abrogated the adverse effects of glycolysis inhibition.

Conclusions: This study identifies acetyl-CoA as a key metabolite for kidney development and sodium-acetate as a potential exogenous substrate to promote kidney growth and development
Funding: NIDDK Support

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Real-Time ATP Imaging Reveals the Metabolic State During Kidney Development
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Background: Maternal malnutrition is associated with a reduced nephron number and an increased risk of hypertension and chronic kidney disease in later life. However, very little is known about what determines the nephron number, and about the metabolic state during nephrogenesis.

Methods: We focused on the cytosolic adenosine 5-triphosphate (ATP) level and its changes to examine an energy metabolism in embryonic kidneys. To explore the spatiotemporal dynamics of the cytosolic ATP level, we used transgenic mice expressing the cytosolic ATP-FRET biosensor, called GO-ATeam2 mice. We performed visualization and analysis of cytosolic ATP level in real-time ex-vivo imaging during branching nephrogenesis and examined the dependence of ATP production on glycolysis and oxidative phosphorylation during nephrogenesis.

Results: We succeeded in visualizing the cytosolic ATP level at a single cell level and investigated the spatiotemporal dynamics of the cytosolic ATP level in both ureteric bud (UB) and cap mesenchyme (CM) cells. The UB forms the collecting ducts through repeated bifurcation of the ureteric tree, while the CM differentiates into nephron epithelial cells. The reciprocal interaction between UB and CM cells is crucial for proper kidney development. During branching nephrogenesis, ATP levels of UB tip cells were significantly lower than those of UB stalk and CM cells. Glycolytic inhibition in the early branch phenotype (day 15.5) by addition of 2-NPy (E12.5) resulted in reduced CM ATP level in both cells in a dose dependent manner, but ATP reduction was faster and more prominent in UB cells rather than in CM cells. In addition, the expression of specific markers for UB and CM cells were significantly reduced and electron microscopy images showed a loosening of cell-cell adhesion and irregular cell alignment in CM cells after glycolysis inhibition. Furthermore, glycolytic inhibition resulted in suppressed UB branching and reduced number of both branch segments and UB tips. On the other hand, these effects were not observed by an oxidative phosphorylation inhibitor.

Conclusions: The mice allowed us to perform real-time ex-vivo ATP imaging of embryonic kidneys. We found that UB branching was heavily dependent on glycolysis and that UB cells in the early branching phase were sensitive to glycolytic inhibition.

SA-PO342

Highly Parallel Production of Designer Kidney Organoids by Mosaic Patterning of Progenitors
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Background: Kidney organoids derived from human induced pluripotent stem cells (iPSCs) are a promising approach for congenital and adult disease modeling, regenerative medicine, and gaining fundamental understanding of organogenesis. However, organoids are limited in their production scale, reproducibility, and physiologic function and structure, posing a considerable barrier to their application. Thus, an important open question is the extent to which engineering control over culture conditions can guide organoid development and specific outcomes in composition and organization. Here, we study this by precisely controlling iPSC-derived kidney progenitor cell numbers and ratios in microwell-format organoid cultures.

Methods: We began by adapting transient 2D cell patterning technology to a microwell format suited for transition to long-term 3D organoid culture. We first applied our validated culture system to study the effect of initial nephron progenitor (NP) number on organoid morphology. Since reciprocal interactions between NPs and ureteric bud (UB) tip cells influence nephron endowment during kidney organogenesis, a major predictor of kidney disease, we next examined how modulating ratios of these cells affects organoid morphogenesis.

Results: In our NP-only organoids, we discovered that throughout culture, organoid sizes directly depend on the number of initial NPs. Moreover, larger nephron organoids display a shift in final composition, with a significant increase in proximal tubule proportion from 40% to 61% from 2D cell pattern size diameters 200 to 500 µm. Preliminarily, we have found that regardless of cell ratio, transition of 2D cell pattern size to 3D suspension culture facilitates cell sorting and discrete compartment formation early in organoid development, which resembles physiologic organization. Furthermore, UB tip cells and NPs synergistically aggregate stromal cell populations.

Conclusions: Here, we contribute an integrated cell patterning and long-term culture platform that decouples organoid size from well geometry, enables 3D suspension culture, and permits discrete organoid cultures. Our approach makes significant advances in organoid homogeneity relevant to drug screens and modeling of development and diseases as well as improved control over tissue interface formation crucial to engineered microenvironment efforts.

Funding: NIDDK Support, Other NIH Support - NIH NIGMS MRA R35GM133380 to Alex Hughes, Other U.S. Government Support
SA-PO325

Generation of Human Kidney Organoids with Three-Dimensional Vascular-Like Systems

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Background: Kidney organoids are hampered by their inability to imitate mature organ architecture since they lack of vasculature, which creates essential niches. Here, we demonstrate two novel paradigms for generating three-dimensional vascularized kidney organoids.

Methods: Method 1. We differentiated the HiPSCs into kidney organoids and blood vessel organoids respectively. Then we co-cultured the 3D blood vessel networks with kidney progenitor aggregates to form the assembloids. Method 2. We induced the HiPSCs into the kidney progenitor aggregates. Then we transfected with mCherry-hETV2 plasmids into kidney progenitor cells. 7 days later, the organoid got matured.

Results: Generation of assembloids from blood vessel networks and kidney progenitor aggregates. To study organ-to-organ communication circuits within different organoids, we co-cultured the blood vessel organoid and kidney organoid. At later stage, the blood vessel networks penetrated the entire kidney organoid and assembled into multiple lineage organoids, enabling us to study the characteristic of the micro-physiological system within different organoids. hETV2 promotes the vascularization of kidney organoids. We transfected with mCherry-hETV2 plasmids into the kidney progenitor aggregates. The hETV2 overexpressing kidney organoid positioned podocytes (NPHS1+) and tubular parts (LTL+) packed with numerous endothelial networks (CD31+).

Conclusions: 1) Blood vessel organoids penetrated the kidney progenitor aggregates, and formed entirely blood vessel networks within kidney organoids. 2) hETV2 transcription factor elicited the process of vascularization for kidney organoid.

Funding: Government Support - Non-U.S.

SA-PO326

Deletion of Crkl Splice Isomers in the Mouse Kidney Disrupts Intercompartamental Signaling Required for Progenitor Renewal and Branched Morphogenesis

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Background: We previously showed that haplosufficiency and point mutations in CRKL drive kidney and urinary tract malformations in the DGeorge, or 22q11.2 Syndrome (DGS) and in sporadic CAKUT, respectively. Here, we examined the developmental requirement of the two Crkl splice variants (T1 & T2) when conditionally and differentially deleted in the metanephrine mesenchyme (MM).

Methods: We characterized phenotypic abnormalities in developing kidneys from mice with conditional deletion of both T1 and T2 (“No Crkl”), or only the T1 isoform (“T2 only”), specifically within the MM. Bulk and scRNAseq data were acquired and analyzed from embryonic kidneys isolated from 13.5 and 15.5dpc wild-type and mutant mice. IHC and ISH analyses were used to validate and identify key signaling pathways.

Results: At P0, both “No Crkl,” and “T2 only” kidney phenotypes were characterized by severe hypoplasia and near-absence of nephrogenic progenitors (NP). Morphometric analysis of the renal collecting system at 13.5 and 15.5dpc shows a hyperbranched phenotype in the “No Crkl” mice. The expression of only T2 led to a hypobranched phenotype. Using our single-cell data to “deconvolve” bulk RNAseq data, we found an overrepresentation of early proximal tubule (ePT) markers in “No Crkl” mice, and an underrepresentation in “T2-only” mice, suggesting a cell type-based contribution to the divergent branching phenotypes. Both groups of mutants also showed an underrepresentation of NP markers, where scRNAseq and ISH analyses confirmed decreased expression of Fgfl and Fgfl in NPs and renal vesicle. Lastly, in-depth time-based analyses of bulk RNAseq datasets revealed 3 differentially regulated gene sets that may explain the divergent branching phenotype between the two mutants.

Conclusions: Genetic and epigenetic defects of Crkl lead to a hyperbranched renal collecting system at 13.5 and 15.5dpc. This study provides insights into the mechanisms of type 1 Crkl haplosufficiency and the role of branching morphogenesis in kidney development.

Funding: NIDDK Support

SA-PO327

HNF4A Re-Expression Restores A Proximal Tubular Phenotype in Cultured Primary Cells

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Background: The tubular part of the nephron is composed of distinct segments. The transcription factor hepatocyte nuclear factor 4α (HNF4A) is a master regulator for the phenotype of the proximal tubules, controlling features such as brush border formation and transport. Culture of primary proximal tubular cells is an essential model system for kidney research, but during culture, the cells display a less differentiated phenotype with expression of markers associated with kidney injury. The aim of this study was to evaluate if HNF4A transduction of cultured primary proximal tubular cells could revert the cells to a more mature phenotype.

Methods: Primary proximal tubular cells obtained from human cortical kidney tissue were cultured and harvested at consecutive passages. The change in protein expression at different passages was evaluated using immunohistochemistry. HNF4A adenoviral transduction was performed on primary proximal tubular cells, followed by RNA sequencing and bioinformatic analysis. The effects of HNF4A transduction were furthermore analyzed by qPCR, Western blot, and immuno electron microscopy.

Results: Culture of primary proximal tubular cells resulted in major HNF4A loss. In contrast, the mesenchymal and injury marker vimentin was induced. HNF4A was successfully reintroduced by adenoviral transduction and this caused upregulation of known target genes associated with brush border formation, transport, and metabolism. Gene set enrichment analysis revealed pathways linked to absorption, transport, and digestion as well as microvilli and brush border. Using immuno electron microscopy, morphological features of proximal tubular cells could be visualized in HNF4A-positive cells.

Conclusions: In summary, human primary proximal tubular cells rapidly lose HNF4A expression during culture, but by reintroduction of HNF4A using adenoviral transduction, the cells regained expression of genes essential for brush border formation and transport. This suggests that HNF4A expression may improve the reliability of in vitro models of proximal tubular cells.

Funding: Government Support - Non-U.S.

SA-PO328

High-Throughput Discovery of Novel Therapeutic Candidates for Human Podocytopenathies

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Background: Chronic kidney disease (CKD) impacts 12% of the world population. Currently, the best treatment options for patients experiencing advanced stages of CKD include dialysis or kidney transplantation. Therefore, there is an urgent need for novel therapies that address the underlying causes of kidney dysfunction and disease progression. Damage to podocytes is associated with CKD. In addition to comorbidities and predisposition factors, CKD occurrence can be aggravated by the administration of nephrotoxic drugs. These compounds include the chemotherapy drug Adriamycin (ADR), which exhibits off-target nephrotoxic effects in podocytes.

Methods: By employing our established protocol for hiPSC-derived podocytes, we developed a high-throughput screening (HTS) strategy to help discover new protective biomolecules and potential therapeutic candidates for podocytes. We screened the hiPSC-podocytes with a library of bioactive molecules and ADR. To eliminate the compounds that did not protect against ADR injury, the threshold for positive hits was considered above ADR control viability. These compounds were selected as potential hits and were subjected to low-throughput secondary validation metrics. The cells co-treated with the bioactive hits and ADR seemed to have been protected from ADR-induced injury by retaining healthy cell spread, and cytoskeletal

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structures such as actin fibers. In subsequent 48hrs experiments, podocytes were pre-treated with the compounds in low-throughput environments, and podocyte cell viability and cytoskeleton arrangement were protected against ADR injury.

**Conclusions:** Our preliminary work led to the identification of three new compounds that protected human stem cell-derived podocytes from severe injury by ADR treatment in vitro. Ultimately, a podocyte-directed therapeutic could protect cells against known nephrotoxic drugs, potentially reducing the need for dialysis or kidney replacement in the future.

**Funding:** Other NIH Support - A.D.B. is a recipient of the NIH T32 Predoctoral Research Fellowship in the Center for Biomolecular and Tissue Engineering (CBTE) at Duke University (Grant No. T32GM144291), Private Foundation Support

**Figure 1**

(A) Schematic of HTS and validations. (B) Fluorescent images of potential therapeutic hits compared to controls.

**SA-PO329**

**T Cell-Mediated Immune Rejection of B2M Knockout Induced Pluripotent Stem Cell (iPS)-Derived Kidney Organoids**

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**Background:** "Stealth" induced pluripotent stem cell (iPSC)-derived kidney organoids represent an attractive strategy and could potentially be used in clinical transplantation. Genetic modification of the human leukocyte antigen (HLA) class I molecules in inPSCs prior to transplantation of their derived tissues could prevent immune rejection. Here we evaluated the effect ofβ2-microglobulin (B2M) knockout on T cell-mediated rejection of iPSC-derived kidney organoids.

**Methods:** Specific genetic modification achieved by CRISPR-Cas9 was used to knockout B2M gene expression and prevent HLA class I surface expression on iPSCs. Kidney organoid immunogenicity was determined in vitro by co-culture with allogeneic T cells and in vivo following transplantation in humanized mice.

**Results:** We found that iPSC-derived B2M−/− kidney organoids were protected from T cell rejection in vitro. To evaluate in vivo protection, unmodified (control) and B2M−/− kidney organoids were transplanted in humanized mice that were engrafted with human peripheral blood mononuclear cells (PBMCs). Successful engraftment of the human PBMCs was validated and 4 weeks after PBMC injection we observed the infiltration of CD4+ and CD8+ T cells in the kidney organoids. There was no difference in the infiltration rate of CD4+ and CD8+ T cells, proliferation of T cells and T cell cytotoxicity between control and B2M−/− organoids. Control and B2M−/− organoids tissue integrity was similarly affected, showing tubulitis and loss of tubule integrity. Although the B2M−/− organoids were unable to express HLA class I on the cell surface, we found increased expression of HLA class II in control and B2M−/− organoids that were transplanted in mice with human PBMCs. HLA class II expression was expressed not only by endothelial, but also epithelial cells of the kidney organoid, posing an additional immunological barrier to the transplantation.

**Conclusions:** We conclude that knockout of the B2M gene alone is not enough to protect iPSC-derived kidney organoids from T cell mediated immune rejection and highlight the importance of HLA class II signaling in the graft rejection process.

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**Therapeutic Potential of Induced Nephron Progenitor Cells and Their Extracellular Vesicles in Aristolochic Acid-Induced CKD: Insights from Organoid and Mouse Models**

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**Background:** CKD affects 15% of US adults, with Aristolochic acid (AA) being a valuable model for CKD. We explored CKD therapies using induced nephron progenitor cells (iNPs) and their extracellular vesicles (iNP-EVs). iNPs are engineered to secrete a pharmaceutically relevant compound, AA, for 48 hrs. AA was followed by 24 hrs of exposure to either iNPs or iNP-EVs. *In vivo* experiments were performed in NSG mice, an immunocompromised mouse strain, to avoid an immune response to iNPs. In brief, mice were injected with 2 mg/kg AA three times per week for two weeks; then, the injury was allowed to develop for an additional two weeks, then mice were treated with iNPs or iNP-EVs.

**Results:** iNP-treated organoids showed decreased Dickkopf-1 (DKK1) levels compared to EV-treated, untreated, and control organoids. Both iNPs and EVs treatment reduced macrophage colony-stimulating factor (M-CSF) compared to untreated organoids, to a more pronounced effect. Immunofluorescent staining revealed increased alpha-smooth muscle actin (α-SMA) levels in AA-treated organoids, with lower expression in iNP and EV-treated organoids.

**Conclusions:** Analysis of tissue sections stained for α-SMA showed that the AA + iNPs treatment group had fewer myofibroblasts than the AA-only and AA + iNP-treated groups. All groups receiving AA had more α-SMA staining than the untreated control group. DKK1 is a Wnt signaling inhibitor, suggesting that iNPs may encourage proliferation through a non-exosomal mechanism. The M-CSF reduction suggests an iNP EV-dependent immunomodulatory effect. M-CSF is released from activated fibroblasts, so decreased M-CSF levels could indicate reduced numbers of myofibroblasts, supported by the improvement in α-SMA levels. In conclusion, iNPs and iNP-EVs may mitigate fibrosis in mouse and human models of AA-induced CKD.

**Funding:** Other NIH Support - NIH T32 ES007028, Veterans Affairs Support

**SA-PO331**

**Kidney Organoid Transplantation Promotes Endothelial Cell Proliferation and Transition Toward a Human Fetal Afferent/Afferent Arteriolar-Like Phenotype**

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**Background:** Kidney organoids (KORs) derived from induced pluripotent stem cells hold potential for regenerative medicine and kidney modeling. However, KORs lack proper vascularization, hindering maturation despite the emergence of endothelial cells (ECs).

**Methods:** Day7+12 KORs were transplanted into chicken embryos for 1 or 8 days, or further cultured in vitro for the same time period. FACS-sorted CD31+ KOR ECs underwent scRNA-seq (11,996 ECs). A human fetal kidney EC reference (8-17 weeks of gestation, >3,000 ECs) was created from publicly available scRNA-seq data. Immunostainings were performed to validate the findings.

**Results:** Both time and transplantation altered KOR EC transcriptionomes, with the latter having a greater impact. KOR transplantation induced a metabolic transcriptome switch from oxidative phosphorylation to glycolysis, associated with hypoxia response geneset enrichment at day 1. Day 8, KOR transplantation prevented DNA damage response and decreased nuclear division, while upregulating antigen presentation, matrix deposition, angiogenesis, blood coagulation/circulation genesets, indicating response to stress and tissue regeneration. Consistent with angiogenesis, EC proliferation was increased in that condition (especially in M phase), as confirmed by Ki67 staining. ECs also underwent a major vein-to-arterial phenotypic transition, with a decreased pool of NR2F2+ ECs and the emergence of arterial ECs, and upregulated EC tissue-specific genes (especially related). Arterial ECs characterized by laminar shear stress response and Notch signaling, showed a similar transcriptome as human fetal kidney arterial/afferent arteriolar ECs. Transplantation-induced EC reprogramming involved SOX7 transcription factor upregulation and regulon enrichment.

**Conclusions:** KOR transplantation led to the development of arterial ECs alike human fetal kidney artery/afferent arterial ECs, likely via SOX7 and blood flow exposure. These findings provide insights for the development of KOR vascularization strategies.

**SA-PO332**

**Vessel-Promoting Factors naps4l1/cloche and hand2 Act in Parallel to Inhibit Intermediate Mesoderm Specification**

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**Background:** Proper organ formation depends on precise organ territories containing defined numbers of progenitor cells. Kidney progenitors reside in the intermediate mesoderm (IM), two bilateral stripes of cells in the posterior mesoderm. Previously, we showed that the transcription factors Hand2 and Osr1 are essential for defining the dimensions of the IM by balancing the specification of IM and laterally adjacent vessel progenitors. Recently the transcription factor Naps4l1/Cloche – well characterized as an early, essential regulator of vessel specification and kidney formation – was shown to inhibit kidney development. Here we determine how kidney and IM specification is coordinated among hand2, osr1, and naps4l1.

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

**Underline represents presenting author.**
Methods: Taking advantage of the robust genetic, optical, and experimental benefits of the zebrafish model organism, we interrogated the IM at the single cell level. Here we employ a combination of loss and gain-of-function genetic analyses and whole mount RNA in situ and antibody staining.

Results: First, hand2 and osr1 regulate the development of npas4l-expressing lateral ventricle progenitors (LVPs). Interestingly, like hand2 loss-of-function, npas4l loss-of-function rescues osr1 mutant kidney developmental defects. However, unlike in hand2; osr1 double mutants in which LVP specification is restored, vessel progenitor formation is not rescued in npas4l; osr1 mutants, suggesting that hand2 and npas4l may implement different factors in kidney and vessel progenitor lineages. The stem cell fate associated with npas4l and hand2 overexpression can inhibit kidney formation independent of one another suggesting the factors function in parallel to inhibit kidney specification. Importantly, like hand2 mutants, npas4l mutants have expanded IM, but in npas4l mutants the expanded IM is not restricted to hand2-expressing cells suggesting alternative sources of increased IM within the two mutants. Finally, consistent with parallel functions for hand2 and npas4l in IM inhibition, hand2; npas4l double mutants have increased IM beyond that seen in either single mutant.

Conclusions: Together our findings reveal that proper kidney specification depends on parallel genetic pathways that inhibit IM specification while promoting vessel progenitor formation

Funding: NIDDK Support

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Profiing the Epigenetic Landscape of the African Spiny Mouse, A Mammalian Model of Kidney Regeneration

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Background: The African spiny mouse is the first mammal to demonstrate full restoration of kidney function without fibrosis after injury (Okamura et al., 2021) and provides an opportunity to elucidate mechanisms promoting kidney regeneration. The transcriptome of the spiny mouse and house mouse kidneys is the same, but its response to injury is remarkably different, indicating that epigenetic control of gene expression may be the key to its regenerative capacity. We hypothesize that the African spiny mouse kidney is poised to respond differently before injury occurs through accessible chromatin for critical genes that are regulated by histone methylation.

Methods: Single nuclei ATAC-seqning identified accessible regions of chromatin in normal African spiny mouse kidneys (n=3). Cleavage Under Targets and Release Under Nucleases (CUT&RUN) identified which regulatory elements were targeted by activating (H3K4me3) and repressive (H3K27me3) histone marks in spiny mouse kidney (n=2). Data was aligned to a spiny mouse reference genome we constructed with long-read DNA sequencing. CUT&RUN peak calling and HOMER for peak annotation and motif detection.

Results: Single nuclei ATAC-seq data mapped to the spiny mouse reference genome at >85%. Over 4,300 high quality peaks were generated from 27,000 cells, generating 10 distinct clusters. CUT&RUN sequencing data mapped to the reference genome at >95%, 2608 consensus H3K4me3 peaks and 1560 consensus H3K27me3 peaks were detected. Several key progenitor motifs marked by H3K4me3 were significantly enriched in the spiny mouse kidney (p<0.01) and had accessible chromatin based on ATAC-seq data, including Hand2, Osr1, Myb and Tead2.

Conclusions: This work demonstrates that chromatin for nephrogenic progenitor genes in spiny mouse is accessible and poised for transcription through histone methylation. These experiments are being extended to injured kidneys of the spiny mouse to identify how their regenerative function is controlled by histone marks in the setting of kidney regeneration. These results will have an important positive impact by providing targets and potential mechanisms for the redirection of kidney injury towards regeneration of functional tissue.

Funding: NIDDK Support, Private Foundation Support

SA-PO334

Inflammatory Cytokine Signaling in New Nephron Formation After Aki in Adult Zebrafish

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Background: Adult progenitor cells in the mesonephric zebrafish kidneys are required during neo-nephrogenesis replacing injured tubules by forming new nephrons. Single-cell RNA transcripts of adult kidney progenitor cells point to components of NF-κB and inflammatory cytokine receptors that may initiate stem cell-based nephrogenesis. Here, we present evidence that gentamicin induces inflammation-associated injury, which potentially stimulates stem cell-based nephrogenesis. The stem cell fate associated with npas4l gene knock-down in embryonic kidney explants rescued ureteric branching to normal levels. Genome-wide RNA expression analysis in IkB-T713L knockout in ureteric kidney explants demonstrated elevated expression of Cebpa and Gzma.

Methods: Adult zebrafish were injected i.p. with gentamicin or LPS at day 0. NF-κB signaling was determined 4 days post-injection (dpi) by NF-κB-GFP detection of the NF-κB reporter line Tg(NF-κBEGFP) and NF-κB-associated gene expression using qRTPCR. NF-κB signaling during regeneration was evaluated by pharmacological NF-κB inhibition. Bulk RNAseq analysis of positive-selected GFP+ Lhx1+ cells at 7 dpi with gentamicin confirmed the induction of cytokine receptor expression, which was not induced by LPS in the absence of injury, is sufficient to induce neo-nephrogenesis.

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

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The Transcription Factor Tcf21 Protects Stomal Cell Precursors During Kidney Development

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Background: Normal kidney development requires coordinated interactions between ureteric progenitor cells. FOXL1 + cells are critical for normal nephrogenesis and their heterogeneity is increasingly appreciated. However, the molecular mechanisms and trajectories that drive the differentiation of FOXL1 + cells toward the renal stroma, capsule, mesangial cells, renal cells, pericytes, and vascular smooth muscle cells (VSMCs) are poorly understood. Tcf21 is a mesoderm-specific MLLH transcription factor critical for embryogenesis.

Methods: To investigate the developmental origins of Tcf21 effects on stroma, we performed single-cell RNA sequencing (scRNA-seq) on GFP+ cells from E14.5 mOsR1-Fosfox+Cel+Tcf21+ kidneys and control kidneys.

Results: Clustering of the entire dataset identified a large stromal population and a smaller representation of non-stromal lineages. Subclustering of stromal cells identified eight populations: proliferating, medullary/perivascular, ‘Tcf21 mutant’, uroepithelial/ureter, nephrogenic zone, collecting duct, ureteric associated stroma, and mesenchymal mesenchyme. Loss of Tcf21 resulted in a dramatic reduction in the proliferating, medullary/perivascular, nephrogenic zone, and collecting duct associated stromal populations. Immunostaining confirmed that mutants had severe reduction in the medullary and collecting duct stromal space of mutants. A unique cluster, exclusively present in mutant kidneys and named ‘Tcf21 mutant’, expressed high levels of extracellular matrix (Spracil, Fras1), perivascular cells (Rgs5, Akr1b7), and endothelial cells (Endomucin) genes. Mutant cells showed upregulation of pathways involved in extracellular matrix organization, VSMCs and fibroblast proliferation, and negative regulation of angiogenesis.

Conclusions: These data underscore a role for Tcf21 in the emergence of the milieu of FOXL1 + derivatives, whereas loss of Tcf21 leads to stromal cell fate change that results in abnormal kidney development.

Funding: NIDDK Support

SA-PO336

Increased mTOR Signaling Secondary to a Human Integrin-Linked Kinase (ILK) Missense Variant Inhibits Nephrogenesis with Decreased ATP Generation

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Background: Signaling pathways that control nephrogenesis are critical to our understanding of kidney health and disease. Previously, we demonstrated increased mTOR signaling in vitro by overexpression of a CAKUT-associated missense variant (R629Q) of Integrin-linked Kinase (ILK), a key regulator of renal development. Here, we investigate the hypothesis that ILK-T713I disrupts renal development in vivo via dysregulation of mTOR signaling.

Methods: mTOR signaling was analyzed in Ikk-T713I knock-in mice with Ikk-T713I replacing the WT Ikk allele. Morphogenic effects of Ikk-T713I on renal development were quantitated. Ureteric and non-ureteric cell populations were isolated by FAC sorting. Gene expression was analyzed by whole genome RNA microarray and qPCR. Cell proliferation and nephron maturation were evaluated by immunostaining and specific markers. Energy metabolism was characterized using the Seahorse assay.

Results: Homozygous Ikk-T713I knock-in mice were characterized by a 13.6% decrease in nephron number (n=6, P=0.04), a 35.2% decrease in ureteric branching (n=5, P=0.006) and an 88% increase in mTOR signaling (n=3, P=0.01). Rapamycin treatment of Ikk-T713I knock-in embryonic kidney explants rescued ureteric branching to normal levels. Genome-wide RNA expression analysis in Ikk-T713I knock-in ureteric and non-ureteric cell populations demonstrated elevated mTOR signaling in non-ureteric cells only. Ikk-T713I knock-in non-ureteric populations expressed a 43% increase in Oxrl

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

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(n=3, P =0.002), a mesenchymal cell progenitor marker, and a 54% decrease in α-SMA (n=3, P <0.0001), a marker of myofibroblasts. Ilk-T173I knock-in embryonic kidneys demonstrated a 2075% increase in phospho-Histone H3-labeled cells (n=3, P <0.0005), an indicator of cell proliferation, in the ureteric, nephrogenic and stromal lineages, and a 16.1% decrease in the percentage of S-shaped bodies (n=4, P <0.01), the mature form of nephron progenitor cells. Metabolic profile of Ilk-T173I knock-in, non-ureteric cells exhibited a 17% decrease in both oxidative ATP production (n=3, P <0.04) and total ATP production (n=3, P <0.02).

Conclusions: These data show that human Ilk-T173I variant impairs renal development in a mTOR-dependent manner, specifically acting within the non-ureteric cell population by increasing proliferation and disrupting maturation and cell metabolism.

Funding: Government Support - Non-U.S.

SA-PO337

PRRX1 Is a Master Regulator of Renal Fibroblast Cell Fate and Regulates Myofibroblasts Activation in Response to TGF-β via Alteration of the Chromatin Landscape

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Background: Emerging evidence suggests that changes in the chromatin landscape in response to TGFβ likely contributes to the pathogenesis of diabetic kidney disease (DDK). Using iPSC derived kidney organoids, we have recently shown that TGF-β signalling to chromatin unleashes a programme of gene expression initiating fibroblast to myofibroblast activation. We hypothesise that SMAD3 and the Polycomb Repressive Complex 2 core component, EZH2, co-occur regulatory regions within chromatin to deploy nephrogenic intermediates. We have therefore tested if altering TGFβ-driven changes in the chromatin landscape which drives fibroblast activation in DDK. Our data shows that PRRX1 acts as a master transcription factor in regulating fibroblast to myofibroblast differentiation through association with SMAD3/EZH2. To characterise this proposed epigenetic mechanism, genetic and proteomic and transcriptomic analysis was performed on iPSC-derived kidney organoids treated with TGFβ.

Methods: Histone extraction was performed on undifferentiated iPSCs, iPSC-derived nephron progenitor cells, iPSC-derived kidney organoids, and kidney organoids treated with recombinant TGFβ1. Histones were then subjected to LC-MS/MS for analysis of global histone modifications. Single cell RNA-sequencing (scRNA-seq) was performed on iPSC derived kidney organoids treated with EZH2 inhibitor, GSK343, for 1h prior to TGFβ1 treatment for 48 hours.

Results: Mass Spectrometry data revealed differential abundance of trimethylated lysine residues on Histone 3 (H1K27me3) between TGFβ1 treated and control, indicating dynamic changes in transcriptionally permissive states. scRNA-seq analysis of kidney organoids treated with TGFβ1 revealed clustered specific changes in PRRX1 expression in response to TGFβ1, specifically in stromal cells and activated myofibroblast clusters. These changes in PRRX1 in response to TGFβ1 were consistently observed in other fibroblast cell lines.

Conclusions: TGFβ1 is a key driver of chromatin dynamics as evidenced by H1K27me3 and likely contributes to gene repression through interaction between SMAD3 and EZH2. We propose that subsequent silencing of PRX1 expression in iPSC derived kidney organoids treated with TGFβ1.

SA-PO338

Regeneration-Associated Cell-Derived Extracellular Vesicles Preserve Kidney Function After Acute Ischemia Injury

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Background: Under vasocgenic conditioning, pro-inflammatory cell subsets of kidney injury induce the formation and delivery of extracellular vesicles (EVs) composed of regulatory factors. These vesicles are implicated in the regeneration of damaged organs. However, it is not known how EVs are generated during regeneration. In this study, we evaluated the therapeutic efficacy of RAC-derived extracellular vesicles (RACev) compared with a vehicle-treated group using the rat kidney ischemia-reperfusion injury (I-R) model.

Methods: Human PBMCS were cultured with defined growth factors for seven and then two days to harvest RACs and RAC-ev, respectively. EV sizes were characterized by nanoparticle tracking analysis. Transmission electron microscopy revealed a b-layered membrane structure and flow cytometry confirmed the presence of EV-specific markers (CD9, CD63, and Alix).

Results: Notably, systemic injection of RACev significantly decreased serum creatine and blood urine nitrogen (P <0.01 and P <0.005) at day three after the onset of I-R injury than the control group. Histologically, the treatment group showed less fibrosis in the cortex and medullary areas (P =0.04 and P <0.01) compared to the control group. CD31 staining confirmed enhanced capillary densities at the cortex and medullary areas in the treatment group compared to the control group (P <0.003). These beneficial effects were coupled with significant expression of angiogenesis (miR-126-3p, misR-195-3p, misR-17-5p, misR-20b-3p, anti-inflammation (miR-10a-3p, miR-21-3p, miR-24-2p), and anti-apoptosis miRs by RACev. In vivo bioluminescence analysis showed preferential accumulation of RACev in the IR-injured kidney.

Conclusions: In conclusion, systemic transplantation of RACev improved kidney function via protecting from tissue fibrosis, anti-inflammatory, and angiogenesis miR delivery to the ischemic tissue.

SA-PO339

Partitioning-Defective (Par1) Inhibition Protects Against Kidney Fibrosis in Mice

Kobayashi.1

Background: Partitioning defective (Par1) a and b (MARK2/3) expression is required for normal kidney development and increases in damaged tubules following tubular injury by unilateral ureteral obstruction (UUO) and follicular acid (FA) injection in mice. Par1a/ Par1b MARK3 expression in human kidney tissues correlates with kidney fibrosis and eGFR. Par1a mutant (MARK3) mice are protected against kidney fibrosis following UUO and FA induced injury. We hypothesized tubular Par1a/b expression is maladaptive following kidney injury and sought to test the effect of tubular Par1a/b deletion and chemical Par1 inhibition on fibrosis following kidney injury.

Methods: We generated tubular conditional Par1a/b knock out mice (Par8-rtTA-tet-O-Cre:Mark2flox/flox:Mark3flox/flox) mice. Tubular deletion was induced using doxycycline treatment day 7 prior to injury by UYO. Sham operated (for UUO) mice was used as control for the injury model. Both injured and uninjured uninduced Par8-rtTA-tet-O-Cre:Mark2flox/flox:Mark3flox/flox mice and doxycycline treated Mark2flox/flox:Mark3flox/flox mice were used as controls. A MARK-Par1 Activity Inhibitor (Sigma, 39621) was injected via IP injection for 3 days after UUO injury. Kidney phenotype was analyzed at 7 days post UUO injury or sham surgery.

Results: Par1a (MARK3) gene expression is highest in injured, dedifferentiated proliferating (Sexs9 and Ki67+) tubular cells. Dual Par1a/b EKO mice were protected from injury induced fibrosis following UUO induced injury (p<0.001). MARK Inhibition after injury protected against UUO induced fibrosis.

Conclusions: Genetic tubular deletion of Par1a/b before injury and inhibition post UUO induced injury was protective against kidney fibrosis. Ongoing experiments are testing other models of kidney injury and mechanisms of Par1a/b protection.

Funding: NIDDK Support

SA-PO340

miR-17-20a Alleviates Renal Interstitial Fibrosis by Repressing Fmrmd Expression in Renal Epithelia

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Background: An estimated 37 million Americans have chronic kidney disease (CKD), and its prevalence is increasing with higher rates of diabetes mellitus, hypertension and obesity. Regardless of the underlying etiology, renal fibrosis is the final manifestation of CKD. microRNAs (miRNAs) are endogenous, small non-coding RNAs that bind to target mRNAs and regulate their expression. In this study, we investigated the role of the miR-17-92 cluster in renal fibrosis.

Methods: Genetic mouse models of inducible epithelial-specific miR-17-92 loss-of-function (miR-17-92EpiLOF), gain-of-function (miR-17-92EpiLOF) were generated by crossing Pax8Cre-rtTA; LCr-cre mice with miR-17-92 floxed mice or with a mouse line containing a constitutively active CAG promoter ahead of a loxP-flanked STOP cassette preventing transcription of the downstream miR-17-92 sequence, respectively. Unilateral ureteral obstruction (UUO) and acute kidney injury (AKI) to CKD model were performed. Renal fibrosis was assessed by immunostaining with antibodies to collagen I and III and anti-α-SMA antibodies, followed by semi-quantitative analyses with ImageJ. The human proximal tubular epithelial cell line HK2 was transfected with either empty vector or a vector containing the Fmrmd cDNA. HK2 cells were used for experimental identification of miR-17-92 target genes using PAR-CLIP.

Results: miR-17-17a, -17a, and -20a were upregulated in UUO and the AKI to CKD model. Interestingly, miR-17-92EpiLOF mice exhibited increased predisposition to renal fibrosis with aging and after UUO, which was accompanied by increased expression of miR-17-92 fibrotic targets, p-Stat3 and p-Smad3. Conversely, UO-induced fibrosis was ameliorated in imir-17-92EpiLOF kidneys. Fmrmd, an activator of Hippo signaling, was identified as a novel miR-17-20a target. Fmrmd was increased in the tubular epithelium of obstructed miR-17-92EpiLOF kidneys compared to controls. Finally, overexpression of Fmrmd in HK2 cells resulted in increased expression of the mesenchymal markers SNAIL1 and FNI, and elevated secretion of collagen III in conditioned media.

Conclusions: Together, our findings indicate that the miR-17-92 cluster in renal epithelial cells functions to limit fibrosis by regulating multiple pro-fibrotic pathways.

Funding: NIDDK Support
SA-PO341

miR193a-VDR/RXR Axis and Renin Expression in the Transition of Parietal Epithelial Cells to Podocytes

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Background: Loss of kidney cells is a predominant cause of impaired kidney function in aging kidneys. Renin-expressing cells make a pool of renal progenitor cells, where the lack of renin expression determines their differentiation potential. Since microRNAs are the regulators of gene expression, we analyzed the role of the miR193a-VDR/RXR axis in regulating the renin expression and the sternness of Parietal Epithelial cells (PECs).

Methods: Human PECs were grown and analyzed for the expression of miR193a, renin, VDR, and RXR using real-time PCR and Western Blotting. PECs were transitioned to podocytes by transfecting either miR193a plasmid or an inhibitor of miR193a. The PECs transition potential was also analyzed under the overexpression of VDR and RXR. Immunoprecipitation assays were performed to evaluate the potential interaction of VDR/RXR and Renin. Luciferase experiments were carried out to elucidate the binding of miR193a to VDR 3UTR. In vivo, studies were carried out in control (Balb/C) and miR193a transgenic mice.

Results: Differentiated podocytes (DPD) overexpressing (OE) VDR showed enhanced expression of VDR and podocyte markers but a decreased renin expression (Figure A). Renal tissues of miR193a transgenic mice not only showed attenuated podocyte markers (Nephrin, podocalyxin [PDX], WT1) and VDR/RXR but also showed enhanced renin expression when compared to control mice (Figures B and C). The miR193a expression inversely regulated the VDR expression, and the downing of VDR enhanced expression of VDR and podocyte markers but a decreased renin expression in miR193a transgenic mice.

Conclusions: miR193a-VDR/RXR regulates renin expression and determines the efficient transition of PECs to podocytes.

Funding: NIDDK Support

SA-PO342

Modeling Kidney Development, Disease, and Plasticity with Clonal Expandable Neprhon Progenitor Cells and Neprhon Organoids

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Background: During kidney organogenesis, nephron progenitor cells (NPCs) self-renew and differentiate into nephrons, the functional units of the kidney. Dysregulation of NPC fates underlies a number of congenital kidney diseases while uncontrolled proliferation of NPCs in Wilms tumor is the most prevalent pediatric kidney cancer. Thus, a deeper insight into NPC biology is central to improving an understanding of kidney development, congenital disease, and cancer, and to applying developmental insight to regenerating kidney functions.

Methods: A synthetic niche is formulated that allows the in vitro long-term clonal expansion of primary mouse and human NPCs, and induced NPCs (iNPCs) from human pluripotent stem cells. Organoids are generated from cultured NPCs following a chemically-defined differentiation protocol. Genome-wide CRISPR screening is performed in the cultured NPCs to identify novel genes associated with kidney development and disease. Multiplexed CRISPR/Cas9 genome editing in the cultured NPCs generate a rapid, efficient, and scalable organoid model for polygenic kidney disease (PKD), allowing drug screening.

Results: Cultured iNPCs resemble closely primary human NPCs, generating nephron organoids with abundant distal convoluted tubule cells, which are not observed in published kidney organoids. The synthetic niche reprograms differentiated nephron cells into NPC state, recapitulating the plasticity of developing nephron in vivo. Scalability and ease of genome-editing in the cultured NPCs allow for genome-wide CRISPR screening, identifying novel genes associated with kidney development, congenital kidney diseases, and Wilms tumor. Cystic PKD organoid models are generated directly from genome-editing in the cultured NPCs to identify novel genes associated with kidney development, congenital kidney diseases, plasticity, and regeneration.

Funding: NIDDK Support, Private Foundation Support

SA-PO343

TRIM72 Immunomodulatory Functions Protect the Kidney During Inflammation

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Background: TRIM72 (Mg53) is a muscle-motor predominant protein and functions as a circulating myokine that appears to confer tissue protection during ischemia-reperfusion (IR) acute kidney injury and UUO-mediated kidney fibrosis. We discovered the functional quality of TRIM72 in kidney protection serving as a membrane repair protein and also modulating the immune system by suppressing NF-kB signaling during kidney inflammation. Here we explored the biological role and therapeutic potential of engineered Mg53-containing extracellular vesicles (EVs) in the treatment of kidney inflammation.

Methods: TRIM72 protein expression was characterized in human kidney, immortalized kidney parenchymal cell lines, and mouse proximal tubular epithelial cells derived from wildtype (mG53−) or trim22-null (mG53−) age and gender-matched mice. Next, we investigated whether IR-induced kidney injury or TRIM72-containing EVs could be applied as a means of protection. Furthermore, we engineered TRIM72 expression in several cell systems and further investigated whether TRIM72 affected the cells’ inflammatory cytokine profile.

Results: TRIM72 expression was detected in total human kidney lysates and in immortalized human podocytes and mesangial cells. A serum pro-inflammatory cytokine panel confirmed elevation of pro-inflammatory cytokines in trim22-null mice. The relative fold increase in trim22-null mice compared to wildtype mice were: CXCL1−1.2; IL−2.1; TNF−1.38; IL−5−2.8; IL−1−1.5. IR-injured kidneys recruited TRIM72-containing EVs derived from C2C12 myotubes as shown by IVIS imaging of DiR-labeled EVs 2 hours post-injury. The kidneys from trim22 null mice that received C2C12 EVs over 4 weeks expressed comparable levels of TRIM72 to that of wildtype mice.

Conclusions: TRIM72 is detected in the kidney that may be an endogenous inhibitor of pro-inflammatory cytokine expression. EVs loaded with TRIM72 are recruited to acutely injured kidneys, and can replenish renal TRIM72 levels in trim22 null mice. These results suggest that TRIM72-loaded EVs may be applied therapeutically to control kidney inflammation.

Funding: NIDDK Support, Other NIH Support - NIA, NIADDK

SA-PO344

Development of a System for the Replacement of Animal Fetal Kidneys with Human Nephrons: Toward Clinical Application


Background: Our focus is on “xenogenic regenerative medicine,” aiming to regenerate human nephrons using porcine fetal kidneys as a scaffold. Crucial to this approach is the replacement of porcine nephron progenitor cells (NPCs) with human NPCs. Previous studies using mouse models have shown complete replacement of the host nephrogenic niche with exogenous nephrons through Six2 (+) NPC suicide driven by diphtheria toxin (DT) or tamoxifen (TAM). However, there are limitations, such as DT’s inability to target human NPCs and concerns about TAM’s side effects. To facilitate future clinical applications, we have developed a novel inducible-caspase 9 (Cas9p9) system. It activates the intrinsic apoptotic pathway upon the administration of a chemical inducer of dimerization (CID) without harming the surrounding renal tissue. Importantly, our study demonstrates efficient cell clearance using this new system in animal models.

Methods: Six2-Cas9p9 mice were generated using TALEN-mediated gene modification. The knock-in vector was positioned downstream of the ETV1 exon 72 enhancer in vivo in mice or neonatal mice with either Six2-Cas9p9−/− or Six2-Cas9p9−/− genotype. Additionally, exogenous mouse and rat progenitor cells, as well as induced human NPCs, were injected into Six2-Cas9p9−/− fetal kidneys with CID administration.

Results: In the culture of Six2-Cas9p9−/− fetal kidneys, treatment with CID induced efficient apoptosis of all NPCs within 18 hours, whereas the conventional TAM-driven model showed insufficient apoptosis at the same time point. In vivo administration of CID to neonates also led to the complete removal of NPCs. On the other hand, NPC removal was not observed in the Six2-Cas9p9−/− mice. Following the injection of exogenous progenitor cells, successful nephron replacement was achieved in Six2-Cas9p9−/− fetal kidneys.

Conclusions: We successfully developed an iCas9p9 system that enables rapid and complete cell clearance, providing an optimal environment for NPC replacement and subsequent nephron regeneration in an animal model. The phenotypic differences between homozygotes and heterozygotes might be attributed to the varying levels of Cas9p9 expression. This achievement marks a clinical advancement in the development of the porcine fetal replacement system.

Funding: Government Support - Non-U.S.

SA-PO345

The Role of Gat3 in Renin Cell Identity

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Background: Renin cells are precursors for other cell types in the kidney and show high plasticity in postnatal life in response to challenges to homeostasis. Our scRNA-seq studies revealed that the dual-zinc finger transcription factor Gat3, important for cell
lineage commitment and differentiation in many tissues, is expressed in mouse renal cells under cell-injury conditions and has protective effects. Based on our Chip-seq data, we found an enhancer associated with Gata3 in renal cells. In addition, we identified a potential Gata3 binding site upstream of the renin gene leading us to hypothesize that Gata3 is essential for renin cell identity.

Methods: We studied 60 and 120-day-old mice carrying a conditional deletion of Gata3 in renin cells: Gata3flo/flo (Gata3-KO), and control Gata3flo/flo counterparts. BUN and plasma renin levels were measured from blood samples collected by cardiac puncture. Ren1, Acta2, and Gata3 were visualized in kidney sections by immunohistochemical analysis on adjacent kidney sections with hematoxylin and cosin (H&E), periodic acid-Schiff (PAS) solution, or Mason’s Trichrome reaction. The juxtaglomerular area (JGA) index was calculated as a ratio of renin-positive JGAs per the total number of glomeruli and expressed as a percentage.

Results: Gata3−/− mice have: 1) a reduced marking in Gata3 staining; 2) a reduced marking in Gata3 staining; 3) a significantly decreased in circulating plasma renin compared to controls under basal conditions and physiological stress; 4) a significantly reduced JGA index; 5) flattened JGCs compared to the plump and rounded morphology of control mice; 6) glomeruli with abnormal misplaced renin staining in the Bowman’s capsule; 7) an absence of cubical epithelial cells in the Bowman’s capsule, dilation of distal tubules, dilation of the glomerular capillaries and evidence of glomerular sclerosis and fibrosis. There was prominent glomerular hemorrhage with aneurysms and evidence of perivascular, peritubular, and periglomerular infiltration of inflammatory cells; 8) misplaced Acta2 staining in the intraglomerular mesangium, interstitium, and Bowman’s capsule.

Conclusions: Our results suggest a role of Gata3 in the identity of the cells of the renin lineage.

Funding: NIDDK Support

SA-PO346

Repetitive Administration of Cultured Human CD34+ Cells Improve Adenine-Induced Kidney Injury in Mice

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Background: There is no established treatment to impede the progression of diabetic kidney disease in human.

Methods: We evaluated the efficacy of cultured human CD34+ cells with enhanced proliferative potential in chronic kidney injury model in mice. Human umbilical cord blood (UCB)-derived CD34+ cells were incubated for one week in vasculogenic conditioning medium. This culture method significantly increased the number of CD34+ cells (60-fold) and their ability to form endothelial progenitor cell colony-forming units (40-fold). Adenine-induced tubulointerstitial chronic kidney injury was induced in NOD/SCID mice, and cultured human UCB-CD34+ cells were administered at a dose of 1 × 10⁶ mouse on days 7, 14, and 21 after the start of adenine diet (cell therapy group n=18). In the control group (n=17), vehicle was administered at the same time point. Time-course of kidney function, pathological damage, and CD31-positive peritubular capillary density and macrophage infiltration in the kidney at the time of sacrifice (day 28) were evaluated.

Results: Repetitive administration of cultured UCB-CD34+ cells significantly improved the time-course of serum creatinine levels in the cell therapy group compared with that in the control group (1.09 ± 0.09 mg/dL vs 1.41 ± 0.14 mg/dL on day 28, p<0.05). Both interstitial fibrosis area and tubular injury score were significantly reduced in the cell therapy group compared with that in the control group (interstitial fibrosis: 8.1 ± 5.4% vs 16.3 ± 7.0%, p<0.01; tubular injury score: 1.48 ± 2.78 vs 2.31 ± 1.0, p<0.05). Peritubular capillary density was significantly preserved in the cell therapy group compared with that in the control group (57.3 ± 6.4% vs 31.0 ± 6.1%, p<0.01). Macrophage infiltration in the kidney tissue was dramatically decreased in the cell therapy group compared with those in the control group (1.3 ± 0.3% vs 14.4 ± 1.1%, p<0.001).

Conclusions: Repetitive administration of cultured human UCB-CD34+ cells significantly improved kidney dysfunction and chronic tubulointerstitial damage in adenine-induced kidney injury in mice via the protective effect of microvascular integrity and anti-inflammatory effects. A clinical trial using cultured human UCB-CD34+ cells for progressive kidney disease might be expected.

SA-PO347

A Clinical Trial of Comprehensive Regenerative Treatment for Acute and Chronic Kidney Injury by Autologous Granulocyte-Colony Stimulating Factor (G-CSF)-Mobilized Peripheral Blood-Derived CD34+ Cells Administration

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Background: Stem cell-based therapy as a potential alternative to conventional drug therapy for kidney diseases has attracted significant attention. While mesenchymal stem cells have been extensively studied in early clinical trials for various kidney diseases, research on urine-derived stem cells (UDSCs) remains limited. This study aims to evaluate the efficacy of UDSC administration in improving Adriamycin (ADR)-nephropathy using both in vivo and in vitro models. UDSCs were cultured in a 2D and 3D setting. The urine albumin/creatinine ratio (ACR) was measured on days 0, 7, 14, and 21, and kidney function.

Methods: Autologous G-CSF-mobilized peripheral blood-derived CD34+ cells were administered to 10 week-old male BALB/c mice divided into four groups: sham, ADR, ADR+HS (single dose of UDSC), ADR+HM (three doses of UDSC) to establish the in vivo model. ADR administration was done on day 0, followed by UDSC administration on days 7, 14, and 21. Kidney function was assessed by urine albumin/creatinine ratio (ACR).

Results: ADR induced a significant increase in ACR compared with the sham group. ADR+HS and ADR+HM groups showed a significant decrease in ACR compared with the ADR group after 21 days. ADR+HM group showed the most significant decrease in ACR compared with the ADR group. ADR+HM group showed the most significant decrease in ACR compared with the ADR group.

Conclusions: ADR+HM group showed the most significant decrease in ACR compared with the ADR group.
Development, Organoids, Vascularized Kidneys, Nephrons, and More

Conclusions: Our findings suggest that the increase of Treg cells induced by enhanced differentiation, oxidation, and protein-energy wasting. These results provide insights into the potential role of these adipose tissue changes in the systemic conditions associated with CKD.

Funding: Government Support - Non-U.S.

SA-PO353

Comparison of Therapeutic Effects of Adipose- and Bone Marrow-Derived Mesenchymal Stem Cells on Renal Fibrosis
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Background: Mesenchymal stem cells (MSCs) exert the anti-inflammatory effect by secreting various humoral factors, which contribute to the regeneration of damaged tissues. Among these factors, adiponectin (Adipo-2/3) can enhance the anti-inflammatory effects of MSCs and the enhancement of regulatory T (Treg) cell induction is thought to be an underlying mechanism. In this study, we investigated the effects of Treg cell induction by IFN-γMSCs on renal inflammation and fibrosis.

Methods: Rats were subjected to contralateral nephrectomy and unilateral renal ischemia reperfusion injury (IRI) by clamping the renal artery. Subsequently, phosphate-buffered saline, untreated MSCs (control MSCs), or IFN-γMSCs were administrated to the renal artery. At 7 or 21 days after administration, rats were sacrificed and their kidneys were used to examine renal inflammation and fibrosis. In addition, in vitro experiments were performed to examine expression levels of indoleamine 2,3-dioxygenase (IDO), the key regulator of Treg cell induction, in IFN-γMSCs. Finally, we examined the therapeutic effects of IFN-γMSCs transplanted with IOD1 siRNA in IRI rats.

Results: Administration of IFN-γMSCs induced Treg cell levels and inhibited infiltration of inflammatory cells in IRI rats more drastically than control MSCs. In addition, administration of IFN-γMSCs more significantly attenuated renal fibrosis compared with administration of control MSCs. IFD expression levels in conditioned medium from MSCs were enhanced by pretreatment with IFN-γ. Functional experiments demonstrated that KO1 knockdown in IFN-γMSCs reduced their anti-inflammation- and anti-fibrotic effects in IRI rats by reducing Treg cell induction.

Conclusions: These results suggest that IFN-γMSCs may potentially be a useful therapy to prevent renal fibrosis progression.

SA-PO352

Tonsil-Derived Mesenchymal Stem Cells Alleviate Gentamicin (GM)-Induced AKI by an Amelioration of Oxidative Stress and Apoptosis via an Incorporation into Damaged Renal Tubules
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Background: The therapeutic effect of mesenchymal stem cells (MSCs) in repairing damaged renal cells in AKI has been demonstrated. Human palatine tonsil is an attractive alternative high-yield source of adult stem cells since they are readily available from surgically removed tissue. The aim of this study is to investigate the therapeutic potential of T-MSCs in GM-induced AKI.

Methods: Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, intraperitoneal injection for 10 days), GM-TMSCs (1×10^6 cells, intravenous injection at 1 day after the GM injection), and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histological analysis including TUNEL staining were performed on 16 days of GM injection. Effects of T-MSC on renal tubular cells was also evaluated using a transwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H_2O_2 generation, NOX mRNA expressions with DCF-DA staining.

Results: The infusion of T-MSCs in GM-induced AKI rats preserved renal function with a decrease in proteinuria. T-MSCs injection decreased apoptotic cells and the expression of Bax, cytochrome C, and cleaved caspase and increased Bel-2. T-MSCs suppressed oxidative stress as reflected by a decrease in the level of urinary 8-OHdG with an increased antioxidative enzyme (glutathione peroxidase and catalase) in the kidneys. Anti-human nuclei and PKH-26 stained demonstrated the localization of T-MSCs in the tubules of renal cortex. In vitro study revealed that T-MSC or T-MSC-conditioned media ameliorated GM-induced NOX-1 expression, H_2O_2 generation, and apoptosis of NRK cells.

Conclusions: Our study demonstrated that T-MSCs ameliorated GM-induced AKI by directly incorporating into the damaged renal tubules, exerting anti-apoptotic and anti-oxidative effects.

Funding: Government Support - Non-U.S.

SA-PO350

Depot-Specific Alterations in Visceral Adipose Tissue-Derived Mesenchymal Stem Cells in CKD: Insights from Single-Cell RNA Sequencing
Ayumu Tanaka,1 Kisho Miyasaki,1 Yoshiki Tanaka,1 Keisuke Morimoto,1 Kensuke Sasaki,1 Takao Masaki,1 Hiroshima Daigaku Byoin, Hiroshima, Japan; 2Yamanashi Daigaku Igakubu Fuzoku Byoin, Chuo, Japan

Background: While previous studies have explored inter-organ communication to understand these effects in IRI rats by reducing Treg cell induction.

Methods: We identified depot-specific alterations in ADMSCs and adipose tissue characteristics in CKD patients. Further investigations were needed to elucidate the potential role of these adipose tissue changes in the systemic conditions associated with CKD.

Funding: Government Support - Non-U.S.
SA-PO354
Selected Renal Cells Improve Renal Function in a Canine Model of CKD
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Background: Selected renal cells (SRCs) express podocyte, ueretic bud and cap mesenchyme markers associated with glomerular barrier function, renal filtration and urine concentration. In the present study we tested the hypothesis that cortical administration of autologous SRCs improves renal filtration and preserves renal microarchitecture in the canine subtotal nephrectomy (Nx) model of renal hypertensive chronic kidney disease.

Methods: SRCs were sourced from the excised contralateral kidneys of adult male mongrel dogs subjected to Nx. At weeks 15 and 43 post Nx, dogs were administered SRCs (~300x10^5 cells/dog) into the remnant renal cortex, n=4) or placebo (n=4). Renal filtration was monitored over weeks 44 through 57 and renal microarchitecture (Masson’s Trichrome) evaluated at sacrifice. A sham cohort served as control.

Results: There was no difference between the two Nx cohorts prior to randomization. SRC treatment was associated with increased body weight (p<0.01), reduced urine protein (p<0.01) and urine protein to creatinine ratio (p<0.01), and improved serum albumin (p<0.01) and creatinine clearance profiles (p<0.05, A-D). SRCs did not reduce blood pressure, rather their activity appeared to be directly related to preservation of renal microarchitecture evidenced by reduced - glomerular hypertrophy, tubular dilatation, cast deposition, inflammation and fibrosis (E).

Conclusions: These data suggest that SRCs, a standalone cell-based platform, has anti-inflammatory and anti-fibrotic activity and preserves glomerular and tubular microarchitecture and improves multiple indices of renal function in a large animal model of renal disease.

Funding: Commercial Support - ProKidney

SA-PO355
Renal Involvement After Pediatric Liver Transplantation: A Large Single-Center Cohort
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Orith Waisbourd-Ziman,2,4 Orly Haskin,3 Shelly S. Levi,3 Daniel Landau,3
Hadas Alfantady,2,3 ’Schneider Children’s Medical Center of Israel Department of Internal Pediatrics A, Petah Tikva, Israel; ’Schneider Children’s Medical Center of Israel Institute of Pulmonology, Petah Tikva, Israel; ’Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Israel; ’Schneider Children’s Medical Center of Israel Institute of Gastroenterology Nutrition and Liver Diseases, Petah Tikva, Israel; ’Schneider Children’s Medical Center of Israel Institute of Nephrology, Petah Tikva, Israel.

Background: Survival after pediatric liver transplantation has increased dramatically over the years, revealing extra-hepatic complications including impaired renal function. We conducted a large single center retrospective study to evaluate thoroughly renal outcomes after pediatric liver transplantation.

Methods: Pre and post-transplant data was collected from electronic charts of participants > 18 years and compared to the same participants prior to age 18.

Results: Among 313 participants who attained age 18 with an average GFR of 47 mL/min/1.73m2, the prevalence of high blood pressure (BP) was 38% among young adults (864 person-visits) with a median age of 19.8 [IQR: 18.8, 21.1], compared to 26% among the same participants prior to age 18 (1332 person-visits) at a median age of 15.2 [12.8, 16.7] with an average GFR of 50. There were no significant differences in obesity (21% vs. 19%) or hyperglycemia (6% vs. 7%). Older age was associated with an unadjusted prevalence odds ratio for high BP of 1.70 (95%CI: 1.40 to 2.09), which remained significant in an adjusted model (OR: 1.63, 1.30 to 2.04).

Conclusions: Among young adults with pediatric CKD who had not reached ESKD, the prevalence of high BP was significantly higher compared to when they were younger. Adult nephrologists receiving patients with pediatric CKD should be vigilant for the potential worsening of BP control during the transition period.

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

SA-PO356
Increasing Cardiovascular Burden Among Young Adults with Pediatric CKD at Time of Transition to Adult Care
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Background: Transition to adult care for young adults with pediatric chronic kidney disease (CKD) is critical phase of clinical care and may present challenges for cardiovascular disease (CVD) management. To investigate CVD burden among young adults, we assessed the prevalence of cardiovascular and metabolic comorbidities among participants > 18 years and compared to the same participants prior to age 18.

Methods: Using data from the Chronic Kidney Disease in Children (CKiD) study, we estimated prevalence of high blood pressure (elevated, Stage 1 or 2), obesity, and hyperglycemia before and after age 18 among those who reached young adulthood free of ESKD. Logistic models with generalized estimating equations for prevalence odds ratios (older vs. younger) for each comorbidity, adjusting for GFR, proteinuria and diagnosis.

Results: Among 313 participants who attained age 18 with an average GFR of 47 mL/min/1.73m2, the prevalence of high blood pressure (BP) was 38% among young adults (864 person-visits) with a median age of 19.8 [IQR: 18.8, 21.1], compared to 26% among the same participants prior to age 18 (1332 person-visits) at a median age of 15.2 [12.8, 16.7] with an average GFR of 50. There were no significant differences in obesity (21% vs. 19%) or hyperglycemia (6% vs. 7%). Older age was associated with an unadjusted prevalence odds ratio for high BP of 1.70 (95%CI: 1.40 to 2.09), which remained significant in an adjusted model (OR: 1.63, 1.30 to 2.04).

Conclusions: Among young adults with pediatric CKD who had not reached ESKD, the prevalence of high BP was significantly higher compared to when they were younger. Adult nephrologists receiving patients with pediatric CKD should be vigilant for the potential worsening of BP control during the transition period.

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

SA-PO357
Food Insecurity Is Associated with Short Stature, Slow Growth Velocity, and Lower Cognitive Function in the Chronic Kidney Disease in Children (CKiD) Cohort
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Background: Food insecurity is defined as the state of being without reliable access to an adequate amount of affordable and nutritious food. Food insecurity is associated with disparities in chronic kidney disease in adults; however less is known in children.
Methods: The Chronic Kidney Disease in Children (CKiD) study is a multicenter, observational cohort of children with eGFR 30-90ml/min/1.73m². Food insecurity screening was added in 2022 via the Hunger Vital screen. Cross-sectional analyses used Wilcoxon rank-sum test or Fisher’s exact test, as appropriate, to determine the association between food insecurity and disease outcomes related to growth and cognition.

Results: Of the 181 participants included, 9% of subjects (n=17) reported food insecurity. Food insecure subjects had a median age of 9.7 (IQR: 8.4-17.9), median GFR of 42 (IQR, 26, 66), 53% were male, and 18% had glomerular disease. Food insecure patients had a higher prevalence of short stature and lower growth velocity. None of these patients were on growth hormone; however, food insecure patients were significantly more likely to be seen by a nutritionist (p=0.003). Food insecure patients performed worse on IQ tests (mean 89 vs 102, p<0.03) and were from households with lower income and maternal education. Follow-up analyses found the effect of food insecurity on IQ to be independent of pediatric education.

Conclusions: Children with CKD and food insecurity, which is frequently associated with lower household income, and lower maternal education, are more likely to present with impairments in growth and lower performance on IQ testing. This study highlights the need to screen for food insecurity as early identification and intervention may improve CKD-related health outcomes. Further analyses will investigate the impact of food insecurity on longitudinal outcomes of CKD progression and cardiovascular factors.

Funding: NIDDK Support

SA-PO358

Performance of CKD-EPI GFR Estimating Equations in a Cohort of Young Adults with Pediatric CKD

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Background: The Chronic Kidney Disease in Children (CKiD) study previously documented an overestimation bias by the 2009 age-sex-race CKD-EPI equation among young adults aged 18 to 24 with a history of pediatric CKD. However, the recently updated 2021 race-free CKD-EPI equations have not been evaluated among young adults with a history of pediatric CKD.

Methods: Using CKiD data from young adults 18 to 25 years, we evaluated three CKD-EPI equations: 2021 SCR (with age and sex); AS, 2012 Cystatin C, and the 2021 SCR-Cystatin C (AS) Bias (eGFR - mGFR), accuracy (proportion within 10% and within 30%) and root mean square error (RMSE) were estimated.

Results: Among 313 person-visits, the median age was 19.4 years [IQR: 18.6, 20.6] and the median mGFR was 44.8 ml/min/1.73m² [IQR: 31.3, 65.1] Table 1 summarizes agreement metrics. The average biases were +8.81 (95%CI: +7.09, +10.53), +5.73 (+2.04, +5.41), and +4.31 (+2.84, +5.78) for the SCR-Cystatin C, and combined CKD-EPI equations, respectively. The proportion of eGFR within 30% of mGFR was 69.0%, 78.3% and 81.5%, respectively. The lowest RMSE was observed for the combined equation (11.75) and the creatinine-based and cystatin C-based equations RMSEs were 14.83 and 14.03, respectively.

Conclusions: Application of the new CKD-EPI SCR equation to CKiD data demonstrated overestimation of measured GFR and high root mean square errors. The cystatin-based and combination equations performed better than creatinine alone. As previously published, the race-free CKD-EPI U25 equations had no significant bias (range: -0.89 to -0.70) and p30 between 85-90% among young adult participants, but performance is expected to be better in internal validation because it randomly differed from the data used to develop the U25 eGFR. For pediatric CKD patients transitioning to adulthood, care needs to be increased when using disparity equations that yield abrupt differences in estimates of GFR. Use of U25 eGFR through 25 years is recommended for this population.

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

Agreement between CKD-EPI eGFR and mGFR (bias, p10, p30, and root mean square error (RMSE) among 208 young adults participants in CKiD (≥ 18 years) with 313 assessments of mGFR

<table>
<thead>
<tr>
<th>CKD-EPI eGFR</th>
<th>mGFR 60-90 ml/min/1.73</th>
<th>mGFR 45-59 ml/min/1.73</th>
<th>mGFR 30-44 ml/min/1.73</th>
<th>mGFR 15-29 ml/min/1.73</th>
<th>RMSE (ml/min/1.73²)</th>
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<tbody>
<tr>
<td>2021 SCR only</td>
<td>0.41 (1.07)</td>
<td>0.40 (1.05)</td>
<td>0.33 (1.03)</td>
<td>0.31 (1.02)</td>
<td>9.06</td>
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<tr>
<td>2012 Cystatin C only</td>
<td>1.77 (2.04)</td>
<td>2.10 (2.09)</td>
<td>2.36 (2.07)</td>
<td>2.70 (2.10)</td>
<td>14.55</td>
</tr>
<tr>
<td>2021 SCR-Cystatin C</td>
<td>1.77 (2.04)</td>
<td>2.10 (2.09)</td>
<td>2.36 (2.07)</td>
<td>2.70 (2.10)</td>
<td>14.55</td>
</tr>
<tr>
<td>Combined</td>
<td>4.51 (2.36)</td>
<td>4.51 (2.36)</td>
<td>4.51 (2.36)</td>
<td>4.51 (2.36)</td>
<td>11.75</td>
</tr>
</tbody>
</table>

SA-PO359

Development of an Adaptive Clinical Web-Based Prediction Tool for Kidney Replacement Therapy in Children with CKD

Derek K. Ng,1 Matthew Matheson,2 George J. Schwartz,2 Susan R. Mendley,2 Susan L. Furth,3 Bradley A. Warady,4 Chronic Kidney Disease in Children Study.

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Background: Clinicians need improved prediction models to estimate time to kidney replacement therapy (KRT) for children with chronic kidney disease (CKD). We aimed to a) develop and validate a prediction tool using clinical variables for time to KRT from the Chronic Kidney Disease in Children (CKiD) study using statistical learning methods and b) to design an online calculator for clinical use.

Methods: We constructed an elementary model using eGFR, proteinuria and diagnosis as predictors in a parametric generalized gamma (GG) survival model and used penalized likelihood to identify optimal nonlinear combinations of these three. We then used random survival forest (RSF) to identify additional candidate predictors from a large panel of demographics and clinical markers. From the top predictors we used best subset selection, a learning method, to identify the best combination in an enriched GG model.

Results: Among 890 children, 9 candidate predictors were identified from 172 variables in RSF which were added to the elementary model. Best subset selection yielded an enriched model additionally based on blood pressure, 1 year change in eGFR, anemia, albumin, chloride and bicarbonate. Four additional partially enriched models were constructed for clinical situations with incomplete data and integrated as an adaptive tool (Figure). Discrimination was high in cross-validation (c= 0.86) and in an external European cohort (c= 0.85) with strong calibration. We designed an adaptive online tool for clinical use.

Conclusions: This clinical prediction tool for time to KRT in children was developed in a large, representative pediatric CKD cohort with an exhaustive evaluation of potential predictors and statistical learning methods. While models performed well internally and externally, further external validation of enriched models is needed.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI, Other U.S. Government Support

SA-PO360

Validating CKiD U25 eGFR Equations for Differing Body Habitus

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Background: The Chronic Kidney Disease in Children (CKiD) U25 eGFR equations provide unbiased estimates of glomerular filtration rate (eGFR) and strong levels of agreement with measured GFR (mGFR) for CKD patients 1-25 years old. However, the performance of these equations by body habitus has not been assessed.

Methods: Data were from the CKiD U25 validation set comprising 832 observations from 302 participants. Median age was 12 [IQR: 8.16] years and median mGFR was 44 [32.61] ml/min/1.73m². We evaluated three U25 equations: creatinine, cystatin C and the average of the two. Within BMI categories (underweight, normal weight, overweight, obese), we summarize agreement as mean bias (eGFR-mGFR) and percent of eGFR within 30% of mGFR (P30). Mean bias was calculated from a mixed effects model to account for multiple observations per participant.

Results: All equations overestimated GFR in overweight subjects with the two cystatin C-based equations exhibiting statistically significant biases which persisted after adjustment for age and sex. The creatinine-based equation had lower P30 values in underweight compared to non-underweight subjects; these biases were not significantly different than those in the normal weight subjects after adjustment. There was no bias observed in the obese category, suggesting this bias may not be a direct function of larger body habitus for age and sex. All three equations yielded lower P30 values in underweight compared to non-underweight subjects.

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

Underline represents presenting author.

821
Conclusions: U25 eGFR slightly overestimated mGFR in underweight compared to normal weight children, whereas U25 eGFR(r) showed the smallest bias of the three equations in this BMI group. The U25 equations performed well in non-underweight children, adolescents and young adults with CKD.

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

SA-PO361
Neonatal Risk Factors for CKD Progression in Children
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Background: Neonatal risk factors for childhood CKD include prematurity, acute kidney injury (AKI), and sepsis. It is not known how these factors, assessed in the 1st 90 days of life, are associated with early childhood kidney function in children with congenital kidney diseases.

Methods: Neonatal data including gestational age (GA); AKI or sepsis in first 90 days; and serum creatinine (SCr) at discharge was retrospectively collected on Chronic Kidney Disease in Children (CKiD) cohort study participants with congenital abnormalities of the kidneys and urinary tract and other congenital kidney diseases. Participants with ≥1 CKiD study eGFR in follow up were included. SCr at NICU discharge was indexed to published mean SCr for GA and postnatal age (PMID: 34142253). We assessed univariate relationships between each predictor and incidence of eGFR<30 mL/min/1.73m² by age 5 years (eGFR<30), and parametric survival time for eGFR<30 mL/min/1.73m² (eGFR<30).

Results: 123 children (71% male; median [IQR] baseline age 3.0 [1.7, 4.3] y) had available neonatal data. 36% were premature (GA<37 weeks). Median [IQR] birth weight was 3.13 [2.60, 3.46] kg; discharge age was 21 [7, 40] days;median discharge SCr was 1.00 [0.65, 1.55] mg/dL; discharge SCr index was 3.3 [2.0, 4.5]. 40% had history of AKI; 13% had history of sepsis. Prematurity, AKI, and sepsis were not associated with risk of eGFR<30; SCr index >3.5 at discharge was associated with 52% earlier time to eGFR<30. Cumulative incidence of eGFR<30 was 21% for participants with discharge SCr index ≥3.5 and 47% for those with discharge SCr index >3.5 (Figure 1).

Conclusions: SCr index >3.5 by 90 days of age was associated with a significantly higher risk of eGFR<30 mL/min/1.73m² by age 5 years in children with congenital kidney diseases in the CKiD cohort. Prematurity, AKI, and sepsis were not associated with CKD progression risk in this cohort.

Funding: NIDDK Support

SA-PO362
Ultrasound-Based Machine Learning Model and Renal Parenchymal Area as Predictors of Kidney Function Decline in Children with CKD

Background: Few prediction models of kidney function decline include imaging features. Here, we apply machine learning-calculated renal ultrasound features and compare the performance to renal parenchymal area (RPA) in the Chronic Kidney Disease in Children (CKiD) cohort study.

Methods: We determined the predictive performance of a previously developed machine learning algorithm among 119 subjects with non-glomerular chronic kidney disease (CKD) enrolled at 14 sites in the prospective CKiD study. The primary outcome was CKD progression defined as initiation of renal replacement therapy or 50% decline of estimated glomerular filtration rate (eGFR) assessed by the CKiD U25 equation. We assessed the predictive performance of three different models: (1) Clinical model (CM), (2) Deep Learning model (DLM), and (3) Deep Learning + Clinical model (DL+CM). The CM included baseline clinical features: age, eGFR, systolic blood pressure, urine creatinine, urine protein, and serum creatinine. The DLM used features extracted automatically from the first available kidney ultrasound. In a subset of 46 subjects, we compared the performance of ensemble models (3) DL+CM to (4) RPA + Clinical model (RPA + CM). The RPA model included age and the mean RPA values measured by an attending urologist and nephrologist blinded to outcomes. We used a random survival forest model to estimate CKD progression.

Results: Ninety-one subjects with a median age of 11.5 months, IQR [0.2, 78.2] at ultrasound were included in the DL+CM. CKD progress occurred for 20% over a median follow-up of 9 yrs, IQR [3.8, 9.7]. For the subset of 46 subjects, median age at ultrasound was 9.7 months, IQR [1.4, 79.3] and CKD progression occurred in 28% over a median follow-up of 6.4 yrs IQR [4.1, 9.2]. Of the models presented, the DL+CM and RPA + CM had the best performance with C-index of 0.74 and 0.77, respectively.

Conclusions: Our ensemble models accurately predicted CKD progression using imaging features in children with CKD. The comparison of the performance of deep learning features and RPA was limited by the small sample size. These results in a prospectively enrolled cohort suggest that early ultrasound imaging features could identify children at greatest risk of CKD progression in clinical practice.

Funding: NIDDK Support

SA-PO363
Ultrasound Evaluation of Fibrosis in Pediatric Kidney Transplant Recipients

Background: To evaluate doppler resistive indices, ultrasound elastography, and contrast ultrasound as imaging biomarkers of fibrosis in pediatric kidney transplants.

Methods: A prospective study of children with kidney transplant and healthy controls was conducted from February 2020 to May 2023. All subjects underwent ultrasound with spectral Doppler to measure resistive indices (RI) and shear wave elastography to assess renal stiffness. RI were assessed in the upper, interpolar, and lower poles and median elastography values were averaged from 10 regions of interest. Kidney transplant recipients undergoing clinically indicated biopsies underwent contrast-enhanced ultrasound (CEUS) and Time-Intensity Curves were generated. CEUS time to peak, peak enhancement, perfusion index, area under the curve, and mean transit time were examined. All kidney allografts were classified as with interstitial fibrosis and tubular atrophy (IFTA) or without IFTA based on histopathology. Subjects with rejection were excluded. Kruskal-Wallis was used to compare RI and elastography between the three groups. Bland-Altman test was used for post-hoc analysis. For the CEUS studies, Mann-Whitney analysis was used to compare allografts without vs. with fibrosis.

Results: Sixteen healthy control kidneys were examined among 8 subjects with median age 14.5 yrs. Among 11 kidney allografts, six (54.6%) were from living donors; median recipient age 16 yrs. Of the 11 allografts, 4 (33.3%) had IFTA (all grade 1). We found no difference in resistive indices (p=0.53) between allografts without vs. with fibrosis, or controls. Elastography measures differed between controls and all allografts (p=0.01); but did not differ between allografts with or without fibrosis. Among subjects with CEUS, mean transit time was the only parameter significantly prolonged in the allografts with fibrosis (vs. those without) (p=0.04).

Conclusions: In this cohort, RIs did not differ between groups. Tissue stiffness, by elastography, differed between controls and allografts but not between those with and those without fibrosis. CEUS detected differences in mean transit time between allografts with vs. without fibrosis, suggesting CEUS may be a sensitive biomarker to detect fibrosis. A larger sample and longitudinal data are needed for validation.

Funding: NIDDK Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO364

Longitudinal Changes of Left Ventricular Diastolic Function and Fibroblast Growth Factor 23 in Young Hemodialysis Patients

Wacharee Seeherunvong, Chryso P. Katsoufis, Marissa J. Defreitas, Sethuraman Swaminathan, Carolyn L. Abitbol, Michael Freundlich. University of Miami School of Medicine, Miami, FL.

Background: Left ventricular diastolic dysfunction (DD) occurs early in patients on hemodialysis. Both traditional factors like hypertension and non-traditional factors including fibroblast growth factor-23 (FGF23) levels, erythropoietin, and treatment with vitamin D receptor activators such as paricalcitol may affect the progression of DD. Our objectives were to investigate the association of longitudinal changes of diastolic function with FGF23 levels and treatment with paricalcitol and erythropoietin in young dialysis patients.

Methods: Conventional and tissue Doppler imaging measurements and their respective age-adjusted Z-scores were used to measure early (E), late (A) diastolic transmural flow velocities, corresponding mitral annular tissue velocities (e' and a'), and to evaluate DD in 20 young hemodialysis patients age 16.7±3.6 years. DD was defined as an abnormal Z-score of E, A, E/A or E/e' ratios. We analyzed associations of longitudinal DD changes with sequencially measured FGF23 levels, and with doses of erythropoietin and paricalcitol administered while on maintenance hemodialysis throughout a period of 7.1±2.1 months.

Results: Compared with the standardized healthy age-matched controls, echocardiographic markers of diastolic function by Z-score cutoff revealed DD in 93% at baseline and 90% at follow-up. FGF23 levels were markedly elevated at baseline and follow up (25.238±30.244 and 19.153±25.191 RU/ml, respectively). FGF23 levels correlated only with the baseline mitral E/e' ratio, but not with any other measurement of diastolic function. Hypertension correlated with DD. Paricalcitol dose was associated with improved diastolic function while erythropoietin dose showed no correlation with FGF23 or diastolic function.

Conclusions: In young hemodialysis patients, DD is highly prevalent. Elevated FGF23 levels and hypertension may contribute to DD. Erythropoietin is neither associated with FGF23 levels nor with DD while paricalcitol may attenuate DD.

SA-PO365

Urine Proteomic Profiling and Insights into CKD Progression in Children

Jason H. Greenberg,1 Arthur Lee,2 Josef Coshesh,2 Bradley A. Warady,3 Josephin H. Ix,4 Sau-Ying L. Firth,2 Michelle Denburg,2 Yale University, New Haven, CT; 1The Children’s Hospital of Philadelphia, Philadelphia, PA; 2Johns Hopkins University, Baltimore, MD; 3Children’s Mercy Kansas City, Kansas City, MO; 4University of California San Diego, La Jolla, CA.

Background: Chronic kidney disease (CKD) progresses to end stage kidney disease (ESKD) and is associated with mortality rates that are 30-150 times higher than in the general pediatric population. We hypothesized that large scale proteomic measurements may provide insights to the molecular basis of CKD progression in children and may identify therapeutic protein targets.

Methods: In the CKiD Cohort Study, children with CKD were enrolled and eGFR was assessed annually. Among participants with an eGFR of 60-90 ml/min/1.73m2 at baseline, 22 CKiD participants with CKD progression were matched by subtype of kidney disease to 22 CKiD participants without CKD progression. The primary outcome of CKD progression was defined as a composite of 50% decline in eGFR or ESKD. We measured 2044 urine proteins collected at the 6 month visit after enrollment using the Olink Proteomics Explore Assay.

Results: Of the 44 children included, the median age was 12 years, 66% were male, 68% had a glomerular cause of CKD, and baseline eGFR was 68 [IQR, 63, 81] ml/min/1.73m2. In the full cohort, 38/2044 proteins were statistically significantly different (p-value cutoff of 0.000017 using the Bonferroni correction) when comparing those with CKD progression to those without CKD progression (Table). B-cell activating factor, Complex I (C1), C5, all druggable targets, were more than 10-fold higher in children with CKD progression relative to those without progression. Pathway analyses demonstrated that TGF-B1, TNF, IL-1β, IL-4, IFN-γ, and angiotensinogen were key pathways activated in children with CKD progression.

Conclusions: Many urine proteins were elevated, and pro-inflammatory and pro-fibrotic pathways were upregulated in children with CKD progression. The application of large-scale proteomics to the study of CKD in children may inform pathomechanisms and identify novel therapeutic targets.

Funding: NIDDK Support

Top proteins of CKD progression by adjusted p-value using the Olink Proteomic Assay

SA-PO366

Serum FGF23 and Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the CKD in Children Cohort

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Background: Prognosis of chronic kidney disease (CKD) is closely related to early diagnosis and initiation of nephroprotective measures. Current kidney injury biomarkers are suboptimal for predicting kidney disease progression. Fibroblast Growth Factor Factor 23 (FGF23) is well described as an early marker that increases proportionally to worsening CKD stages in adults. Neutrophil gelatinase-associated lipocalin (NGAL) is known to increase early after acute kidney injury, as a marker of AKI severity, however, it has not been validated as an early marker in CKD. The aim of this study is to investigate the association between FGF23, NGAL and glomerular filtration rate (GFR) in children and evaluate their role in ascertaining moderate to severe CKD.

Methods: Children aged 5 to 20 years old requiring kidney function assessment following primary nephropathy, solid organ transplantation or secondary nephropathy were enrolled prospectively in a tertiary hospital of Switzerland for a reference measurement of their GFR, with simultaneous measurement of plasma FGF23 and urinary NGAL.

Results: 123 clearances were analyzed, in children mostly post solid organ transplantation (46%) or with primary nephropathy (37%). 42% had stage I CKD, 40% had stage II CKD and 12% had stage III or IV CKD. FGF23 was significantly higher in stage III or IV CKD (mean: 282.02 UI/ml ± 174.71) compared to stage I (mean: 143.76 UI/ml ± 178.61; p<0.001) or stage II (mean: 104.61 UI/ml ± 63.52; p<0.001). The area under the ROC curve for FGF23 to discriminate CKD stages I-II versus III-IV was 0.864 (95% confidence interval (CI): 0.780-0.947). NGAL values were more elevated in stage III or IV CKD (mean: 103.65 UI/ml ± 129.43) compared to stage I (mean: 36.19 UI/ml ± 100.36; p<0.016) or stage II (mean: 44.86 UI/ml ± 104.66; p<0.082). The area under the ROC curve for NGAL to discriminate CKD stages I-II versus III-IV was 0.688 (95% CI: 0.512-0.864).

Conclusions: FGF23 is significantly associated with decreasing GFR in children and discriminates for the presence of moderate to severe CKD in children. NGAL was not as strongly associated as decreasing GFR. Further studies are needed to evaluate FGF23 and NGAL as markers of CKD progression.

SA-PO367

Association Between N-Terminal pro-B-Type Natriuretic Peptide with CKD Progression in the CKD in Children Cohort

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Background: Elevations in the serum biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) are strongly associated with CKD progression in adults. It is unknown whether these associations are also seen in children with CKD, and may help identify a novel risk factor in this population. The objective of this study was to examine the association of NT-proBNP with CKD progression in youth with mild to moderate CKD.

Methods: We measured serum NT-proBNP at the baseline visit of participants with available samples enrolled in the Chronic Kidney Disease in Children (CKiD) study (N=493). Included participants were aged 1-18 years with an eGFR of 30-90ml/min/1.73m2. Exclusion criteria included history of kidney transplant, dialysis < 3 months, or structural heart disease. CKD progression was defined as a 40% decline in eGFR and/or progression to ESKD. We utilized nested Cox proportional hazards model to test the association between baseline NT-proBNP with CKD progression.

Results: Mean ±SD baseline NT-proBNP and eGFR were 127 ±173pg/ml and 55 ±21ml/min/1.73m2, respectively. Median duration of follow-up was 3.9 years and 107 (22%) met criteria for CKD progression. In unadjusted models, NT-proBNP was
associated with CKD progression (HR, [95% CI] per doubling: 1.36, [1.18, 1.56]). NT-proBNP was not associated with CKD progression in a large, well-characterized cohort of youth with CKD. Potential explanations include physiologic differences across the lifespan and/or relatively short duration of follow-up.

**Funding:** Private Foundation Support

**SA-PO369**

**Health-Related Quality of Life for Pediatric Patients with ESKD:**

**A Systematic Review and Meta-Analysis of the PedsQL™**

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**Background:** The NAPRTCS dialysis registry includes 8923 children from the last 30 years. We aim to describe racial differences in this cohort.

**Methods:** Children on maintenance dialysis at a NAPRTCS center are enrollment eligible. Demographic and clinical data are obtained at dialysis initiation and every 6-months until dialysis terminates. Before 2018 race was categorized as white, black or Hispanic, but race (white, black, other) and ethnicity are now separate. Outcomes include dialysis modality, cardiovascular health, time to transplant and survival.

**Results:** Table 1 shows clinical characteristics at dialysis initiation. There were more white than black children on both peritoneal dialysis (PD) and hemodialysis (HD), although a higher % of blacks were on HD. Those initiating HD with catheter access were more likely white than black (43% vs 29%); no racial difference with AV fistulas (36% white and 36% black). Mean Kt/V and URR were higher for non-black than black race on HD (1.61 vs 1.55, and 72.6 vs 70.7), with similar findings for PD mean Kt/V (2.45 non-black vs 2.14 black). More blacks than non-blacks had hypertension (48% vs 35%), left ventricular hypertrophy (32% vs 29%), and hypercholesterolemia (60% vs 20%). Over time, whites were transplanted more than blacks when listed for deceased donor transplants (50% vs 30% at 12 months; 87% vs 75% at 36 months). In those remaining on dialysis, survival was slightly higher for whites than blacks (89% vs 86% at 36 months).

**Conclusions:** White children have higher rates of kidney developmental anomalies, whereas racial differences are absent with FSGS frequency. Whites receive PD more than non-whites, whereas blacks receive HD at higher rates. Whites are more likely to initiate HD with catheter access. Regardless of modality, blacks demonstrate lower dialysis adequacy and more cardiac health sequelae. Whites are transplanted quicker than blacks. In children remaining on dialysis, 36 month survival is near 90% in both blacks and whites. Further study is needed to understand these disparities and to ensure optimal outcomes for all chronically dialyzed children.

**SA-PO370**

**Clinical Outcomes in Children on Maintenance Dialysis: A Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry**

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**Background:** The NAPRTCS dialysis registry includes data on 8923 children receiving chronic dialysis.

**Methods:** Children on maintenance dialysis at any NAPRTCS center are eligible for registry enrollment. Data is collected at dialysis initiation and at 6-month intervals until dialysis termination. Clinical characteristics and outcomes compared across eras: 1992-2000, 2001-2010, 2011-2020.

**Results:** Hemodialysis (HD) as the initiating dialysis modality increased (34% in 1992-2000 versus 54% in 2011-2020), while peritoneal dialysis (PD) decreased (66% to 46%). HD catheters are placed in the jugular vein more often (87% in 2010-2020 vs 51% in 1992-2000). Use of double cuffed swan neck PD catheters placed with a downward oriented exit site increased over time (5% to 25%). Mean eGFR at dialysis initiation increased from 9.2 (1992-2000), to 11.2 (2011-2020) ml/min/1.73M². Obesity has increased over time (17% affected 2010-2020). Hypertension was common regardless of the era (55% in 2010-2020 vs 39% for entire cohort). Height remains suboptimal, with average height Z scores of -1.34 within a month of dialysis initiation falling to -1.62 at 24 months, with growth hormone use in 30% of PD and 16% of HD children. Survival at 36 months of dialysis was > 90% with children initiating dialysis > 6 years old vs 77% initiating < 1 year old. A Cox proportional hazards model adjusted for age at initiation showed survival improved with initiation after 2020 (p<0.01). Infection accounted for 22% of deaths on dialysis in 1992-2000 but only 15% in 2011-2020, whereas cardiopulmonary causes of death stayed steady at 22%. Death from infection was higher in PD vs HD (22% vs 16%, p<0.01), though annualized rates for penicillins fell from 0.95 (95% CI: 0.89-0.98) between PD initiations in 1992-1996 to 0.28 (0.21-0.35) between 2017-2022.

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

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Cumulative occurrence of transplant from the deceased donor waiting list increased, from 0.56% in 1992-2000 to 0.91% in 2011-2020.

Conclusions: Although survival on chronic dialysis has improved significantly over 30 years, hypertension, obesity, and growth delay in dialyzed children remain common morbidities. Infection rates and related mortality has decreased, but cardiopulmonary mortality has not, highlighting areas that can be improved upon in the future.

SA-PO371
Follow-Up of Low Estimated Glomerular Filtration Rate (eGFR) in Children in the US Military Health System (MHS)

James D. Oliver, Gregory H. Gorman, Robert Nee, Susan R. Mendley, Hardman Mancweek, Amanda Banaga, Alain K. Koyama, Yoshihisa Miyamoto, Fang Xu, Meda E. Pavkov, Tracey L. Koehlmoos. Uniformed Services University of the Health Sciences, Bethesda, MD; Defense Health Agency, Falls Church, VA; Walter Reed National Military Medical Center, Bethesda, MD; National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; Henry M. Jackson Foundation for the Development of the Military Medicine Inc, Bethesda, MD; Centers for Disease Control and Prevention, Atlanta, GA.

Background: For children, calculation of eGFR from serum creatinine (sCr) is typically not available in the electronic record and clinicians may fail to recognize an abnormal eGFR in the absence of previously known kidney disease. We retrospectively analyzed the extent of this issue in a large diverse pediatric population using the MHS Data Repository.

Methods: We extracted data for 1,561,622 children ages 1–17 enrolled in the MHS from 2016-2019, using the CKD-U5-25 equation to calculate eGFR. Low eGFR was defined as the first occurrence of either <75 or <60 mL/min/1.73m². Follow-up was defined as a repeat sCr ≥90 days after the low eGFR. Children with > 8 sCr measurements or with the first low eGFR obtained ≥90 days from the end of 2019 without follow-up were excluded from analysis.

Results: sCr was measured in 128,033 (8.2%) of children. After exclusions there was at least one eGFR <75 and one <60 mL/min/1.73m² in 15,395 (12.0%) and 3168 (2.5%) children, respectively (Table). Follow-up sCr ≥90 days after low eGFR was performed infrequently; it was obtained in 9.7% vs 12.4% of children with eGFR <75 vs. <60 mL/min/1.73m², respectively (2.5%) children, respectively (Table). Follow-up sCr ≥90 days after low eGFR was performed infrequently; it was obtained in 9.7% vs 12.4% of children with eGFR <75 vs. <60 mL/min/1.73m², respectively. First follow-up sCr at ≥90 days were obtained in 13.2% vs.11.6% of children, and no follow-up labs were obtained in 77.1% vs. 76.1%. For eGFR <75 mL/min/1.73m², absence of follow-up labs within 90 days was associated with female sex (odds ratio [OR], 95% confidence interval [CI]) = 1.2, 1.1–1.3, ages 5–9 vs. 1–4 OR, 95%CI=1.2, 1.3–1.4, ages 10–13 vs. 1–4 OR, 95%CI=1.3, 1.1–1.6), and Black vs. White race (OR, 95%CI=1.2, 1.1–1.4), sex, age, and race were not associated with lack of follow-up labs for GFR <60 mL/min/1.73m².

Conclusions: In the MHS, follow-up measurements of decreased eGFR in children were infrequent, suggesting a gap in recognition of reduced kidney function and a potential area for improvement. The views expressed in this abstract are those of the authors and do not reflect the official position of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense, the Department of Health and Human Services, or the US Government.

Funding: Other U.S. Government Support

SA-PO373
Pediatric Nephrology Workforce in the United States and Access to Waitlist Registration in Children with ESKD


Background: Nephrology is one of the pediatric subspecialties with the lowest workforce density in the US with minimal improvements noted over the last two decades. Pediatric nephrologists (PN) are critical partners in preparing children for kidney transplantation (KT), which is the preferred treatment modality. We hypothesized that geographic variations in the density of PN could correlate with variations in the time to waitlist registration and living donor kidney transplantation (LDKT).

Methods: Retrospective cohort study of children <18 years who developed ESKD between 2016 to 2021 among active PN in 40 states with a density of PN ≥0.27 PN/100,000, using the US Renal Data System (USRDS), an administrative database of incident and prevalent cases of ESKD in the Medicare population. We identified children on dialysis from USRDS between 2001 and 2016. Disease etiology was classified as glomerular (n=1,029), non-glomerular (n=701) and unknown (n=313) and comparisons were made across etiologies. Linear regression models determined the relationship between disease etiology and log-transformed LDL, HDL, triglyceride (TG) and total cholesterol (TC) levels levels drawn within 12 months of USRDS entry.

Results: The median (IQR) age of the cohort was 13 (17, 19.4). The majority of the cohort received HD as a primary modality and there were no differences between ESKD etiologies. Adjusting for age, gender, race/ethnicity, modality, time with ESKD and using non-glomerular etiology as the reference, glomerular disease [%95% CI] was associated with 21% (14.8, 26.5) higher LDL, 19% (14.7, 23.8) higher TC, and 22.3% (15.5, 29.5) higher TG (p<0.0001 for all). There was no significant difference in HDL.

Conclusions: Pediatric dialysis patients with ESKD from glomerular causes have higher levels of Total Cholesterol, LDL, and Triglycerides compared to children with ESKD from non-glomerular causes. The long-term impact of this unfavorable lipid profile requires further investigation.

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Persistent Increase in Serum Ferritin Levels Despite Converting to Permanent Vascular Access in Pediatric Hemodialysis Patients: Pediatric Nephrology Research Consortium Study

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Background: Our objective was to examine the change in serum ferritin levels after successful conversion to PVA among children who started hemodialysis (HD) using TCC.

Methods: Retrospective chart reviews were completed on subjects from 20 pediatric HD centers. All patients used TCC prior to PVA. Serum ferritin levels were collected at the creation of PVA and for two years thereafter. Statistical methods included hypothesis testing and statistical modeling after adjusting for relevant demographic variables.

Results: There were 11 (11%) arteriovenous grafts (AVG) and 87 (89%) arteriovenous fistulae (AVF). Their mean TCC use before PVA creation was 10.4 ± 17.3 months. Serum ferritin at PVA creation was elevated at 562.64 ± 492.34 ng/ml, further increased to 753.84 ± 561.54 ng/ml (p= <0.001) at first year and remained significantly elevated at second year 759.60 ± 528.11 ng/ml (p= 0.004). The serum ferritin levels did not show statistically significant linear association with respective serum hematocrit values. In a multiple linear regression model, there were three predictors of serum ferritin at first year PVA follow-up which showed significant association; steroid-resistant nephrotic syndrome as primary etiology (β = -438.93; 95% CI: [-845.41, -32.46]; p=0.035), being from a center enrolling >10 cases (β = 319.85; 95% CI: [2.02, 637.68]; p=0.049) and baseline serum ferritin level (β = 17.96; 95% CI: [3.38, 32.53]; p=0.017).

Conclusions: BIA-BCM can help guide the adjustment of clinical treatment regimens, and chronic dialysis children have some degree of improvement in hydration and nutritional status.

Exploring the Value of Assessing Hydration and Nutritional Status with Bioelectrical Impedance Analysis in Pediatric Chronic Dialysis
Qián Shèn, Hong Xù, Wèi Yuàn. Children’s Hospital of Fudan University, Shanghai, China.

Background: There is a lack of domestic and international clinical studies on the assessment of the hydration and nutritional status of children on dialysis by bioimpedance analysis-body composition monitor (BIA-BCM).

Methods: Children treated on dialysis in the nephrology department of the Children’s hospital of Fudan University between July 1, 2021 and December 31, 2022 were assigned. A total of 100 children were described before and after 3 days of their dialysis, including basic information, biochemical indicators, imaging findings, and BIA-BCM indicators, exploring the correlation between BIA-BCM indicators and clinical indicators.

Results: Totally, 86 children with peritoneal dialysis and 14 children with hemodialysis were included. In peritoneal dialysis group, 19.77% and 36.05% had mild and severe water overload; reduced LTI in 41.54% and increased LTI in 10.77%. In hemodialysis group, 35.71% with mild and severe water overload each; 3 cases with reduced LTI (Fig1). There was a significant linear relationship between BIA-BCM hydration indicators and clinical hydration indicators, and BIA-BCM nutritional indicators and clinical nutritional indicators (Fig2).

Conclusions: BIA-BCM can help guide the adjustment of clinical treatment regimens, and chronic dialysis children have some degree of improvement in hydration and nutritional status.
SA-PO377
Barriers to Growth Hormone (GH) Use in Children with CKD
Isabella M. Hendrickson, Caleb Berta, Alicia Diaz-Thomas, Margaret C. Hastings. The University of Tennessee Health Science Center College of Medicine, Memphis, TN.

Background: GH is safe and effective in improving height in children with CKD. The purpose of this study was to identify barriers to GH use for the treatment of short stature in children with CKD.

Methods: Retrospective chart review identified children treated in the nephrology clinic at Le Bonheur Children’s Hospital with estimated glomerular filtration rates (eGFR) ≤ 60 ml/min/1.73 m² by bedside Schwartz equation between January 1, 2017 until December 31, 2020. Children with age > 18 years were excluded. Of the 94 children on GH at the most recent visit were included regardless of age, eGFR, or height percentile. Children having serum creatinine and height recorded within 7 days of one another during the study period were assessed. Barriers were evaluated for children not on GH with height percentiles ≤ 5%

Results: 94 children were identified with eGFR ≤ 60 ml/min/1.73 m². The cohort was 30% female, 51% black/African American, 41% white, 5% Hispanic/Latino, and had a median age of 11 years. Obstructive uropathy (27%), renal dysplasia (19%), and focal segmental glomerulosclerosis (13%) were the most common causes of CKD. 80 (85%) were not on GH and 14 (15%) were prescribed GH. Of the 14 patients on GH, 13 (93%) were male and 11 (79%) were white. Of the children not prescribed GH, 25 children were not on GH and 14 (15%) were prescribed GH. Of the 14 patients on GH, 13 (93%) were male and 11 (79%) were white. Of the children not prescribed GH, 25 children had height percentiles ≤ 5% making them candidates for GH; there were 14 (56%) females, 13 (52%) black/African American, 9 (36%) white, and 2 (8%) Hispanic/Latino in this group. Barriers identified were missed appointments/lost to follow up (8), severe developmental delay (7), severe hyperparathyroidism (4), delayed growth not identified by clinician (2), perceived adverse reaction (1), liver transplant (1), family declined treatment (1), and family reported not able to obtain (1).

Conclusions: Education on the importance of routine follow up appointments with more aggressive efforts to reschedule missed appointments may be beneficial in improving use of GH in children with CKD. Additionally, further education of families may lead to better control of hyperparathyroidism and other sequelae of CKD. The utility of GH therapy in children with severe neurologic impairments and CKD deserves further study. Finally, higher use of GH in white male children may suggest racial and gender inequality in provision of this treatment.

SA-PO378
Cognitive and Social Functioning of Infants and Preschoolers with Mild to Moderate CKD
Stephen R. Hooper,1 Rebecca J. Johnson,2 Marc Lande,3 Lyndsay Harshman,4 Sharon M. Bartosh,5 Cynthia Wong,6 Joann M. Carlson,5 Camille Wilson,5 Anne E. Dawson,5 Stephen J. Moltior,5 Matthew Matheson,2 Bradley A. Warady,2 Susan L. Furth,1 CKID Study. The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; 1Children’s Mercy Kansas City, Kansas City, MO; 2University of Rochester Medical Center, Rochester, NY; 3University of Iowa Hospitals and Clinics, Iowa City, IA; 4University of Wisconsin-Madison, Madison, WI; 5Stanford University School of Medicine, Stanford, CA; 6Rutgers Robert Wood Johnson Medical School, Piscataway, NJ; 7 Nationwide Children’s Hospital, Columbus, OH; 8Medical College of Wisconsin, Milwaukee, WI; 9Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; 10The Children’s Hospital of Philadelphia, Philadelphia, PA.

Background: Previously published data from the observational CKID Study showed average neurocognitive function for a combined sample of infants and preschoolers with CKD, although 20% to 37% were deemed at-risk for selected neurodevelopmental difficulties (e.g., executive dysfunction). The current study expands upon previous findings with increased sample size and the examination of infants separately from preschool-age children.

Methods: Participants were 38 infants (Mean age = 1.8 yrs) and 225 preschoolers (Mean age = 4.8 yrs) recruited by CKID Study sites. Infants were 76% male, with a median eGFR = 49; preschoolers were 73% male, with a median eGFR = 53. Measures included the Mullen Scales of Early Learning for infants, and the Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV) for preschoolers. Participants across both age bands received the parent-completed Ages & Stages Questionnaire: Social Emotional (ASQ:SE). Covariates included age, sex, maternal education, eGFR, hypertension, anemia/ESA use, proteinuria, seizure history, and abnormal birth history. Multivariate and logistic regressions were employed.

Results: After adjustment for covariates, infant Mullen Receptive Language (p = 0.02) and expressive language (p = 0.03) scores dropped with every 10% decline in eGFR. For the preschoolers, a 10% decline in eGFR (p = 0.004) and a doubling of proteinuria (p = 0.0002) were each associated with lower WPPSI-IV Verbal IQ. On the parent-completed ASQ:SE for the combined sample, about 13% were deemed at-risk for social-emotional problems, although the doubling of proteinuria was associated with at-risk social status (p = 0.01).

Conclusions: CKD progression was associated with lower language-related abilities for infants and preschoolers, and this represents a novel finding in the CKD neurodevelopmental literature. The rate of parental concern for social-emotional difficulties was equivalent to what might be expected in the typical population although the doubling of proteinuria was associated with at-risk social status. Results highlight the need for early identification and ongoing developmental surveillance of young children with mild to moderate CKD, with further attention being devoted to early language and social development.

Funding: NIDDK Support

SA-PO379
Infectious Complications with Two Different Induction Regimens After Pediatric Kidney Transplantation
Javanthi Chandar,1,2 Marissa J. Defreitas,3,2 Vaka Sugirjonsdottir,2 Chryso P. Katsoufis,1 Wacharee Seehurnvong,1 Carolyn L. Abitbol,1 Gaeton Ciancio,1 University of Miami. 1University of Miami, Miami, FL; 2Miami Transplant Institute, Miami, FL.

Background: Pediatric kidney transplant recipients are vulnerable to clinically significant viral replication (VR) because of their need for intense induction and ongoing need for maintenance immune suppression (ISP). In this single-center study, we compare the incidence of VR with CMV, EBV, parvovirus, BKV, and infectious complications on an induction regimen with anti-thymocyte globulin (ATG) consisting of 3 mg/kg (HiATG) versus <3mg/kg (LoATG) and those who did not receive ATG (NoATG). VR was defined if PCR was > 137 copies/ml. Discontinuation of anti-metabolites or specific treatment for viral infection defined viral disease. Rejection was confirmed by kidney biopsy. Rejection was defined if PCR was > 137 copies/ml. Discontinuation of anti-metabolites or specific treatment for viral infection defined viral disease. Rejection was confirmed by kidney biopsy.

Methods: Retrospective analysis was performed in 59 patients with isolated kidney transplants from January 2018 to December 2021. The protocol for HiATG was a cumulative dose of 3mg/kg in the years 2018-2019 which changed to 1 mg/kg in 2020-2021 for LoATG. Those with low pre-transplant vaccine response and/or low CD4 counts received NoATG. Induction ISP included basiliximab and methylprednisolone. VR was defined if PCR was > 137 copies/ml. Discontinuation of anti-metabolites or specific treatment for viral infection defined viral disease. Rejection was confirmed by kidney biopsy.

Results: Median age was 14 years (IQR: 9.5-17). There were no significant differences in the incidence of VR and rejection between HiATG and LoATG in the first 6 post-transplant months. All patients in NoATG had VR (See Table). Opportunistic infections were observed more often in NoATG. Although steroid avoidance was possible in LoATG and HiATG, time to steroid withdrawal was longer in LoATG (p = 0.02). Leukopenia was more prevalent in HiATG. After 6 months of transplants, VR occurred in 4 patients in each of HiATG and LoATG groups with one patient developing post-transplant lymphoproliferative disease during a mean follow-up period of 33±14 months.

Conclusions: Infectious complications occur in all induction regimens. In addition, maintenance ISP contributes to lowering host immunity. Differences in host response are likely to play a significant role in propensity to infections, highlighting the importance of individualizing ISP.

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Clinical Characteristics in the First 6 Post-transplant Months

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<th>Seraphe 100</th>
<th>Cidofovir</th>
<th>Other</th>
<th>BXV Load</th>
<th>PD-1, Tim-3</th>
<th>CD8 Cell Exhaustion</th>
<th>CD8 Cell Exhaustion</th>
<th>Graft Survival</th>
<th>P&lt; 0.05 vs. Control</th>
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*P<0.02; TN (%); tmedian(IQR)

**SA-PO380**

Norovirus Gastroenteritis in Pediatric Kidney Transplant Recipients: A Pediatric Nephrology Research Consortium Study

Sarah J. Kizilbash,1 Ziuou Jiang,2 Rachel M. Engen.1 University of Minnesota

**Background:** Norovirus can cause debilitating diarrhea in transplant recipients. Herein, we describe the clinical course and complications of norovirus infection in children with a kidney transplant.

**Methods:** Four transplant centers participated in this study. We included kidney transplant recipients who developed norovirus infection (confirmed by stool polymerase chain reaction or viral culture) between 1/1/2013 and 12/1/2019. Study variables are summarized as median and proportions. The estimated glomerular filtration rate (eGFR) was determined using the modified Schwartz equation. Acute kidney injury (AKI) was defined based on a change in eGFR per the pRIFLE criteria.

**Results:** Our cohort included 40 patients, 33 (82.5%) requiring hospitalization. The median time to diarrhea onset after transplant was 100, but this has not been reported in pediatrics.

**Conclusions:** Norovirus gastroenteritis can lead to high mortality and morbidity in immunocompromised patients. The Seraph® 100 Microbind® Affinity Blood Filter (Seraph 100) is a hemoperfusion device designed to adsorb pathogens when added to extracorporeal circuits. It has emergency use authorization for the treatment of COVID-19. Preclinical tests show a 62% reduction of adenoviral (ADV) load with Seraph 100, but this has not been reported in pediatrics.

**Case Description:** A 17 y.o. female s/p deceased donor kidney transplant (txp) for underlying FSGS, on chronic therapy with prednisone, tacrolimus, everolimus, presented 2 years post txp with dysuria, hematuria and fevers. She had AKI (creatinine of 2.3, baseline 0.8), elevated transaminases, and high serum ADV (> 10 million copies/mL). Kidney biopsy showed ADV nephritis with patchy areas of necrotizing interstitial inflammation and abundant viral inclusion bodies. Immunosuppression was discontinued but she remained febrile to 41°C, and had ADV levels >log 7 (> 10 million copies/mL). Cidofovir was not used due to AKI, and the risk of nephrotoxicity. After discussing the risks and benefits treatment with Seraph100 filter was started. She received 2 sessions in-line with continuous renal replacement therapy for a total time of 9 hours. Approximately 18 blood volumes were processed. ADV load decreased from 10 million prior to treatment to 148009 copies/mL (log 5.2) after the 2nd session. Fever curve (Fig 1) and transaminases improved. The ADV load continued to decrease despite not receiving additional sessions & restarting txp meds.

**Discussion:** Seraph® 100 filter was effective in reducing ADV load in this adolescent patient with disseminated adenoviral infection post kidney txp, and led to an improvement in her clinical status. She tolerated treatment without significant adverse events. Teaching Point: The Seraph 100 uses heparin coated beads to bind pathogens, and can help debulk the infectious load. More studies are needed in pediatrics on its efficacy.

**SA-PO381**

Clinical Characteristics and T-Cell Exhaustion in BK Polyomavirus Infection After Pediatric Kidney Transplantation

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**Background:** BK virus (BKV) is a significant cause of chronic kidney injury in kidney transplant recipients that results in allograft loss. Inhibitory receptors PD-1 and Tim-3 play a crucial role in regulating CD8 T cell function during chronic infection. The study’s aim was to determine the clinical characteristics of those who had BKV viremia versus those who did not. Aim 2 was to document correlation between exhausted PD-1 and Tim-3 and exhausted T cells during chronic BKV infection.

**Methods:** The retrospective case-control study was conducted from January 2008 to July 2022. The subjects were composed of a total of 32 pediatric KTTRs and 12 with BKV viremia, in which 5 of 12 had BKV viremia. Peripheral blood mononuclear cells (PBMCs) were collected during episodes of BKV viremia. PD-1, Tim-3, and CD8 T cells were evaluated by multiparameter flow cytometry.

**Results:** BKV viremia was observed in 12/32 (37.5%) and BKVN in 5/32 (15.6%). Induction therapy was not significantly different between BKV and non-BKV viremia groups. The mean time for BK detection was 4.1 months after renal transplantation. Percent rise in serum creatinine correlated with intensity of viral load. The first-line therapy after identification of BKV viremia was a decreased dosage in Tacrolimus (100%) and intravenous immunoglobulin, and discontinuing mycophenolate mofetil. When reduction in immunosuppressant was not sufficient to decrease viral load, 4/12 (33.3%) of patients received leflunomide. High expression of PD1 and Tim-3 on CD8 cells with more severe T cells exhaustion was noted during chronic BKV infection. The treatment resistance was also accompanied with persistent high level of PD-1 and Tim-3 expression on CD8 T cells. There was no difference in the percentage of graft survival between BKV viremia and non-BKV viremia after 8 years' follow-up.

**Conclusions:** Patients with the highest viral loads and longest duration of BKV viremia are at risk of BKVN. Expression of PD-1, Tim-3 and CD8 T cells indicate chronic T cell partial exhaustion. BKV viremia and CD8 T cell exhaustion may be a surrogate marker for adjusting immunosuppressant reduction and intravenous immunoglobulin treatment.

**Use of the Seraph® 100 Microbind® Affinity Blood Filter in an Adolescent Patient with Disseminated Adenoviral Disease**

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**Introduction:** Disseminated adenovirus infection can lead to high mortality and morbidity in immunocompromised patients. The Seraph® 100 Microbind® Affinity Blood Filter (Seraph 100) is a hemoperfusion device designed to adsorb pathogens when added to extracorporeal circuits. It has emergency use authorization for the treatment of COVID-19. Preclinical tests show a 62% reduction of adenoviral (ADV) load with Seraph 100, but this has not been reported in pediatrics.

**Case Description:** A 17 y.o. female s/p deceased donor kidney transplant (txp) for underlying FSGS, on chronic therapy with prednisone, tacrolimus, everolimus, presented 2 years post txp with dysuria, hematuria and fevers. She had AKI (creatinine of 2.3, baseline 0.8), elevated transaminases, and high serum ADV (> 10 million copies/mL). Kidney biopsy showed ADV nephritis with patchy areas of necrotizing interstitial inflammation and abundant viral inclusion bodies. Immunosuppression was discontinued but she remained febrile to 41°C, and had ADV levels >log 7 (> 10 million copies/mL). Cidofovir was not used due to AKI, and the risk of nephrotoxicity. After discussing the risks and benefits treatment with Seraph100 filter was started. She received 2 sessions in-line with continuous renal replacement therapy for a total time of 9 hours. Approximately 18 blood volumes were processed. ADV load decreased from 10 million prior to treatment to 148009 copies/mL (log 5.2) after the 2nd session. Fever curve (Fig 1) and transaminases improved. The ADV load continued to decrease despite not receiving additional sessions & restarting txp meds.

**Discussion:** Seraph® 100 filter was effective in reducing the ADV load in this adolescent patient with disseminated adenoviral infection post kidney txp, and led to an improvement in her clinical status. She tolerated treatment without significant adverse events. Teaching Point: The Seraph 100 uses heparin coated beads to bind pathogens, and can help debulk the infectious load. More studies are needed in pediatrics on its efficacy.
Pediatric Nephrology - III

SA-PO383

Correlation Between Percentage Donor-Derived Cell-Free DNA (dd-cfDNA) at Time of Allograft Biopsy and Rejection: Insights from the Multi-Center Pediatric Outcomes of Kidney Care in Renal Allografts (pOKRA) Study

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Background: The is prospective multicenter observational study to assess the accuracy of % dd-cfDNA as a biomarker for the detection of allograft rejection on simultaneous biopsy, in pediatric kidney transplant patients.

Methods: A total of 48 patients from 3 centers who underwent kidney biopsies with available plasma samples were included in the study. We measured %dd-cfDNA levels using a targeted, multiplex PCR-based method analyzing single nucleotide polymorphisms. Patients were divided into two groups based on the presence or absence of allograft rejection, including subclinical rejection.

Results: We studied 77 samples of plasma %dd-cfDNA levels drawn on the same morning before kidney biopsies from 48 unique patients. Of 77 biopsies, 70 (91%) were surveillance biopsies, whereas 7 (9%) were diagnostic. We had 13 biopsy specimens from 12 patients with biopsy-proven acute rejection and 64 biopsy specimens from 44 patients without biopsy-proven acute rejection. At rejection, the %dd-cfDNA median (IQR) level was significantly higher at 1.2% (IQR: 0.5%-2.0%) than the quiescent group (median, 0.26%; IQR, 0.18%-0.49%). The area under the curve was 0.82 (95% confidence interval 0.70 to 0.93). Using a 1% cutoff, %dd-cfDNA had a specificity of 86% (95% CI, 75% to 92%) and a sensitivity of 62% (95% CI, 36% to 82%) in identifying active rejection. At the lower cutoff of 0.5%, %dd-cfDNA had a lower 75% specificity (95% CI, 63% to 84%) but higher 77% sensitivity (95% CI, 50% to 92%) to discriminate biopsy-proven acute rejection from no rejection.

Conclusions: Prospective multicenter dd-cfDNA% levels timed to biopsy show a high accuracy with biopsy-proven acute rejection in children.

Funding: Commercial Support - CareDx

SA-PO384

Using Eculizumab for Immediate Recurrence of ANCA Vasculitis in a Pediatric Kidney Transplant

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Introduction: ANCA-associated vasculitis (AAV) is associated with poor renal outcomes with 20-30% of patients developing chronic kidney disease and up to 20-35% progressing to end-stage kidney disease. Recent advances have led to increasing interest towards complement inhibition as a potential treatment for AAV. We present a case of disease recurrence after pediatric kidney transplantation and the novel use of Eculizumab to save allograft function.

Case Description: A 5-year-old Hispanic male with ESKD due to myeloperoxidase antibody positive AAV vasculitis developed disease recurrence post-kidney transplant. Pre-transplant disease control required multiple rounds of high dose steroids, cyclophosphamide, rituximab, azathioprine, and mycophenolate mofetil. He received a kidney transplant from an deceased donor at 4 years of age. Eculizumab was administered in a compassionate use protocol with success.

Discussion: Prior reports of Eculizumab use for AAV led to our decision to use it for our patient with historically difficult to control AAV. This case illustrates a rare presentation of immediate disease recurrence of AAV in a pediatric kidney transplant and the successful use of C5 blockade. No specific treatment guidelines exist for childhood AAV, currently highlighting the need for further studies to evaluate efficacy and safety of complement inhibitors as treatment for childhood AAV.

SA-PO385

Lipoprotein Apheresis in Pediatric Post-Transplant FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is a common cause of end-stage renal disease (ESRD) in adolescents with a recurrence rate of >30% after transplantation (txp). Lipoprotein apheresis (LDL-A) has been successfully used for post-txp FSGS recurrence (r-FSGS). It has also been used for drug resistant primary FSGS and de novo FSGS (d-FSGS) post-txp. We aimed to describe the efficacy and safety of LDL-A in pediatric patients with FSGS post-txp.

Methods: Retrospective, single center study at a tertiary care pediatric hospital. Outcomes were complete remission (CR) defined as Upc < 0.2; partial remission (PR) defined as Upc 0.2-2 and a 50% reduction in proteinuria from baseline. All Upc in mg/mg.

Results: Five patients, age range 7-21 yrs (2 females; 4 r-FSGS, 1 d-FSGS) underwent LDL-A. Those with r-FSGS, 3 episodes were immediately post-txp, and 1 after 40 mths. D-FSGS was diagnosed 16 mths post txp in a patient with ARPKD. Two had a relapse requiring a 2nd course of LDL-A. Each course had 12 sessions using Liposorber® LA-15 system over a period of 9 weeks. Of those with r-FSGS, 3 had CR or PR at a median of 4 weeks after starting LDL-A. Patient 2 had >50% reduction in Upc from 34 (pre LDL-A) to a nadir of 3.3. A clinical relapse with increase in Upc to 11 was noted 4 months after 1st LDL-A. A 2nd course resulted in CR. Patient 3 with d-FSGS also had a >50% reduction in Upc from 15 (pre LDL-A) to a nadir of 2.7. A relapse with AKI (Upc 10.3, serum creatinine 7.3mg/dL) was seen after 11 mths. A second course of LDL was attempted but patient did not respond, and was transitioned to chronic hemodialysis. No adverse events related to LDL-A were reported. Patient 3 had central line associated thrombus.

Conclusions: We report successful use of LDL-A in 5 pediatric patients. CR/PR was achieved in all with r-FSGS. In d-FSGS, there was significant decrease in proteinuria but no remission. The therapy was well tolerated with the only adverse event secondary to vascular access. More studies are needed to assess its efficacy in primary and d-FSGS post-txp.
Diabetic Ketonacidosis in Pediatric Kidney Transplant Patient After Treatment for Rejection

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Introduction: New onset diabetes after transplantation (NODAT) is reported in 3-20% of pediatric kidney transplant (KT) patients. Diabetic ketoacidosis (DKA) has not been reported in a pediatric KT recipient. We report on the first case of DKA in a pediatric KT patient with NODAT after treatment of acute rejection.

Case Description: A 16yo, nonobese, female who received a deceased donor KT 4mos earlier was diagnosed with biopsy-proven acute T-cell mediated Banff class 1B and acute antibody mediated rejection in the setting of elevated creatinine. Her rejection was treated with thymoglobulin (total dose 5 mg/kg) and methylprednisolone (MP, total dose ~20 mg/kg). After her initial dose of MP, she developed hyperglycemia, was diagnosed with NODAT and managed initially with insulin and then with sitagliptin and metformin. Her hemoglobin Alc ranged from 5.3% – 7.1%. A subsequent kidney biopsy 21 months after KT showed acute T-cell mediated Banff class 1B and acute antibody mediated rejection. This episode was treated with MP (~30 mg/kg) followed by oral prednisone 60 mg daily (~1 mg/kg/day). Her hemoglobin Alc was 5.8% and she remained on sitagliptin and metformin. She presented 41 days later with new onset polyuria and polydipsia. She was found to have 3+ urine ketones, blood glucose 427 mg/dL, bicarbonate 12 mmol/L, anion gap 22 mmol/L, pH 7.23, beta-hydroxybutyrate 3.77 mmol/L, C-peptide 0.33 ng/mL, and hemoglobin Alc 12.4%. Her creatinine was at her baseline of 0.77 mg/dL and her trough tacrolimus level was 3.7 ng/mL, on 4 mg XR tacrolimus daily. She was receiving prednisone 30 mg daily. Type 1 diabetes autoantibodies were negative: glutamic acid decarboxylase-65 antibody, insulin autoantibody, islet cell antibody 512, and zinc transporter 8 antibody. She was admitted and treated for DKA. Her insulin requirement was ~1.6 units/kg/day.

Discussion: Our patient’s NODAT is likely related to intense steroid treatment for rejection and significant insulin resistance. At our center, we have implemented a multidisciplinary pediatric KT and diabetes clinic that promotes communication between providers and with patients. A single clinic visit streamlines care and facilitates management of NODAT. Recognition of the rare complication of steroid induced DKA in pediatric KT recipients is essential to provide prompt diagnosis and management.

Neurocognitive Profile of Pediatric Kidney Transplant Candidates Aged 3 to 17 Years

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Background: Pediatric kidney transplant candidates frequently undergo pretransplant neuropsychological evaluation. However, little is known about the neuropsychological profile of children awaiting a kidney transplant.

Methods: One hundred and one patients aged 3 to 17 years completed pretransplant neuropsychological evaluations at our center. Standardized tests were administered. Correlations between these test scores and age as well as dialysis duration were examined using Pearson Correlations. The effects of the cause of ESKD and race on test performances were evaluated using multivariate analysis of variance (MANOVA), adjusting for dialysis duration and age at testing.

Results: The mean age of our study cohort was 11.1 years (SD=4.2). The mean Full-Scale IQ of our cohort was significantly lower than general population at 87.3 (SD=19.4). Age was significantly correlated with reasoning scores (r=0.36, p=0.003). Dialysis duration was negatively correlated with memory scores as measured by CVLT C (r=-0.23, p=0.02) and visual organization scores as measured by the Rey-Osterrieth copy test (r=-0.28, p=0.003). After adjusting for age at testing and dialysis duration, the cause of ESKD was significantly associated with overall IQ (F(2)=3.3, p=0.04) and verbal comprehension (F(2)=3.3, p=0.05) performance (see figure). Race (F(1)=7.3, p=0.009) and insurance type (F(1)=3.9, p=0.05) were also significantly associated with verbal comprehension.

Conclusions: Pediatric kidney transplant candidates are at high risk for developing neurocognitive deficits, including lower overall IQ. Younger patients are at higher risk for abstract reasoning deficits, and patients with long dialysis duration are at higher risk for developing memory and visual organization difficulties. In addition, our results suggest that patients with C:KUT tend to have lower IQ scores versus patients with nephrotic syndrome, and white patients tend to perform better than patients of color on verbal abilities.

Social Determinants of Health and Kidney Transplant Outcomes in Youths

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Background: Investigating how social determinants of health (SDOH) affect clinical outcomes is important in achieving health equity. The effect of SDOH on the pediatric transplant recipients is not well understood. Our aim was to investigate the association of adverse SDOH with kidney allograft outcomes in a diverse population of youth from a broad referral area.

Methods: In this single-center retrospective cohort study, data were extracted from the electronic health record using biomedical informatics methods. Inclusion criteria were youth 0-18 years who received a kidney transplant and had post-transplant care at our center from 9/25/2012 to 12/31/2022. Exposures were insurance type (public vs private), distance to transplant center, preferred language, and area deprivation index (ADI). Outcomes were graft survival, time to first biopsy-proven acute rejection (IBPAR), and number of BPAR episodes. We used Kaplan-Meier estimates for graft survival and Cox proportional hazards regression models to estimate the associations of exposures with time-to-event outcomes. For BPAR episodes, a negative binomial regression model, adjusted for time followed, assessed the relationship between outcome and exposure.

Results: Of 182 patients, 37% were female; median age at transplant was 8.5 years [IQR 3, 14], median follow-up was 5.0 years [IQR 4, 7.0]. Event-free survival at 1 and 5 years was 100% and 92%. Median number of BPAR was 0 [IQR 0, 2]. Public insurance, greater distance to transplant center, preferred English language, and higher ADI were not associated with higher risk of graft failure or time to first IBPAR. However public insurance was associated with greater BPAR episodes on unadjusted analysis [OR 3.33, CI 1.19-9.30] and after adjusting for race [OR 3.07, CI 1.08-8.73].

Conclusions: Several adverse SDOH were not associated with worse graft survival or safety. The time to IBPAR in this interim analysis of pediatric kidney transplant recipients. However, having public insurance was associated with a greater number of BPAR. Public insurance may represent a risk marker for patients with greater healthcare needs and who may experience inequities in care. Ongoing quantitative and qualitative studies will clarify health-related social needs and patient experiences in this population to identify targeted interventions to achieve more equitable and optimal transplant outcomes.

Neighborhood Socioeconomic Deprivation Among Pediatric Kidney Transplant Recipients

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Background: Addressing social determinants of health is integral to kidney transplant management, although focus has only recently shifted to neighborhood-level effects. Using data from the Scientific Registry of Transplant Recipients, we describe the association between neighborhood socioeconomic deprivation and graft loss in pediatric kidney transplant recipients.

Methods: US recipients ≥18 years of age at time of listing who underwent kidney transplantation January 1st, 2010, to May 31st, 2022 (n=7,919) were included.

Results: Neighborhood deprivation was calculated using patient ZIP codes at time of listing and the Material Community Deprivation Index (MCDI), ranging from 0 (least deprived) to 1 (most deprived). Recipients were stratified into quintiles (Q). Kaplan-Meier and multivariable Cox proportional hazard estimates were calculated.
Results: The median MCDI for the most deprived neighborhoods (Q5) was 0.53 [IQR: 0.47, 0.84] compared to 0.23 [IQR: 0.06, 0.27] in the least deprived (Q1). Black and Hispanic patients were over-represented in the most deprived neighborhoods. As neighborhood deprivation increased, dialysis duration and deceased donation increased, while preemptive transplantation decreased. Recipients living in the most deprived neighborhoods had a 1.67 times greater risk of graft loss compared to the least deprived (CI: 1.42, 1.98).

Conclusions: Pediatric kidney transplant recipients with the highest levels of neighborhood socioeconomic deprivation had a greater risk of graft loss. Increased focus should be placed on the effects of neighborhood environment to address health disparities in pediatric kidney transplantation.

Funding: NIDDK Support

SA-PO390
Recipient Proximity to Transplant Center in US Pediatric Kidney Transplantation
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Background: Recipient proximity to a transplant center varies greatly among US children with kidney failure. Prior studies of US children listed for kidney transplant demonstrated that less proximity to center was associated with greater risk of death on the waitlist. Using data from the Scientific Registry of Transplant Recipients, we describe the association between recipient proximity to transplant center and candidate evaluation and outcomes in US pediatric kidney transplant recipients.

Methods: US children ≤18 years of age at time of listing who underwent kidney transplantation from January 1st, 2001, to December 31st, 2019 (n=12,133) met inclusion criteria. Proximity to the transplant center was calculated using geodetic distance from residence ZIP codes at time of listing. Logistic and linear regression, in addition to multivariable Cox proportional hazard models, were utilized to analyze outcomes of interest.

Results: Seventy-five percent of recipients lived within 83 miles of a transplant center at time of listing. A majority of Black recipients (81.8%) lived within 83 miles (≥75th percentile) of a center, compared to 72.3% of white recipients. Twenty-three percent of recipients in the ≥75th percentile had a primary diagnosis of FSGS, versus 28% in the ≤25th percentile. Proportions of pre-emptive transplant and public insurance were similar across strata. There was no significant difference in survival across strata, with those with least proximity to center having no increased risk of graft failure (aHR 0.96, 95% CI: 0.87-1.06). There was no change in odds of living donor transplantation (aOR 1.01, 95% CI: 0.99-1.03) or delayed graft function (aOR 0.98, 95% CI: 0.95-1.02) with each 100-mile increase from center. Residing within the ≥75th percentile at time of listing increased waitlist time by 3% of one year (10.95 days, 95% CI: 0.6-6%).

Conclusions: No meaningful associations between recipient proximity to center and graft survival, waitlist time, living donor transplantation, or delayed graft function were detected. Future efforts should explore the impact of proximity to center on additional aspects of transplant access, recipient well-being, and caregiver burden.

Funding: NIDDK Support

SA-PO391
Distance to Transplant Center and Pediatric Kidney Transplant Outcomes and Access to Care
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Background: Reliable transportation is necessary for equitable healthcare access. Transportation insecurity poses a barrier to care, contributing to worse health outcomes in chronic disease. However its significance in pediatric transplantation is an area of ongoing investigation. Our aim was to assess the impact of distance to the transplant center on outcomes and post-transplant follow-up care in a geographically diverse cohort of pediatric transplant recipients.

Methods: In a single-center retrospective cohort study, data were extracted from the electronic health record using biomedical informatics methods. Inclusion criteria were youth 0-18 years who received a kidney transplant and had post-transplant care at our center from 9/25/2012-12/31/2022. Our exposure was distance to the transplant center, determined by calculating geodetic distance from participant residence to the transplant center. Outcomes were graft survival, biopsy-proven acute rejection (BPAR), hospitalization rates, and no-shows and cancelled appointments in the transplant clinic. We used Kaplan-Meier curves and Cox proportional hazards regression to estimate associations of exposures with outcomes.

Results: Of 78 participants, 37% were female; median age at transplant was 8.5 years (IQR 3.4); median follow-up was 5.0 years (IQR 1.7). The median distance from the transplant center was 29.0 miles (IQR 13.4,60.1); mean no-show proportion was 5.9% (SD 9.1%); mean cancellation proportion was 26.8% (SD 10.6%). Distance to the transplant center was not associated with higher risk of graft failure, shorter time to first BPAR, higher BPAR, and higher hospitalization rates. Greater distance from the transplant center was associated with a higher proportion of cancelled clinic appointments (p =0.001), Beta coefficient 1.08 per 10 miles, 95% CI [0.63,1.54]).

Conclusions: Greater distance to the transplant center was associated with more clinic cancellations, which can cause delayed care resulting in negative effects on transplant health. Further study by collecting qualitative data on patient transportation access may help us understand the patient experience and what barriers can be mitigated to reduce appointment cancellations. By collecting qualitative data on patient transportation access in this population, we hope to better inform transplant maintenance and optimize long-term care.

Funding: Other NIH Support - The project was supported by the National Center for Advancing Translational Sciences

SA-PO392
Childhood Opportunity Index and Pediatric Kidney Transplant Health
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Background: Social Determinants of Health research has become increasingly important. The Childhood Opportunity Index (COI) is a composite of 29 variables affecting child health and well-being related to Health/Environment (HE), Social/Economic (SE), and Education (E). Research exploring the impact of COI on kidney transplant outcomes is lacking. Our aim was to assess association of COI with pediatric kidney transplant outcomes.

Methods: This was a single-center retrospective cohort study of kidney transplant recipients 0-18 years with post-transplant care at our center from 9/25/2012-12/31/2022. Exposures were overall COI, HE, and SE domains based on 2015 census tract data from diversifyingdatakids.org. Outcomes were graft survival, time to first biopsy-proven acute rejection (BPAR), number of BPARs, hospitalization rates, and transplant clinic no-show and cancellation rates. Statistical analyses included Kaplan-Meier, Cox proportional-hazards, and negative binomial regression models.

Results: Of the N=78 participants; median age at transplantation was 8.5 years [IQR 3.4]; median follow-up 5 years [IQR 4.1,7.0]. Event-free survival at 1 and 5 years was 100% and 92%. COI was not associated with graft survival, number of BPAR, hospitalization rates, or cancelled visits. COI was inversely associated with time to first BPAR (p=0.001, HR=1.10, 95% CI 1.02-1.17). Overall COI and COI-SE were inversely correlated with no-show rates (p=0.039, Beta coefficient=−0.41 per 5 units (95% CI -0.80,-0.02) and p=0.029, Beta coefficient=−0.43 per 5 units (95% CI -0.81,-0.05)). Higher no-show rates were associated with worse graft survival (p=0.018, HR=1.38, 95% CI 1.06-1.79).

Conclusions: Lower COI-SE was associated with higher no-show rates which was associated with worse graft survival. Higher COI-SE was associated with shorter time to first BPAR, possible due to patients maintaining regular follow-up with more timely BPAR diagnosis. Higher no-show rates in individuals from areas of low COI-SE may help us understand the patient experience and what barriers can be mitigated to reduce appointment cancellations. By collecting qualitative data on patient transportation access in this population, we hope to better inform transplant maintenance and optimize long-term care.

Funding: Other NIH Support - The project was supported by the National Center for Advancing Translational Sciences
result in delayed BPAR diagnosis, which could increase risk of graft failure. Future studies could examine if COI predicts other transplant or kidney disease outcomes. To better understand the effects that lower COI may have at the individual level, questionnaires can be used to identify barriers to care such as affordability, perceived cost, transportation, or ability to attend appointments.

Funding: Other NIH Support - The project described was supported by the National Center for Advancing Translational Sciences

SA-PO393

Revisiting Clinical Relevance of Radionuclide-Based GFR Estimation and Comparison with CKID U25 eGFR Equation in Pediatric Liver Transplant Patients

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Background: Renal dysfunction is common in patients with liver transplant recipients and can be present at the time of transplant or develop later during follow-up. Kidney function in these patients is monitored periodically by measuring glomerular filtration rate (GFR). In the absence of appropriate serum creatinine-based estimation equations in the past, GFR measurement by utilizing radionuclide agent such as diethylenetriamine pentaacetaetate (DTPA) have been in common practice. The procedure involves IV line placements, radionuclide agent administration, and blood draws. The value of newer GFR estimating equations such as CKID U25 (derived from Chronic Kidney Disease in Children Under 25) have not been evaluated in these cases.

Methods: Retrospective analysis of all liver transplant patients since 1995 who had their GFR estimated by radionuclide (99mTc-DTPA) for kidney function monitoring. The DTPA-GFR was compared with eGFR calculated by creatinine based CKID U25 equation. All creatinine values were converted to isotope dilution mass spectrometry (IDMS) reference measurement. Patients with any missing data were excluded.

Results: 356 DTPA-GFR measurements (median 4 per patient; range 1 – 9) from 95 patients (57% males; median age at transplant 2.1 years, range 0.45 – 19.2) obtained at a median age of 10 years were available. 53 (15%) serum creatinine values were above the age specific reference range and the eGFR by U25 equation was <90 ml/min for all, while 40 had <90 ml/min, 11 had between 90 – 120, and 2 had >120 ml/min based on DTPA-GFR. 303 serum creatinine values were in normal range and the GFR was >120 ml/min in 209 values. U25 equation classified 147 (90 – 120 ml/min) and 18 (<90 ml/min); while DTPA-GFR classified 115 (90 – 120 ml/min) and 28 (<90 ml/min). The concordance between U25 and DTPA-GFR was ~50% for eGFR 90 – 120 ml/min, and ~15% for <90 ml/min, respectively. Overall, the correlation coefficient (\( r \)) between the two methods was 0.45 (\( p <0.0001 \)).

Conclusions: In the absence of the gold-standard measurement, CKID U25 equation appears to perform better than DTPA-GFR which is a time consuming, cumbersome and expensive procedure. Addition of serum Cystatin C is likely to further improve the eGFR estimation by CKID U25 equation.

SA-PO394

Preventative Dental Practices and Cardiometabolic Health in Adolescents

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Background: Decreased utilization of dental services in adolescence has been linked to cardiometabolic disease in adulthood. The aim was to assess the relationship between preventative dental practices and cardiometabolic health in adolescents.

Methods: Analysis included adolescents aged 13-17 years enrolled in the National Health and Nutrition Examination Survey (NHANES) from 2011-2018 who completed an oral health questionnaire/exam. Untreated caries was defined as having one or more decayed teeth. Severity of dental caries was assessed by the Decayed, Missing, Filled teeth (DMFT) score in permanent dentition (No caries, DMFT=0). Cardiometabolic outcomes included obesity, elevated blood pressure (BP 120-129/80 mmHg), hypertensive BP (BP ≥130/80 mmHg), dyslipidemia (any abnormal lipid level), glucose intolerance (HOMA-IR), uric acid, glomerular hyperfiltration (estimated glomerular filtration rate \( [eGFR] \gtrless=140 \text{ ml/min/1.72 m}^2 \)), and microalbuminuria (urine albumin:creatinine >30 mg/mg).

Regression models adjusted for age, sex, self-identified ethnicity/race, household income, food insecurity, health insurance status, household education, and body mass index (BMI) \( z \)-score examined associations using complex survey design procedures.

Results: Of 2,861 adolescents, 17.6% (9.9%) did not receive dental care in the past year and of those, 20.2% (1.9%) had financial barriers to accessing dental care. Adolescents without dental care had higher odds of overweight/obesity and dyslipidemia. Those with financial barriers had higher levels of non-HDL, lower levels of HDL, and higher odds of dyslipidemia (Table 1).

Conclusions: In a nationally representative population of adolescents, lack of preventative dental practices was associated with cardiometabolic health makers of overweight/obesity and dyslipidemia. In addition, financial barriers to health were associated dyslipidemia.

Funding: NIDDK Support
Hyperfiltration in Obese Diabetic BTBRob/ob Mice Can Be Measured Transcutaneously

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Background: Transcutaneous assessment of glomerular filtration rate (GFR) has only been validated in lean mice. At 24 weeks obese diabetic mice display vasodilatation of the afferent glomerular arteriole and increased glomerular size, yet do not differ in GFR values from lean mice. Hence, we question if hyperfiltration can be assessed transcutaneously in obese diabetic mice.

Methods: We measured GFR and FITC-sinistrin plasma clearance simultaneously in obese diabetic BTBRob/ob and lean non-diabetic BTBR-/- mice at week 12. At week 24 we assessed GFR again and used tissue clearing and light sheet microscopy to assess glomerular size and vasodilatation of the afferent arteriole in mice that were perfused with an infrared fluorescent dye.

Results: While at week 12 GFR significantly differed between the groups with a faster clearance in the diabetic BTBRob/ob mice (both l., of FITC-sinistrin (p=0.0081) and calculated GFR (p=0.0069), no difference was found between diabetic and non-diabetic mice in GFR at 24 weeks. In line with the increased GFR, also FITC-sinistrin plasma clearance was significantly increased at week 12 in BTBRob/ob mice (p=0.0140). At week 24 the diameter of afferent arterioles were significantly larger in BTBRob/ob vs. BTBR-/- mice (p=0.0007) and associated with increased glomerular size (p=0.0136).

Conclusions: The results indicate that hyperfiltration can be detected in diabetic mice by GFR early in the course of disease. In keeping with the findings that no difference in GFR was found at 24 weeks despite morphological parameters that indicate hyperfiltration, our data might be explained by progressive loss of functional nephrons later in the disease. Accordingly, this will reduce total glomerular filtration while increasing glomerular pressure and dilation of the afferent glomerular arterioles (and later in the disease). Accordingly, this will reduce total glomerular filtration while increasing glomerular pressure and dilation of the afferent glomerular arterioles (and presumably single nephron glomerular hyperfiltration) remain in noncrescentic nephrons.

Funding: Government Support - Non-U.S.

The Genetic Architecture of Diabetic Nephropathy in Mice

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in the United States and has a significant impact on human suffering. Leptin-deficient BTBR-/- mice (both l., develop hallmark glomerular features of diabetic kidney disease in humans, whereas leptin-deficient C57BL/6J (B6-/-) mice do not.

Methods: To identify the genetic loci that underlie this strain difference, we constructed an F2 intercross between BTBR-/- and B6-/- mice. We isolated kidneys from 460 F2 mice and used them to histologically score percent mesangial matrix and glomerular volume in ~50 glomeruli per mouse, yielding ~45,000 distinct measures in total. The same histological measurements were made in kidneys from B6 and BTBR mice at 4 and 10 weeks of age, allowing us to assess the contribution of strain, age, and obesity on glomerular pathology. All F2 mice were genotyped for ~5,000 single nucleotide polymorphisms (SNPs), ~2,000 of which were polymorphic between B6 and BTBR.

Results: We were able to identify a quantitative trait locus (QTL) on chromosome 7 at ~30 Mb for percent mesangial matrix, glomerular volume, and mesangial volume. Two podocyte-specific genes in this region, Nphs1 (nephrin) and Kirrel2 (NEPH3 or filtrin), are physically located at the QTL and contain several high-impact SNPs (at splice regions or in missense variants). Both are members of the immunoglobulin superfamily that is involved in cell adhesion molecules and localize to the podocyte slit diaphragm. Furthermore, mutations in these genes have been linked to chronic kidney disease in humans.

Conclusions: Our findings indicate genetic differences in genes known to be crucial to podocyte function and glomerular filtration barrier integrity as drivers of microstructural glomerular changes in diabetic nephropathy. Diabetic nephropathy is likely to be polygenic, with various genes, participating in various pathways, acting synergistically to affect susceptibility to the disease. Our study highlights Nphs1 and Kirrel2 and their role in podocyte function as genes that contribute to susceptibility to diabetic kidney disease and help characterize the structural changes in the glomerulus. Genetic testing of a panel of gene variants may identify patients genetically predisposed to podocyte dysfunction in diabetes and guide care to prevent nephropathy in diabetes.

Funding: NIDDK Support, Other NIH Support - Diabetes Complications Consortium (DiagComp)

Sexual Dimorphism in Glucose Metabolism in Type 2 Diabetic Mice

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Background: The prevalence of non-insulin-dependent diabetes has grown exponentially over the last three decades and today this complication is a major global concern. According to the World Health Organization, the percentage of deaths attributed to high blood glucose is greater in males than females. This fact translates to experimental models of type 2 diabetes, in which obese male show increased blood glucose levels in comparison to female, despite the same degree of obesity. However, the mechanisms underlying this observation are still unclear. Thus, the aim of this study is to investigate the sexual dimorphism in glucose metabolism in BTBR WT and ob/ob mice.

Methods: The mice had blood glucose and body weight evaluated every two weeks. At the 16th week of age, euthanasia was performed to collect urine, liver and the kidneys. Albuminuria and gene expression of glucose metabolism enzymes were further performed.

Results: Preliminary data show that BTBR ob/ob mice, independently of sex, presented increased body weight gain in comparison to corresponding WT mice, but obese male were hyperglycemic than female throughout the experimental protocol. Diabetes and obesity induced albuminuria equally between males and females, which confirms loss of kidney function. In the liver, male and female BTBR ob/ob mice showed decreased Pkdi and increased Ppir transcript levels, suggesting alteration of the gluconeogenesis pathway. However, female BTBR ob/ob mice had increased liver Pkm transcript levels than the corresponding male. In addition, liver Pkm transcript levels positively correlated with the blood glucose levels, which indicates sexual dimorphism in liver glycolysis. On the contrary, increased gene expression of the gluconeogenesis enzymes were observed in obese mice independently of sex, however, Hk1, Pkm and Pfkbp transcript levels were upregulated only in females. Moreover, kidney Pkip transcript levels positively correlated with blood glucose levels, suggesting also sexual dimorphism in kidney glycolysis. Gene expression of glucose transporters in the proximal tubule, SGLT2 and GLUT2, were only affected by obesity and diabetes, being higher in female sex.

Conclusions: Collectively, these data show that there is a sexual dimorphism in expression of glycolysis enzymes in both liver and kidney, which may be associated with differences in blood glucose levels of male and female BTBR ob/ob.

Funding: Government Support - Non-U.S.

The TNF-α Pathway and Podocyte Dysfunction in Male and Female BTBR ob/ob Mice

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Background: Diabetic kidney disease (DKD) is the major cause of chronic kidney disease (CKD) in patients with diabetes. Studies suggest that tumor necrosis factor alpha (TNF-α) pathway signaling is important for DKD progression. TNF-α contributes to glomerular inflammation and injury, however, the mechanisms underlying this dysfunction, especially in podocytes, need to be further elucidated. Thus, the aim of this study is to elucidate how TNF-α may contribute to podocyte dedifferentiation in DKD and whether sexual dimorphism can modulate this process.

Methods: For this, male and female BTBR WT and ob/ob mice, a gold standard model of experimental type 2 diabetes and obesity were studied. The mice were observed for 8 weeks at the 16 weeks of age, and at the end of the experimental protocol, urine and kidneys were collected for analysis of albuminuria and gene expression. In vitro, immortalized mouse podocytes were treated with TNF-α for gene expression analysis.

Results: Preliminary data show that BTBR ob/ob mice presented elevated blood glucose levels and body weight gain in comparison to WT mice. Using these parameters, blood glucose levels were affected by sex, as females were less hyperglycemic than males. In the kidneys, gene expression of TNF-α and TNF-α receptor
Diabetic Kidney Disease: Basic - II

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

SA-PO400
The Association Between Mechanosensitive Ion Channel Piezo2 Expression and Fibrogenesis in Hypertensive Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease, and mechanical factors such as glomerular hyperfiltration are crucial in the pathogenesis and progression of DKD. We previously reported Piezo2 expression in mouse kidneys and its alteration by dehydration and hypertension, however, the role of Piezo2 in DKD is still unclear. We aimed to elucidate Piezo2 expression and regulation in mouse models of DKD.

Methods: We used two types of DKD models (high fat diet (HFD) and streptozotocin (STZ)-treated C57BL/6J mouse, and high salt (HS)-treated type 2 diabetic KK-A*(+/−) mouse) and non-diabetic control C57BL/6J mice. Blood samples and kidneys were collected at 24 weeks of age for HFD+STZ mice and 19 weeks of age for KK-A*(+/−) HS mice. We examined blood and urine analyses, histopathologic and immunohistochemical evaluations of kidneys, and gene expression analysis. The localization of Piezo2 expression was identified using in situ hybridization method.

Results: Both DKD models exhibited significant obesity, hyperglycemia, albuminuria, glomerular hypertrophy, mesangial expansion, infiltration of macrophages, and tubular vacuolization compared to control mice. These findings were more severe in KK-A*(+/−) HS mice than in HFD+STZ mice. Kidney inflammation, there were no significant differences in blood fibrosis between HFD+STZ mice and control mice, whereas severe interstitial fibrosis was observed in KK-A*(+/−) HS mice kidneys. In situ hybridization studies showed no significant difference in Piezo2 expression between HFD+STZ mice and control mice, but Piezo2 expression was increased and localized in the glomerular and interstitial regions in KK-A*(+/−) HS mice. Real-time RT-PCR showed that Piezo2 and Fn1 mRNA were increased in KK-A*(+/−) HS mice compared with control mice. Furthermore, Piezo2 expression was strongly correlated with Fn1 expression (r=0.92, p<0.001).

Conclusions: Our findings suggest that Piezo2 expression is upregulated in glomerular and interstitial regions in the advanced stage of DKD with increased glomerular mechanical stress, and Piezo2 is associated with kidney fibrosis.

SA-PO401
Effects of Electronic Cigarette Aerosol Exposure on Kidney Health in Diabetic/Obese Mice

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Background: Diabetes is one of the most important risk factor for chronic kidney disease (CKD) and end stage kidney disease. Tobacco smoking accelerates the progression of CKD of different etiologies including diabetes. However, whether e-cigarette use also has a deleterious effect on CKD progression is unknown. The aim of this study was to examine the effects of e-cigarette use and opens the door for further research concerning the impact of e-cig use on kidney health.

Funding: NIDDK Support, Other NIH Support - NCI

SA-PO402
Investigation of Urinary Exosomal miRNA and lncRNA Expression Profiles and eRNA Network in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is one of the major cause of end-stage renal disease (ESRD), it is important to detect diagnostic biomarkers of DKD. This study aims to explore expression profiles of urinary exosomal mRNA and lncRNA in DKD patients, and their possible regulatory mechanism in DKD.

Methods: We performed urinary exosomal mRNA and lncRNA expression profile in DKD, DM patients and healthy subjects, and analyzed biological functions of differentially expressed miRNAs and lncRNAs. And then we focused on the important mRNA ZEB1/2 which were related to DKD, constructed a ceRNA network.

Results: We identified differentially expressed 47 miRNAs and 61 lncRNAs of urinary exosome of DKD. GO and KEGG analysis showed target genes of miRNAs were involved in IκB kinase, nuclear factor kappa B, TNF-alpha, TNF and NF-kappa B signaling pathway.

Conclusions: Conclusion: Urinary exosomal lncRNA-miRNA may involved in the pathogenesis and therapeutic targets of DKD.
SA-PO405

Oxidative Stress-Related Mitochondrial and Lysosomal Quality Control Mechanisms in Renal Cortex During the Nonalbuminuric Stage of Diabetes Mellitus

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Background: Oxidative stress during the nonalbuminuric stage of type 1 diabetes mellitus (DM) damages renal cortical mitochondria. Subsequent mitochondrial autophagy (mitophagy) produces autophagosomes destined for lysosomal degradation; hence, any lysosomes damaged in DM must be either repaired or degraded and removed in order for mitophagy to reach fruition. We aimed to determine if oxidative stress in DM triggers not only renal cortical mitophagy, but also lysosomal repair and elimination through lysosome-selective autophagy (lysophagy).

Methods: Four groups of rats (n=5 per group) received one of the following treatments: 1) STZ group: rats with DM induced by streptozotocin injection (STZ, 65 mg/kg, i.p.); 2) Sham group: rats receiving the STZ vehicle; 3) STZ+TLM group: STZ rats treated with telmisartan (TLM, an angiotensin receptor blocker; 10 mg/kg/day in chow); and 4) Sham+TLM group: TLM-treated Sham rats. Two weeks later, blood glucose levels, blood pressure, glomerular filtration rate (GFR), and urinary excretion of albumin and N-acetyl-β-D-glucosaminidase (NAG) were measured in each rat. Renal cortex homogenates were assayed for 3-nitrotyrosine (3-Nit, an oxidative stress marker measured by HPLC). Western blot was used to quantify proteins related to mitophagy (PINK1, BNIP3, LC3-II, p62), lysosomal repair (Galectin-3), and lysophagy (LAMP2, FBXO27).

Results: Blood glucose levels were higher in STZ rats than in Sham rats (P<0.05) and were unaffected by TLM. Blood pressure, albumin excretion, and NAG excretion were unaltered by STZ or TLM. GFR and renal cortical 3-Nit levels were increased in STZ rats (P<0.05) but both changes were prevented by TLM (P<0.05). STZ rats had increased renal cortical LC3-II, PINK1, Galectin-3, and FBXO27 protein levels compared with Sham (P<0.05), with these effects prevented by TLM (P<0.05). INP13, p62, and LAMP2 levels did not differ among groups.

Conclusions: DM-induced renal cortical mitophagy, lysosomal repair, and lysophagy were blunted by the antioxidant effects of TLM, suggesting that these may be closely related quality control mechanisms triggered by oxidative damage.

SA-PO406

Liraglutide’s Unveiled Renoprotective Mechanism in Type 1 Diabetes: Insights into Macrophage Polarization

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Background: Diabetic Kidney Disease is a major complication of type 1 (T1D) and type 2 (T2D) diabetes. While the GLP-1RA liraglutide, has shown promise in protecting the kidneys of individuals with T2D, its effects in T1D are not well-studied. Additionally, the underlying mechanism through which liraglutide provides renoprotection in T1D or T2D requires further investigation. Macrophages are known to contribute to the development and progression of DKD. Upon infiltrating the glomeruli, they tend to adopt a pro-inflammatory M1 phenotype rather than an anti-inflammatory M2 phenotype. In addition to inflammation, excessive production of ROS is implicated in DKD progression. This study aims to investigate the renoprotective effects of liraglutide in T1D and examine its influence on shifting macrophage polarization towards the anti-inflammatory M2 phenotype by modulating NADPH oxidase.

Methods: C57/BL6J adult male mice were divided into 3 groups (n=5/group): C group, T1D group (induced by 3 consecutive doses of STZ), and T1D group treated with liraglutide (0.3 mg/kg twice daily). After a 13-week treatment period, the mice were sacrificed, and kidneys were isolated for analysis.

Results: Our results show that liraglutide improves kidney injury in T1D mice manifested by a reduction in kidney hypertrophy, BUN, ACR, proteinuria, glomerular hypertrophy, glomerulosclerosis, as well as glomerular collagen deposition. These findings were associated with decreased expression of inflammatory cytokines, as well as the M1 macrophage specific markers. Moreover, the levels of the anti-inflammatory cytokines were increased, and this was associated by an increase in the M2 macrophage specific markers. Furthermore, liraglutide treatment attenuated ROS production manifested by decreased NADPH oxidase activity through an inhibition of NOX2 and NOX4. Of interest, liraglutide treatment was associated with activation of the NADPH oxidases DUOX isoforms, indicating a more controlled and regulated ROS production, which may be involved in redox signaling and tissue homeostasis.

Conclusions: Our data highlight an anti-inflammatory renoprotective effect of liraglutide. This is manifested by a notable shift in macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, through the modulation of NADPH oxidase activity in T1D.
SA-PO407

MiR-200b Induces ZEB1-Mediated Upregulation of Matriptase and Affects Expression of Podocin: A Proposed Mechanism of Podocyte Effacement and Proteinuria in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease and a predominant reason for renal failure. Evidence from previous research indicates that abnormal expression of microRNAs (miRs) links closely to the occurrence and progression of DKD.

Methods: Expression of miRs in urine samples from DKD patients and in cultured renal cells stressed with transforming growth factor beta 1 (TGF-β1) was evaluated by TaqMan assay. The emerging miR of interest and its downstream targets were analyzed in human renal sections, in cultured human podocytes and in zebrafish.

Results: Cell free urine screening showed increased abundance of miR-200b in samples from patients with DKD when compared to healthy controls. In situ hybridization confirmed expression of miR-200b in kidney specimens from DKD patients, but was not detected in healthy renal parenchyma. Transcriptome profiling of cultured human podocytes overexpressing miR-200b identified this miR as a regulator of the ZEB1 mediated matrisome (ST14)/podocin pathway and found TGF-β1 and high glucose (HG) stress to be upstream activators of miR-200b expression in these cells. Immunofluorescence analysis of kidney sections from DKD patients showed increased expression of ST14 and decreased expression of podocin when compared to healthy controls. Furthermore, injection of a miR-200b mimic in zebrafish larvae caused an upregulation of ST14 and was accompanied by phenotypic changes such as edema, proteinuria and podocyte effacement.

Conclusions: Our results show that miR-200b is expressed in glomeruli and found at elevated levels in urine of DKD patients. Stressors such as high glucose or TGF-β1 can activate transcription of miR-200b in human podocytes, leading to increased levels of matrisome, a serum protein previously shown to cleave podocin. The observed decrease in podocin levels in glomeruli from DKD patients, together with the effect of a miR-200b mimic on proteinuria and ultrastructure of the pronephros in zebrafish positions miR-200b as a key regulator that modulates matrisome overactivation in DKD and warrants further studies.

SA-PO408

PACSIN2 Regulates the Inflammatory Response in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is associated with hemodynamic and metabolic alterations including chronic low-level inflammation. Podocytes, the glomerular epithelial cells, are damaged by the inflammatory milieu in DKD via poorly understood mechanisms. Our study identifies protein kinase C and casein kinase substrate in neuron 2 (PACSIN2) as a new regulator of inflammation in the kidney.

Methods: This study relies on PACSIN2 knockout (KO) mice, in which we modeled DKD. We also used isolated human glomeruli and cultured human podocytes. We analyzed samples by quantitative Western blot, and immunofluorescence or immunohistochemical stainings.

Results: At the age of 12 months, compared to controls, PACSIN2 KO mice had paler kidneys, increased albumin to creatinine ratio, and altered glomerular vasculature. This coincided with increased circulating IL6, increased glomerular macropage infiltration, and disrupted oxidative process in the glomeruli. Treatment of human glomeruli ex vivo with IL6 led to increased expression of PACSIN2. In cultured human podocytes, the expression and phosphorylation of PACSIN2 varied in response to inflammatory stimuli. PACSIN2 also interacted with Nfkb and Gsk3β depending on the stimulus. Diabetic PACSIN2 KO mice were lighter than diabetic controls, had lower glycemia, lower albuminuria, and excreted less urine per 24h. We found no difference in macroage infiltration and oxidative damage between diabetic WT and diabetic PACSIN2 KO mice. Nevertheless, the expression of Nfkb and Gsk3β was increased in glomerular lysates of diabetic PACSIN2 KO mice.

Conclusions: Our results indicate that lack of PACSIN2 alone causes kidney damage and increases inflammation in the glomeruli. In the context of DKD, lack of PACSIN2 improved metabolic and kidney parameters. Our study uncovers PACSIN2 as a novel regulator of inflammation and highlights the contextual regulation of the inflammatory response in the glomeruli.

Funding: Private Foundation Support

SA-PO409

Exploring the Role of CXCL16 in Diabetic Kidney Disease: Insights into Inflammation, Lipid Disorders, and Therapeutic Potential of Curcumin

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Background: Diabetic nephropathy (DN) is a common complication of diabetes characterized by progressive presence of albumin in the urine and the destruction of glomeruli. Elevated levels of soluble C-X-C chemokine ligand 16 (CXCL16) have been associated with inflammatory and lipid responses, which play a significant role in the development of renal dysfunction in patients with diabetes. However, the precise mechanisms through which CXCL16 affects DN are not yet fully understood.

Methods: To address this, we conducted a comprehensive study to investigate how CXCL16 contributes to podocyte injury in DN.

Results: CXCL16 were associated with abnormal lipid metabolism. The addition of CXCL16 to podocytes led to the formation of lipid droplets, along with increased expression involved in lipid synthesis and storage. CXCL16 treatment inhibited the movement of Nrf2 into the nuclei of podocytes. To explore potential therapeutic approaches, we evaluated the effects of curcumin, a compound known to activate Nrf2, on podocyte senescence and injury. Our results demonstrated that curcumin treatment reduced the accumulation of lipid droplets and mitigated podocyte injury, as evidenced by a decrease in cellular senescence. Importantly, we found that the protective effects of curcumin were inhibited when CXCL16 was reduced by CXCL16 siRNA. Meanwhile, curcumin treatment prevented CXCL16-induced oxidative stress and inflammation, preserved the expression of synaptophysin, and inhibited the abnormal movement of Nrf2. Through molecular modeling and docking analysis, we discovered that curcumin directly targets a specific region in the CXCL16 protein, blocking its kinase activity. In a mouse model of DN, we validated the therapeutic potential of curcumin.

Conclusions: Taken together, our findings suggest that CXCL16 may serve as a promising therapeutic target for the treatment of DKD.

SA-PO410

Effects of Stimulating and Inhibiting IL11 Pathway in Kidney Fibrosis

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Background: IL11 has been widely implicated as a major downstream effector of TGFβ signaling driving fibrogenesis and extracellular matrix deposition in several organs including the kidney. Here, we aimed to test fibrotic effects of IL11 in vivo and in vitro kidney disease models.

Methods: Primary renal fibroblasts and human precision-cut kidney slices (PCKS) were treated with TGFβ to stimulate driving fibrogenesis and extracellular matrix deposition in several organs including the kidney. We also used isolated human glomeruli and cultured human podocytes. We analyzed samples by quantitative Western blot, and immunofluorescence or immunohistochemical stainings.

Results: At the age of 12 months, compared to controls, PACSIN2 KO mice had paler kidneys, increased albumin to creatinine ratio, and altered glomerular vasculature. This coincided with increased circulating IL6, increased glomerular macroage infiltration, and disrupted oxidative process in the glomeruli. Treatment of human glomeruli ex vivo with IL6 led to increased expression of PACSIN2. In cultured human podocytes, the expression and phosphorylation of PACSIN2 varied in response to inflammatory stimuli. PACSIN2 also interacted with Nfkb and Gsk3β depending on the stimulus. Diabetic PACSIN2 KO mice were lighter than diabetic controls, had lower glycemia, lower albuminuria, and excreted less urine per 24h. We found no difference in macroage infiltration and oxidative damage between diabetic WT and diabetic PACSIN2 KO mice. Nevertheless, the expression of Nfkb and Gsk3β was increased in glomerular lysates of diabetic PACSIN2 KO mice.

Conclusions: Our results indicate that lack of PACSIN2 alone causes kidney damage and increases inflammation in the glomeruli. In the context of DKD, lack of PACSIN2 improved metabolic and kidney parameters. Our study uncovers PACSIN2 as a novel regulator of inflammation and highlights the contextual regulation of the inflammatory response in the glomeruli.

Funding: Private Foundation Support
NLRP3 Inflammasome Activation Mediated by Lysyl Oxidase-Like 2 in Human Podocytes in Diabetic Condition
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Background: Diabetic kidney disease (DKD), a major complication of diabetes mellitus, is a most common cause of kidney failure. Sterile inflammation is a hallmark of DKD. The NLR family pyrin domain containing 3 (NLRP3) inflammasome is a mechanism of sterile inflammation known to be activated by metastatic stimuli and reactive metabolites associated with DKD. Recently, lysyl oxidase-like 2 (LOXL2) has been reported to associate with tissue fibrosis, inflammation, and oxidative stress, all of which are implicated in the pathogenesis of diabetes and its complications. In this study, we investigated the expression of LOXL2 in human kidney and podocyte, and its contribution to NLRP3 inflammasome expression in podocyte with high-glucose condition.

Methods: We evaluated the expression of LOXL2 in human kidney using immunofluorescence staining. Real-time PCR and western blotting analysis for LOXL2 mRNA and protein expression were performed using cultured human immortalized podocytes. After fully differentiated, cultured human podocytes were exposed to high glucose (HG) for 48 hours. Podocyte-specific LOXL2 knock-down cells using CRISPR-Cas9 was generated.

Results: By real-time PCR and immunofluorescence staining, LOXL2 expression was identified in human glomerulus and was significantly increased in that with diabetic kidney disease compared with normal control. mRNA of NLRP3 inflammasome expression was also significantly increased in podocyte with HG condition (6.79±0.32 vs. 1.06±0.26, P<0.05). Gene silencing of LOXL2 significantly reduced mRNA and protein expression of NLRP3 inflammasome in immortalized human podocytes with HG compared to control. Western blot analysis showed that collagen I and phosphorylated Smad2 protein expression were significantly decreased in LOXL2 knock-down podocytes.

Conclusions: Our results showed that NLRP3 inflammasome activation may attenuated by gene silencing of LOXL2 in podocytes in diabetic condition.

Inhibition of YAP Impairs the Expression and Function of WT1 in Diabetic Podocytes
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Background: Podocyte injury and loss are hallmarks of diabetic nephropathy (DN). The molecular mechanisms underlying these phenomena are poorly understood. Yes-associated protein (YAP) is a transcriptional coactivator that regulates cell proliferation, differentiation, and apoptosis. Nuclear YAP in podocytes is crucial for differentiation, cell survival, and structural maintenance. However, the role of YAP in diabetic podocyte injury is unclear.

Methods: Inducible podocyte-specific YAP depletion (Yap-creERT2) mice and wild-type Yap+/- mice were generated by crossing podocin.iCreERT2 (+) mice with Yap-creERT2 (+) mice with Yap floxed mice. Unilateral nephrectomized (UNX) Yap+/-, Yap+/+, FVB/NJ mice, and mice with an inactive allele of the Wt1 gene (Wt1+/-) were subjected to streptozotocin injections to induce type 1 diabetes. Proteinuria and diabetic podocyte injury were assessed. The expression of YAP, TAZ, WT1, TEAD1 and other podocyte-specific proteins in isolated glomeruli was analyzed by immunofluorescent staining or western blot analysis. Proteinuria and diabetic podocyte injury were more susceptible to diabetic podocyte injury, as evidenced by earlier proteinuria and diabetic podocyte injury were assessed. The expression of YAP, TAZ, WT1, TEAD1 and other podocyte-specific proteins in isolated glomeruli was analyzed by immunofluorescent staining or western blot analysis. Proteinuria and diabetic podocyte injury were more susceptible to diabetic podocyte injury. Inhibition of YAP impairs WT1 expression, and subsequent inhibition of TEAD1 expression may represent an unrecognized mechanism of diabetic podocyte injury.

Funding: NIDDK Support, Veterans Affairs Support
SA-PO415
Blocking LFA-1 Reduces Diabetic Kidney Disease in a Mouse Model of Type 2 Diabetes

Background: Diabetic dyslipidemia, characterized by elevated triglyceride-rich lipoproteins (TRLs), is a known risk factor for renal function decline. At the same time, macrophage accumulation has been observed in kidney biopsies in individuals with diabetic kidney disease (DKD). Thus, we wanted to test the role of monocyte infiltration in the progression of diabetic kidney disease.

Methods: BTBR WT (WT) and leptin-deficient (OB, diabetic) mice with LDL receptor deficiency were maintained on a high-fat diet to promote human-like dyslipidemia. Results: OB diabetic mice with human-like dyslipidemia have a dramatic increase in DKD (glomerular size: 4164 ± 385 µm² in WT mice and 8299 ± 622 in OB mice). albuminuria to creatinine ratio: 374.3 ± 71.0 µg/mg in WT mice and 4648 ± 1021 in OB mice). This was associated with increased monocyte recruitment, glomerular macrophage accumulation, and glomerular foam cells, suggesting a pathogenic role for macrophages in DKD progression (Mac-2 positive cells per glomerulus in WT mice was 1.0 ± 0.2 and 6.8 ± 0.6 in OB mice). Notably, diabetes increased the expression of the adhesion molecule ICAM-1 in the glomerulus and in isolated kidney endothelial cells (ICAM-1 µg per glomerulus in WT mice was 11.2 ± 3.1 and 54.7 ± 15.0 in OB mice) with a concomitant increase in monocyte binding partner, LFA-1. To test if LFA-1 facilitates monocyte infiltration into the glomerulus and exacerbates DKD injury, we treated WT and OB mice with a control blocking antibody or an anti-LFA-1 blocking antibody (9095). After 4 weeks, LFA-1 was still highly expressed on blood glucose and lipid levels, but resulted in a reduction in glomerular hypertrophy and urinary albuminuria in OB mice (glomerular hypertrophy: 6209 ± 346 µm² in control antibody-treated OB mice compared to LFA-1 treated OB mice 546 ± 164.0).

Conclusions: Together, these data suggest that diabetes promotes monocyte infiltration into the glomerulus, which in turn contributes to DKD.

Funding: NIDDK Support, Other NIH Support - National Institutes of Health (R01 DK121756)

SA-PO416
The Insulin/Insulin-Like Growth Factor Axis Is Crucially Important in the Kidney Poecyte Controlling Gene Transcription and Spliceosome Function
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Background: Insulin signalling to the podocyte via the insulin receptor (IR) is crucial for kidney function and insulin-like growth factor 1 (IGF1) signalling through the structurally related insulin-like growth factor 1 receptor (IGFIR) is also known to directly affect the podocyte. Since the IR and IGFIR are both present in podocytes, this study sought to elucidate the role of the insulin/IGF1 axis in podocyte function using mouse and cell culture models deficient in both receptors.

Methods: To examine the effects of combined receptor loss in vivo, a transgenic mouse model with conditional inactivation of podocyte IR and IGFIR was generated. In vitro, conditionally immortalised mouse podocytes were cultured under permissive and nonpermissive conditions and exposed to a diabetic milieu containing high ambient glucose and insulin as well as proinflammatory conditions, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with tidegusib, a highly-selective small molecule inhibitor of GSK3β. Podocyte injury was assessed and signaling pathways examined.

Results: Upon diabetic insult, podocytes demonstrated prominent signs of cytotoxic changes, marked by loss of homeostatic marker proteins like synaptopodin, increased oxidative stress and apoptosis, and stress-induced premature senescence, as evidenced by increased staining for the acidic senescence-associated-β-galactosidase activity, amplified formation of γH2AX foci, and elevated expression of mediators of senescence signaling, like p21 and p16INK4a. Podocyte injury was associated with a reduction in inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In podocytes overexpressing S9A, diabetic podocytopathy was worsened, concomitant with a desensitized insulin signaling activity, enhanced senescence response, impaired Nrf2 antioxidant response and the ensued exacerbation of oxidative damages. Conversely, GSK3β knockdown potentiated the insulin signaling, reinforced Nrf2 antioxidant response, and suppressed senescence, resulting in an improvement in podocyte injury. This protective effect was mimicked by tidegusib co-treatment, suggesting that GSK3β hyperactivity plays a key role in mediating diabetic podocytopathy.

Conclusions: Our findings suggest that GSK3β hyperactivity contributes to glomerular podocyte injury in diabetic kidney disease.

Funding: NIDDK Support

SA-PO417
Podocyte-Specific Deletion of SHP-1 Restored SUMOylation of Podocin and Reversed the Progression of Diabetic Kidney Disease
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Background: Both clinical and experimental data suggest that podocyte injury is involved in the onset and progression of diabetic kidney disease (DKD). Although the mechanisms underlying the development of podocyte loss is not completely understood, critical structure proteins such as podocin have been shown to play a major role in podocyte survival and function. We have reported that SHP-1 (a protein tyrosine phosphatase) expression is increased in podocytes of diabetic mice and glomeruli of patients with diabetes. However, the contribution of SHP-1 in podocytes has not been investigated.

Methods: Conditional podocyte specific SHP-1 deficient mice (Podo-SHP-1⁻/-) have been generated to evaluate the impact of SHP-1 on podocin expression (albuminuria and GFR) and kidney pathology. Deletion of SHP-1 was performed at 4 weeks of age (prevention group; prior to the onset of diabetes) and after 16 weeks of diabetes (reversibility group). Mice were euthanized at 24 weeks of age for renal function and histology assessment.

Results: Elevated albuminuria and GFR seen in the diabetic mice were preserved in the diabetic mice with specific podocyte ablation of SHP-1 at 4 weeks of age. Interestingly, late deletion of SHP-1 in podocytes after 16 weeks of diabetes also restored renal function and prevented kidney disease progression. Structural changes such as mesangial cell expansion, glomerular hypertrophy, GBM thickening, podocyte foot process effacement and podocyte loss induced by diabetes were also blunted and even reversed with deletion SHP-1 specifically in podocytes. Moreover, podocyte-specific deletion of SHP-1 at 4 weeks and 20 weeks of age prevented diabetes-induced expression of Coll IV, fibronectin, Rhoa, and ROCK1, whereas it restored nephrin, podocin and TRPC6 expression. Mass spectrometry analysis revealed that SHP-1 reduced SUMO2 expression and is associated with podocin which was also confirmed by immunoprecipitation and co-immunofluorescence in patients with diabetes kidney disease, while podocyte-specific deletion of SHP-1 allow to maintain podocin integrity and stability in a diabetic context.

Conclusions: Our data uncovered a new role of SHP-1 in the regulation of cytoskeleton dynamics and slit diaphragm protein expression and stability, and specific deletion of SHP-1 contribute to preserve podocyte function and even reverse DKD progression.

Funding: Government Support - Non-U.S.

SA-PO418
GSK3β: A Key Regulator of Glomerular Podocyte Injury in Diabetic Kidney Disease
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Background: Emerging evidence suggests that glycol synthase kinase (GSK3β), a critical transducer downstream of the insulin signaling pathway, acts as a convergent point for myriad pathways implicated in kidney injury, repair, and regeneration. However, its role in the pathogenesis of diabetic kidney disease remains highly controversial and was examined here.

Methods: Conditionally immortalized mouse podocytes were cultured under nonpermissive conditions and exposed to a diabetic milieu containing high ambient glucose and insulin as well as proinflammatory conditions, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with tidegusib, a highly-selective small molecule inhibitor of GSK3β. Podocyte injury was assessed and signaling pathways examined.

Results: Upon diabetic insult, podocytes demonstrated prominent signs of cytotoxic changes, marked by loss of homeostatic marker proteins like synaptopodin, increased oxidative stress and apoptosis, and stress-induced premature senescence, as evidenced by increased staining for the acidic senescence-associated-β-galactosidase activity, amplified formation of γH2AX foci, and elevated expression of mediators of senescence signaling, like p21 and p16INK4a. Podocyte injury was associated with a reduction in inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In podocytes overexpressing S9A, diabetic podocytopathy was worsened, concomitant with a desensitized insulin signaling activity, enhanced senescence response, impaired Nrf2 antioxidant response and the ensued exacerbation of oxidative damages. Conversely, GSK3β knockdown potentiated the insulin signaling, reinforced Nrf2 antioxidant response, and suppressed senescence, resulting in an improvement in podocyte injury. This protective effect was mimicked by tidegusib co-treatment, suggesting that GSK3β hyperactivity plays a key role in mediating diabetic podocytopathy.

Conclusions: Our findings suggest that GSK3β hyperactivity contributes to glomerular podocyte injury in diabetic kidney disease.

Funding: NIDDK Support

SA-PO419
Photobiomodulation Protects High-Fat Diet-Induced Diabetic Kidney Injury via Inhibition of Inflammation
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Background: Innovative therapeutic strategies for DKD are urgently needed due to limitations of current treatments. PBM, using red or near-infrared light to modulate cellular function, has gained increasing interest among available therapeutic strategies for many diseases due to its wide variety of positive effects, such as suppressing inflammation, improving mitochondrial activity, and alleviating oxidative stress, which are all inherent in DKD. However, the potential role of PBM in treating DKD has not yet been explored.

Methods: In vitro, human proximal tubular cells (HK2 cells) pre-treated with low dose (4.32 J) or high dose (8.64 J) PBM were then incubated with TGFB-β1 (2 ng/ml)
SA-PO420

C/EBPα Exacerbates Diabetic Nephropathy by Inducing ACSL4-Mediated Ferroptosis in Tubular Cells

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Background: Diabetic nephropathy (DN) is a serious complication of diabetes, leading to the progressive decline of kidney function. In this study, we examined the increased expression of CCAAT/enhancer binding protein alpha (C/EBPα) in DN patients and investigated its potential role in DN pathogenesis.

Methods: Pepck-Cre+/Cebpa+/ (WT) and Pepck-Cre+/Cebpa+/ (KO) mice were streptozotocin (STZ)-induced for diabetes. Renal histopathology, UACR, BUN, SCr, and Cystatin C levels were assessed for renal injury. Kidney tissues were analyzed for ferroptosis markers (GPX4, 4-HNE, MDA). C/EBPα transcriptional activity was examined using CUT&TAG, dual-luciferase, and ChIP-qPCR.

Results: STZ-treated WT mice showed more severe pathological injury, elevated SCr, cystatin C, BUN, and UACR. They also displayed pronounced signs of ferroptosis, including increased MDA, 4-HNE, and reduced GPX4. We further demonstrated that C/EBPα attenuated renal ferroptosis by binding to the TRS of ACSL4, a key enzyme of lipid peroxidation.

Conclusions: We discovered that C/EBPα regulated ACSL4 expression by binding to its TRS, triggering lipid peroxidation and subsequent ferroptosis. And knockout of C/EBPα could alleviate ferroptosis and ameliorate tubular injuries in DN.

Funding: Government Support - Non-U.S.

SA-PO421

PDI4 Ameliorates Renal Tubular Pyroptosis via Suppressing IRE1α-/sXBP1 Pathway in Diabetic Kidney Disease

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Background: Accumulating evidences imply the vital role of tubular injury in the pathogenesis of DKD, as well as of ER stress, the regulatory machinery of protein homeostasis. ER stress results in the activation of distinct unfolded protein response (UPR), and the effect of conserved UPR branch IRE1 on the diabetic tubular injury is still elusive.

Methods: We evaluated the activation of IRE1α/sXBP1 and NLRP3 inflammasome, as well as pyroptosis in the high glucose-stressed tubular cells. Furthermore, effects and underlying mechanism of PDI4 on the activation of IRE1α induced by high glucose were investigated.

Results: We identified the activated IRE1α/sXBP1 and NLRP3 inflammasome, as well as pyroptosis via analyzing the differential genes expression in the diabetic tubules, which was further confirmed in the glucose-stressed tubular cells and biopsy samples from patients of DKD. Consistently, silencing down of IRE1α or administration of IRE1α inhibitor alleviates high glucose-induced NLRP3 inflammasome and pyroptosis. Furthermore, we revealed that PDI4 suppresses the high glucose-induced tubular IRE1α/sXBP1. Immunoprecipitation and crosslinking assay demonstrated that high glucose promotes the dynamic interaction among PDI4, Bip with IRE1α and Bip with PDI4, while increase of PDI4 with IRE1α. Bond of PDI4 with IRE1α depends on -CHGC motif, and thus suppresses the activation of IRE1α/sXBP1. Dual-luciferase assay revealed that sXBP1 transcriptionally induces HSC70, hence results in the decrease of PDI4 via CMA dependent degradation. In vivo, we overexpressed PDI4 in two mouse models of DKD via injection of AAV9- PDI4. Our data demonstrated the ectopic overexpression of PDI4 alleviates the diabetic tubular injury and inflammation reaction, accompanied with the reduced IRE1α/sXBP1 and NLRP3 inflammasome.

Conclusions: Altogether, we revealed that the stress of high glucose activates IRE1α/sXBP1 pathway, NLRP3 inflammasome and pyroptosis in renal tubular cells. XBP1s reduces PDI4 via induction of HSC70 and thus selective CMA degradation. Reciprocally, PDI4 exhibits inhibitory effect on IRE1α/sXBP1 pathway via bond with oligomerized IRE1α.

Funding: Government Support - Non-U.S.
SA-PO422
Screening for Small-Molecule Inhibitor for KIM-1 and Its Functional Validation in Kidney Fibrosis
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Background: Kidney Injury Molecule-1 (KIM-1) is a glycosylated protein upregulated following proximal tubular injury in humans and mice. With acute and chronic injury, KIM-1 mediates the uptake of apoptotic cells, oxidized lipids, advanced glycated end products (AGEs), and albumin-bound to long-chain fatty acids. Overexpression of KIM-1 causes chronic kidney disease (CKD) in mice.

Methods: We developed a cell-based high throughput functional assay for KIM-1 mediated uptake of Dil labeled ox-LDL and screened 14,414 unique compounds. After setting up a score based on each compound’s potential to inhibit cellular ox-LDL uptake, we selected 240 potential hits and cherry-picked them from the primary screening. We performed secondary assays to confirm whether TW-37 quenches the fluorophore or it cleaves the extracellular domain of KIM-1. We employed cell-based binding assays, competitive inhibition assays, and Raman spectroscopy to investigate the binding of recombinant human KIM-1 to a top-hit molecule, TW-37.

Results: We found several hits, with TW-37 as the top hit. TW-37, a second-generation benzyl derivative of gossypol, had the highest inhibitory effect on ox-LDL uptake. TW-37 is known to be an inhibitory activity; however, Bcl-2 blockade with another specific Bcl-2 inhibitor, ABT-263, did not inhibit KIM-1-dependent ox-LDL uptake, showing that the effects of TW-37 and were not related to Bcl-2 inhibition. TW-37 is not toxic to epithelial cells at concentrations up to 11 µM. Our results from fluorescence quenching experiments confirmed that TW-37 does not quench Dil-fluorophore nor cleave KIM-1. In silico docking, experiments revealed a putative TW-37 binding pocket spanning residues 37 to 52 of KIM-1. Raman spectroscopy showed that TW-37 specifically binds to recombinant human KIM-1 and not to the BSA. TW-37 significantly decreased the cellular binding of ox-LDL and BSA-conjugated palmitic acid.

Conclusions: We have identified and characterized TW-37 as an inhibitor of KIM-1 binding. Thus, TW-37 has potential use as a therapeutic for treating kidney disease where chronic KIM-1-mediated uptake of lipid-laden albumin into the proximal tubule contributes to fibrosis and CKD.

Funding: NIDDK Support, Other NIH Support - American Heart Association

SA-PO424
Non-Steroidal Mineralocorticoid Receptor Antagonists (MRAs)-Finerenone Ameliorates Mitochondrial Dysfunction via PI3K/Akt Signaling Pathway in Diabetic Tubulopathy
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Background: Diabetic tubulopathy (DT) is gradually evaluated as same as glomerular pathology in the pathophysiological perturbations of diabetic kidney disease (DKD). The mitochondria-centric view of DT is emerging as a vital pathological factor in metabolic diseases including DKD. Finerenone (FIN), a novel non-steroidal MRAs, attenuates proteinuria and fibrosis in tubules in DM, but these precise pathomechanisms remain unclear.

Methods: We investigated the role of mineralocorticoid receptor (MR) activation in perturbation of mitochondrial function via PI3K/Akt signaling pathway, including mitochondrial dynamics and mitophagy, under a DM state or hyperglycemia condition.

Results: In vitro, the molecules were examined in kidneys of DM and FIN treatment mice as well. Notably, FIN administration partially attenuated mitochondrial fragmentation, oxidative stress, and apoptosis and restored mitophagy via PI3K/Akt signaling pathway both in HK-2 cells subjected to HG and tubular cells of DM mice.

Conclusions: These results suggest a novel mechanism linking MR activation to mitochondrial dysfunction via PI3K/Akt signaling pathway during tubular injury in the pathogenesis of DKD and it provides evidence support for FIN as a agent for the treatment of DKD.

SA-PO423
Renal Tubule-Specific Angiotensinogen Knockout Ameliorates Diabetic Kidney Disease in Type 1 Diabetic Akita Mice
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Background: Angiotensinogen (AGT), the sole precursor of angiotensins in the renal renin-angiotensin system (RAS), is highly expressed in the renal proximal tubules (RPTs) of mice and patients with diabetic kidney disease (DKD). We reported previously that mice specifically overexpressing AGT in RPTs (AGT-Tg) develop hypertension and kidney injury. However, the pathophysiological roles of the intrarenal RAS in DKD progression is not well-defined. We investigated whether genetic deletion of AGT specifically in renal tubules (RT) could improve kidney injury in type 1 diabetic Akita mice.

Methods: We generated Akita mice with RT-specific Agt knockout (Akita AgtKO) by crossbreeding Akita AgtKO mice with AgtKO mice (tubule-specific FasX-Cre) mice. Male, 8 weeks, KO Akita (AgtKO) mice (AgtKO), non-diabetic RT-KO (RT KO) mice, and non-diabetic AgtKO mice were studied at 20 weeks of age. Physiological data, kidney function, and urinary angiotensin II (Ang II) were assessed. Immunostaining on kidney sections, western blotting (WB) and real-time quantitative PCR (RT-qPCR) were performed to assess protein and gene expression in isolated RPTs.

Results: Agt deletion in RT did not significantly affect systolic blood pressure in Akita mice. Fasting blood glucose levels were lower in Akita AgtKO mice vs. Akita mice. Glomerular filtration rate was increased in Akita mice, but was normalized in Akita AgtKO mice. The urinary albumin-creatinine ratio (ACR) and Ang II levels were increased in Akita mice, but significantly decreased in Akita AgtKO mice. Akita mice exhibited glomerular and tubular hypertrophy, tubular luminal dilation, and necrosis; these abnormalities were markedly attenuated in Akita AgtKO mice. Podocyte number (defined by P57 and WT1 staining) was decreased in Akita mice, but was partially restored in Akita AgtKO mice. Sodium-glucose cotransporter 2 (SGLT2) expression was lower in Akita AgtKO mice than in Akita mice. Urinary glucose excretion was higher in Akita AgtKO mice than in Akita mice.

Conclusions: Deletion of Agt in RT decreased hyperglycemia, glomerular hyperfiltration, ACR, kidney injury, and SGLT2 expression in Akita mice, demonstrating that inactivation of the intrarenal RAS attenuates DKD progression, at least in part, via down-regulation of SGLT2 expression.

Funding: Government Support - Non-U.S.
SA-PO426

SIRPα Contributions to Muscle Kidney Cross-Talk in Diabetic Kidney Disease
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Background: Fatty acid oxidation (FAO) is a preferred energy source for highly metabolic cells including cardiomyocytes and proximal tubular cells. The kidney is second only to the heart in mitochondrial numbers and oxygen consumption. ATP generation occurs mainly through fatty acid oxidation in the proximal tubular cells. Lipotoxicity has been linked to worsening kidney disease. Specifically, ATP depletion increases lipid accumulation, tubular necrosis and maladaptive repair ultimately leading to kidney dysfunction. Here we examined the role of muscle mediator, signal regulatory protein alpha (SIRPα) and its role in kidney FAO and function. Circulating serum SIRPα has been identified in patients with CKD, therefore we have examined the effects of SIRPα in a diabetic model of kidney disease.

Methods: Control flox mice, muscle (m)-specific and adipose (a)-specific SIRPα knockout (KO) mice were subjected to a 50% high fat diet and compared to mice on standard chow. Metabolic processes including mRNA, protein expression, and oxygen consumption rates (Seahorse Bioscience) were identified. Triglyceride content was evaluated by triglyceride clearance assay.

Results: Control flox mice display elevated levels of serum SIRPα in response to HFD. mSIRPα KO mice but not adipose-specific SIRPα KO mice exhibit evidence of improved body weight, intracellular insulin signaling in peripheral tissues, and adipokine profile. Additionally, these mice demonstrate less intramuscular fat when compared to control mice on HFD. Also, exogenous SIRPα impaired proximal tubular FAO while reducing ATP production. Finally, kidney tissues in mSIRPα KO mice unlike aSIRPα KO mice displayed improved renal fatty acid oxidation, a reduction in kidney triglyceride content, less kidney fibrosis, and importantly protection against diabetic kidney disease (cystatin C similar to control) despite obesity-induced diet.

Conclusions: These results suggest the importance of the muscles contribution to kidney disease, specifically, myokine SIRPα in exacerbating diabetic kidney disease. Our discoveries provide insight in correcting metabolic defects associated with kidney FAO and to prevent diabetic kidney disease.

Funding: Private Foundation Support

SA-PO427

ALCAT1-Mediated Cardiolipin Remodeling Contributes to Podocyte Mitochondrial Dysfunction in Diabetic Kidney Disease
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Background: Recent studies suggested that mitochondrial damage resulting from abnormal cardiolipin remodeling was associated with the pathogenesis of diabetic kidney disease (DKD). As a cardiolipin acyltransferase, ALCAT1 was confirmed to be involved in Parkinson’s disease and other aging-related diseases by regulating pathological CL remodeling. The purpose of this investigation was to determine the role of ALCAT1 in DKD.

Methods: We used db/db mice to conduct the in vivo experiments. Double immunolabeling and Western blots (WB) were performed to assess ALCAT1 distribution and expression in glomeruli. Mitochondrial structure was examined by transmission electron microscope (TEM). CL composition was assessed by lipidomics analysis. We cultured conditionally immortalized human podocytes to perform the in vitro studies. Lipidomics, TEM and WB analysis were similar to the in vivo study. Mitochondrial function was evaluated by measuring ATP production, mitochondrial membrane potential, mitochondrial ROS and ATP. The overexpression plasmids and siRNA were transfected to further investigate the changes of podocyte mitochondrial injury following overexpression or knockdown of ALCAT1.

Results: ALCAT1 expression was increased in glomerular podocytes of db/db mice and high-glucose (HG) cultured podocytes, accompanied by increased oxidized CL (ox-CL) and mitochondrial damage. ALCAT1 deficiency effectively blocked HG-induced ox-CL and podocyte mitochondria damage. In contrast, ALCAT1 upregulation enhanced ox-CL and mitochondria malfunction. Moreover, CL antioxidant SS-31 treatment markedly inhibited mitochondrial dysfunction and cell injury. ALCAT1 treatment could partly reverse the damage caused by ALCAT1 overexpression. We further found that ALCAT1 could mediate the key regulators of mitochondrial dynamics and mitophagy.

Conclusions: Our results demonstrated that ALCAT1-mediated cardiolipin remodeling played a crucial role in diabetic kidney disease and provided new insights for its treatment.

Funding: Government Support - Non-U.S.

SA-PO428

IL-6-ZIP14-GPX4 Axis Is Involved in Ferroptosis in Diabetic Kidney Disease
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Background: Ferroptosis is caused by lipid peroxidation and iron accumulation. Our previous study have shown that ZIP14 is involved in ferroptosis in Diabetic kidney disease (DKD), but the mechanism is unknown. Interleukin-6 (IL-6) can specifically increase the expression of ZIP14. Thus, we hypothesize that IL-6-ZIP14-GPX4 axis is involved in ferroptosis in DKD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
Methods: Renal biopsies of patients with DKD were collected to detect the changes related to ferroptosis. We induced DKD in 8-week-old male rats with streptozotocin (STZ) and treated with GPX4-Adeno-associated viral (AAV) via tail vein to analyze the degree of renal injury. The expression of GPX4, IL-6 and ZIP14 was detected in kidney.

Results: The expression of GPX4 was down-regulated in DKD. While the levels of IL-6 and ZIP14 were up-regulated in kidney of STZ rats. Iron deposition was confirmed in kidney of DKD. The mitochondria of renal biopsy presented reduced mitochondrial volume and missing mitochondrial cristae. The levels of malondialdehyde (MDA), and Fe2+ in STZ group were higher than in the control. While the levels of GSH and SOD were lower than in the control. Over-expression of GPX4 decreased the expression of IL-6 and ZIP14 in kidney of STZ rats. Also, the urine protein-creatinine ratio, and the degree of renal injury. The expression of GPX4, IL-6 and ZIP14 was detected in kidney. (STZ) and treated with GPX4-Adeno-associated viral (AAV) via tail vein to analyze the degree of renal injury. The expression of GPX4, IL-6 and ZIP14 was detected in kidney.

Conclusions: The IL-6-ZIP14-GPX4 axis is involved in ferroptosis in DKD.
SA-PO431

Dampening Protein Translation Abrogates the Development of Albuminuria in a Diabetic Mouse Model

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Background: Diabetes remains a major cause of chronic kidney disease and end stage kidney disease. The pathophysiological processes leading to the development of kidney disease in diabetes are poorly understood because it is not common practice to obtain kidney biopsies in diabetic patients without diabetic kidney disease (DKD). We have previously demonstrated that translation, the fundamental process in protein synthesis, is increased in the kidney in a mouse model of diabetes. This increase in translation was observed prior to the onset of DKD. We here investigate where direct inhibitors of protein translation, such as tetracyclines, can mitigate the development of proteinuria.

Methods: Db/db mice on a Kaslis strain background which are prone to developing manifestations of DKD over time were used. These mice demonstrate an increase in translation starting as early as six weeks. Treatment with minocycline (50mg/kg daily x 4 weeks by gavage) was started at 8 weeks and the kidneys were harvested for polyribosomal profiling (PRP). In a parallel set of experiments, 6-week old Db/db mice (n=10) were treated for up to 10 weeks with minocycline (50mg/kg daily in drinking water) and urine was collected weekly for measurement of albuminuria. Finally, a separate group of Db/db mice were treated with the SGLT2 inhibitor (dapagliflozin; 1mg/ kg, po) for 4 weeks and kidneys were harvested for PRP.

Results: Treatment with minocycline resulted in a 30% reduction in global protein translation as measured by polyribosomal count treated mice developed only significant albuminuria (albumin/creatinine ratio between 0.6-6 µg/g). In contrast, in all mice treated with minocycline albumin/creatinine ratios < 0.5 µg/g. Interestingly, SGLT2 inhibition also resulted in reduction of protein translation as measured by PRP.

Conclusions: Increased protein synthesis in the kidney is a feature of diabetes before the onset of DKD. Pharmacologic strategies to reduce protein synthesis may serve as a new therapeutic avenue to prevent the development of DKD.

Funding: NIDDK Support

SA-PO432

The Effect of Altered Branched-Chain Amino Acid (BCAA) Metabolism on Proteinuria and Mesangial Expansion in db/db Mice Treated with SGLT2 Inhibitor

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Background: Increased protein synthesis in the kidney is a feature of diabetes before the onset of DKD. The molecular mechanisms of this increase in translation are not completely understood. The branched chain amino acids (BCAAs) play important roles in protein metabolism. We have previously shown that treatment with the SGLT2 inhibitor tofogliflozin (1 mg/kg daily) for 8 weeks significantly reduced proteinuria in db/db mice and that this reduction was due to a decrease in mesangial expansion.

Methods: 

- Treatment group (db/db mice treated with tofogliflozin): n=10
- Control group (db/db mice without treatment): n=10
- High fat diet group (db/db mice maintained on a high fat diet): n=8
- Tofogliflozin treatment group (db/db mice treated with tofogliflozin plus high fat diet): n=8

Results: Tofogliflozin treatment for 8 weeks reduced albuminuria by 71% (p<0.01) compared to the control group. This reduction in albuminuria was accompanied by a decrease in mesangial expansion (p<0.05) and a decrease in the expression of phosphorylated S6 kinase (pS6K) indicating mTORC1 activation. The higher expression of pS6 in the mesangial cells of db/db mice compared to db/m mice (p<0.05). Tofogliflozin reversed the changes in proteinuria and mesangial expansion in db/db mice treated with high fat diet (p<0.01). Tofogliflozin reduced the expression of phosphorylated S6K in db/db mice treated with high fat diet (p<0.01). Tofogliflozin treatment for 8 weeks significantly reduced the expression of phosphorylated S6K in db/db mice treated with high fat diet (p<0.01).

Conclusions: Tofogliflozin treatment reduces the development of albuminuria in db/db mice by modulating mTORC1 activation. The higher BCAA levels in db/db mice treated with tofogliflozin were associated with a decrease in mesangial expansion by modulating mTORC1 activation.

Funding: Commercial Support - Kowa Company, Ltd.

SA-PO433

Renal Tubule-Specific Nrf2 Deletion Downregulates SGLT2 and Angiotensinogen Expression and Ameliorates GFR and Kidney Injury in Akita Mice

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Background: Nuclear factor erythroid-2 related factor 2 (Nrf2) expression is increased in kidneys of mice and patients with diabetes. We have reported that overexpression of Nrf2 in renal proximal tubular cells (RPTCs) increases sodium-glucose co-transporter 2 (SGLT2) and angiotensinogen (AGT) expression and exacerbates diabetic glycaemia and progression of nephropathy in type 1 diabetic (T1D) Akita Nrf2+/− Nrf2ΔRC (tg) mice (Diabetes 2021). However, the pathophysiological role of renal Nrf2 in the progression of diabetic kidney disease (DKD) is not well understood. We now report the impact of Nrf2 deletion specifically in renal tubules (RT) of Akita mice on the expression of SGLT2 and AGT in RPTCs in the setting of hyperglycemia and kidney injury.

Methods: Akita RT-specific Nrf2 knockout (Akita Nrf2−/− KO) mice were generated by crossing Akita with Nrf2−/− KO mice using Pax8-Cre (through breeding male Nrf2−/− KO mice). Immunostaining on kidney sections, Western blot (WB) and real-time qPCR (RT-qPCR) were employed to assess protein and gene expression in isolated RPTs. Physiological and kidney morphological changes were assessed in male Akita Nrf2+/− KO, Akita Nrf2−/− KO, diabetic Nrf2−/−−/− and Nrf2−/− KO mice at the age of 10 to 20 weeks.

Results: SGLT2 and AGT expression in RPT were significantly lower in Akita Nrf2−/− KO mice compared to Akita mice. Glomerular filtration rate (GFR) was increased in Akita mice but was normalized (reversed glomerular hyperfiltration) in Akita Nrf2−/− KO mice. Fasting blood glucose, glomerular tuft volume, RPTC volume, tubular luminal dilation, tubular injury score, kidney weight and urinary albumin-creatinine ratio (ACR) were significantly increased in Akita mice vs non-diabetic Nrf2−/−−/− and Nrf2−/− KO mice. These abnormalities were greatly reduced in Akita Nrf2−/− KO mice, except for fasting blood glucose. Functional excretion of glucose was increased in Akita mice and increased further in Akita Nrf2−/− KO mice.

Conclusions: Our results show that RT-Nrf2 deletion ameliorates GFR and kidney injury in Akita mice, indicating renal Nrf2 is important in tubuloglomerular feedback via down-regulation of intrarenal SGLT2 and AGT expression.

Funding: Government Support - Non-U.S.

SA-PO434

Residues L667 and L658: Critical Players in the Functional Activation of SGLT2 by MAP17

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Background: Sodium-glucose cotransporter 2 (SGLT2) is crucial for renal glucose reabsorption. Unlike its family member SGLT1, SGLT2 requires an activator protein, MAP17, for its transport activity. However, the mechanism of this unique activation is unclear. A recent cryogenic electron microscopy (cryo-EM) study predicted interactive residues on SGLT2-MAP17 complexes, but their functional significance requires validation.

This study aims to investigate the role of specific SGLT2 amino acid residues in the functional activation of SGLT2 by MAP17 and their effect on glucose transport.

Methods: Five SGLT2 residues predicted to interact with MAP17 were selected based on cryo-EM predictions and aligned sequences of SGLT2 homologues. Mutations (mostly to alanine or cysteine) were designed to assess the effects of side chain and polarity changes. Transport studies were conducted using Xenopus oocytes expressing wild-type SGLT2 (SGLT2-WT) proteins or mutants and co-expressing MAP17. Oocytes were co-injected with mRNA for SGLT2-WT or SGLT2 mutants, and MAP17 mRNA was co-injected. Negative controls included H2O-injected oocytes and SGLT2-only injected oocytes. Glucose transport in each oocyte was assayed by perfusing solutions containing 86 mM Na+ and 20 mM glucose and measuring whole cell currents generated by glucose-activated Na+ transport using two-electrode voltage clamp.

Results: Three SGLT2 mutations (L667C, L667M, and L658C) significantly inhibited glucose transport compared to SGLT2-WT. Specifically, L667C inhibited transport by 88%, L667M by 72%, and L658C by 70% (p<0.01). Notably, mutations F666A, F666Y, L667C, L667M and L658C mutations inhibited glucose transport potentially by disrupting the interaction between SGLT2 and MAP17, likely through altered hydrophobicity or disulfide bond formation. While other predicted interaction sites have minimal contribution to SGLT2 function, the pair Leu667-Met668 emerges as a critical residue, displaying conservation and divergence among species and family members. This study confirmed the effects of cryo-EM predicted residues on SGLT2-MAP17 interaction and identified novel critical amino acids (L667 and L658) for SGLT2 function and MAP17 interaction.

Funding: Private Foundation Support
Combination Therapy with Lisinopril and Dapagliflozin Rescues GFR Decline and Glomerular Damage in the Akita Mouse Model of Diabetic Kidney Disease


Background: We previously showed that male AkK/ mice develop DKD with progressive decline of GFR upon high fat diet feeding together with a vasoconstrictor. In this study, efficacy of combination therapy with an ACE-inhibitor (lisinopril) and SGLT2-inhibitor (dapagliflozin) on renal function and histopathology was investigated.

Methods: Male AkK/ mice underwent uninephrectomy (UNX). After recovery mice received high fat diet (45% LARD) and 50 mg/L LNNA in drinking water (w/0%). At week 4, lisinopril (2.5 mg/kg/day) and at week 8 dapagliflozin (5 and 20 mg/kg/day) were started. Body weight, blood glucose, food and water intake and albuminuria were determined regularly. GFR was measured transcardially by FITC-sinistin clearance. Mice were terminated at week 16 and kidney histology was scored. Non-induced and induced non-treated mice were used as controls.

Results: Treatment of AkK/ mice on HFD+LNNA with Dapagliflozin reduced blood glucose immediately. Combination therapy with Lisinopril and Dapagliflozin (5 mg/kg/day) rescued the progressive GFR decline to levels seen in non-induced control mice. Pathology showed that the percentage of healthy glomeruli increased from 14% to 26% after combination therapy (lapa 5). Interstitial fibrosis and tubular atrophy were significantly reduced by combination therapy.

Conclusions: Male AkK/ mice on a HFD and LNNA developed DKD resulting in CKD. Combination therapy with Lisinopril and Dapagliflozin rescued GFR decline and reduced glomerular damage. However, the underlying mechanism(s) of this model is clinically relevant and can be used to study compound efficacy in both early and more advanced stages of DKD.

Funding: Commercial Support - Janssen, BPM, Government Support - Non-U.S.

Figure 1: Dapagliflozin decreased blood glucose levels. Combination therapy with Lisinopril and Dapagliflozin rescued GFR decline, glomerular damage and interstitial fibrosis and tubular atrophy.

Canagliflozin Inhibits Hedgehog Interacting Protein (Hhip)-Mediated Renal Tubular Cell Senescence in Type 1 Akita Mice

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Background: We have recently reported that hedgehog interacting protein (Hhip) activates sodium-glucose cotransporter 2 (Slc5a2) expression and promotes tubular senescence-association secretory phenotype (SASP) in murine diabetic kidney disease (DKD) (Diabetologia 2021). However, the underlying mechanism(s) are poorly understood. Here, we aimed to elucidate the functional impact of the SGLT2 inhibitor, Canagliflozin (Can) on tubular Hhip-mediated cell senescence in vivo and in vitro.

Methods: Akita renal proximal tubular cells (RPTC)-specific Hhip transgenic (Tg) mice (Akita/Hhip-Tg, Akita/Non-Tg) and their respective controls (Hhip-Tg or Non-Tg) were studied. Cana was administered to Akita mice (Akita/Hhip-Tg vs. Akita/Non-Tg) in water (10 or 30 mg/kg/day) from 6 to 20 weeks of age. Primary RPTCs and rat immortalized RPTC cells (IRPTCs) were also employed.

Results: Hhip-Tg mice were fertile and phenotypically normal cf. non-Tg. Compared to respective controls at 20-weeks, both Akita/Hhip-Tg and Akita/Non-Tg mice displayed typical DKD dysfunction (hypertension, hyperglycemia, polycythemia, increased urinary albumin/creatinine ratio and glomerular filtration rate) and dysmorphology (renal hypertrophy, glomerulosclerosis, tubulopathy). These features were more pronounced in Akita/Hhip-Tg than in Akita/Non-Tg. Cana administration ameliorated DKD features in a dose-dependent manner. There was evidence of renal tubular SASP—Heightened β-galactosidase activity was seen in Hhip-Tg cf. Non-Tg mice, and its activity was more pronounced in Akita/Hhip-Tg cf. Akita/Non-Tg mice. In contrast, Cana more effectively inhibited tubular SASP in kidneys of Akita/Non-Tg cf. Akita/Hhip-Tg mice. In IRPTCs, excessive Hhip gene expression through either engineered overexpression or high glucose (25mM D-glucose) stimulation promoted extracellular vehicle (apoaptotic bodies and microvesicles)-mediated cellular senescence, and their effects were inhibited by the addition of canagliflozin (50mM).

Conclusions: Canagliflozin appears to be capable of offsetting DKD-related tubulopathy and tubular senescence, possibly, via the inhibition of excessive Hhip delivered extracellularly in DKD.

Funding: Government Support - Non-U.S.

SA-PO437
Cholesterol 25-Hydroxylase Protects Diabetic Kidney Disease by Regulating ADP Ribosylation Factor 4

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Background: Cholesterol 25-hydroxylase (CH25H) is a cholesterol hydroxylase which is actively involved in lipid metabolism. In kidney, CH25H predominantly expressed in endothelial cells and macrophages, which are renal resident cells and immune cells that have been proved of great importance in context of DKD progression. Intriguingly, the expression of CH25H is upregulated in diabetic mice. In this study, we determined the effects of CH25H and its product 25HC in DKD.

Methods: C57BL/6 wild type (ch25h-/-), ch25h KO (ch25h-/-/lepr-/-), diabetic (ch25h-/-/lepr-/-) and DKO (ch25h-/-/lepr-/-/lepr-/-) were utilized in this study. The mice were sacrificed at the age of 24 weeks. C57BLKS/J male lepr-/- and lepr-/- mice were used for in vivo experiments. All studies were conducted with human umbilical vein endothelial cells and immortalized human podocytes.

Results: CH25H predominantly expressed in glomerular and peritubular endothelial cells. Lepr-/- and STZ-induced diabetic mice have an elevated level of CH25H mRNA level in glomeruli. Global deletion of ch25h in Lepr-/- mice aggravated DKD, showing more albuminuria and worse glomerular hypertrophy and mesangial matrix deposition, and can be alleviated by 25HC treatment. In vivo studies revealed that 25HC binds to a GTP-binding protein Arf4, enhancing its activity by inhibiting the interaction between Arf4 and its GTPase-activating protein Asap1. Interesting, Asap1 expressed mostly in endothelial cells and its expression is increased in the diabetic kidney. In Golgi apparatus, Arf4 activity is required for maintaining essential protein transportation and cellular function, while in cytosol Arf4 inhibits the activity of Aldolase and accumulation of methylglyoxal, thereby preventing cells from death.

Conclusions: Lack of CH25H aggravated DKD and can be rescued by exogenous supplement of its catalytic product 25HC. 25HC protects DKD by maintaining Arf4 activity via inhibiting Arf4 interaction with its GAP Asap1. Activated Arf4 is required for promoting protein transportation in golgi apparatus and suppressing methylglyoxal production in cytosol, thereby preventing cells from injuries.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO438
Targeting the LXR/mTOR Signaling Axis: A Novel Therapeutic Strategy for Modulating Autophagy in Diabetic Kidney Disease

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Background: Autophagy, vital for maintaining kidney homeostasis, is impaired in podocyte dysfunction and diabetes-induced podocyte injury. However, the underlying mechanisms behind autophagy alteration remain poorly understood. Both mTOR complexes and oxidative stress have been implicated as potential key players in diabetes-related autophagy imbalance, yet the mechanisms leading to their alterations are unclear. Additionally, the role of Liver-X-Receptor (LXR) in autophagy and its interaction with other pathways in diabetic kidney disease (DKD) is not well defined. This study aims to elucidate the role of the LXR/mTOR axis in autophagy and its connection to podocyte injury in type 2 diabetes (T2D).

Methods: In vitro experiments were performed using cultured human podocytes while in vivo experiments were conducted using control mice and T2D mice. T2D mice (db/db mice) with different inhibitors of autophagy drugs inhibiting specific components of the mTOR complex: rapamycin for mTORC1, JR-AB2-011 for mTORC2, and PP242 for mTORC1/mTORC2. Another group of T2D mice was treated with T0 to activate LXR. In parallel, control mice were treated with Hydroxychloroquine (HCQ), an autophagy inhibitor, to further investigate the effects of LXR activation.

Results: High glucose levels or hyperglycemia can lead to podocyte injury and dysregulation of autophagy. This is primarily caused by the production of reactive oxygen species (ROS) through NADPH oxidase activation. Additionally, LXR deactivation and activating mTORC1/mTORC2 activation contribute to these effects. Activation of LXR using T0 restores renal homeostasis by reducing proteinuria, reversing histological and phenotypical changes, and inhibiting NOX4. Moreover, LXR activation improves diabetes-induced autophagy alteration by restoring the expression of LC3B and p62. LXR activation also reduces the activation of both mTORC1 and mTORC2. Furthermore, inhibiting mTORC1, mTORC2, or mTORC1/mTORC2 pathways replicates the effects of LXR activation on ROS production and renal injury, but it does not affect the LXR pathway. Conversely, inhibiting autophagy in control mice using HCQ alone is enough to induce kidney injury.

Funding: NIDDK Support, Veterans Affairs Support

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

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**Conclusions:** This study presents evidence for a novel role of LXR/mTOR in regulating oxidative stress and autophagy during the onset and progression of diabetic kidney disease (DKD).

**SA-PO439**

**Phenotypic Features of Advanced Nephropathy in a Murine Model of Metabolic Syndrome: Focus on Sex Differences**

**Sharma S, Prabhakar, Texas Tech University Health Sciences Center, Lubbock, TX.**

**Background:** Diabetes nephropathy (DN) which is often an integral part of obesity and metabolic syndrome (MS), is the most common cause of ESRD in most countries. We had originally characterized nephropathy in ZSF rats, a rat model of DN and MS (Prabhakar S, JASN 2007). While male ZSF rats developed advanced features of DN and MS, there were no female ZSF rats which have the same genetic background have not been well described. The goals of this study are to examine and compare the expression of MS in male and female ZSF rats at an advanced age.

**Results:** The data here represent the results at 46th week in ZSF and CD rats. Obesity was first evident in ZSF rats at 20 wk but progressed steadily. Male ZSF rats were heavier than female ZSF rats (73±31 vs. 58±44g p<0.0001) CD male rats were also heavier than female (802±111 vs. 306±31, p<0.0001) Male ZSF and CD rats did not differ significantly in their weights. Male ZSF rats developed significant hypertension compared to female rats (169±126 vs. 139±90 mmHg p<0.05) Male ZSF and female rats had similar BP (139±102 vs. 136±90 mmHg p<NS). Proteinuria was significantly high in male ZSF rats (2±1 g/l vs. 1 g/l) and CD rats had trace or no proteinuria. Male ZSF rats developed overt diabetes compared to mild diabetes in female ZSF rats.

**Conclusions:** These findings indicate that despite having similar genetic make-up, obese ZSF rats displayed major differences in male and female sexes. In general male rats displayed more florid features of metabolic syndrome. These observations warrant more intensive investigations to explore the etiologic basis and factors to account for such differences between sexes.

**Funding:** Private Foundation Support

**SA-PO440**

**Discovery and Development of a Therapeutic Lead Compound for Diabetic Kidney Disease**

**Rachel Njiej,1 Haley M. Donow,2 Judith T. Molina David,1 Jeffery D. Pressly,1 Haley Gye,1 Sandra M. Merscher,2 Marc Giuliani,1,3 Alessia Foroni,1,3 Hassan Ali.1 University of Miami School of Medicine, Miami, FL; 2Florida International University, Miami, FL.**

**Background:** Diabetic kidney disease (DKD) is a leading cause of kidney failure worldwide. We previously demonstrated that the accumulation of lipid droplets (LDs) in podocytes leads to lipotoxicity and cell death in DKD. Drugs that lower circulating lipids do not halt DKD progression. However, directly reducing LD accumulation in podocytes was shown to slow disease progression in experimental DKD. We hypothesize that a drug that specifically targets LD accumulation in podocytes will be effective at halting or reversing DKD progression.

**Methods:** We developed a phenotypic assay using immortalized human podocytes and deployed it to screen a combinatorial library representing over 45 million unique compounds. We performed mechanistic analyses on hit compounds using transcriptomic, proteomic, and phenotypic techniques. We conducted medicinal chemistry to improve drug-like properties and tested one compound in a murine model of DKD.

**Results:** We identified and synthesized a series of novel compounds that effectively inhibit LD accumulation in podocytes and protect them from injury and cell death. RNAseq analysis revealed that these compounds significantly reduce the expression of genes that mediate tumor necrosis factor (TNF)-signaling, a pathway associated with LD accumulation and podocyte injury, and alter the expression of lysosome-associated membrane glycoprotein (LAMP), a regulator of autophagy. Mechanistic studies confirmed that these compounds robustly activate autophagy/lypophagia, leading to a significant reduction in LD accumulation in podocytes. We tested one compound with improved drug-like properties in an experimental model of DKD, db/db mice, and found that it significantly prevented the progression of DKD, as evidenced by a reduction in albumin-to-creatinine ratios (ACR) and the reduced pathological renal damage associated with DKD.

**Conclusions:** Our screening assay successfully identified compounds that protect podocytes from LD accumulation by inducing lipophagy. We developed a lead candidate from our initial hit series that demonstrates remarkable efficacy in preventing DKD progression in vivo. We are continuing lead optimization efforts toward generating a clinical candidate for testing in a clinical trial.

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

**SA-PO442**

**siRNA Inhibition of Lysophosphatidic Acid Receptor 1 (LPAR1) Attenuates Kidney Fibrosis and Improves Kidney Function in a Rat Model of Hypertensive CKD**

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**Background:** LPAR1 plays an important role in fibrosis. Its expression is upregulated in kidneys of different injuries. We developed a LPAR1 siRNA-LNP that shows a good kidney cell distribution and improves kidney fibrosis and function in diabetic and Adriamycin-induced models of CKD. Here we demonstrate these efficiencies in rats of hypertensive CKD.

**Methods:** Dahl salt-sensitive rats were fed an 8% high-salt diet for 6 weeks and then treated with the LPAR1 siRNA-LNP at 1 or 2 mpk once/wk for 4 weeks. A group with an ACEi, Perindopril treatment (Tx) at 3 mpk daily and a combination Tx group was also included in one study. Kidney LPAR1 knockdown, uAcr, urine KiM-1 and Cystatin C, kidney hydroxyproline (HP), the expression of the key fibrogenic and inflammatory genes and others were measured. Histological changes were determined.

**Results:** LPAR1 siRNA Tx causally dose-dependent reduction in uAcr (~80% reduction with 2 mpk), urine KiM-1 and Cystatin C levels (both were nearly normalized at 2 mpk). The Tx also dose-dependently lowered blood pressure (systolic pressure dropped from ~176 to 142 mmHg in the 2 mpk group) and improved animal survival (~50% in control group vs 100% in 2 mpk group). The Tx significantly decreased kidney HP content. Histological analysis found that the Tx improved both glomerular and tubular histology, including mesangioendothelial scar formation and tubulointerstitial fibrosis. RNAscope analysis found that Tx at 2 mpk normalized LPAR1 expression. RNAseq analysis indicated that the Tx significantly lowered fibrogenic and inflammatory signaling activities and increased mitochondrial TCA cycle and oxidative phosphorylation activities. RT-PCR confirmed increased expression in expression of the key fibrogenic inflammation genes including TGFβ, CTGF, Col1α1, Col2α1, RAGE and NFκB. Though both LPAR1 siRNA and Perindopril lowered serum creatinine levels to a similar degree, LPAR1 siRNA showed a much better efficacy than the ACEi in improving kidney histology. Combination Tx showed additive effects on serum creatinine and kidney histology.

**Conclusions:** These data support the hypothesis that LPAR1 inhibition of LPAR1 improves kidney fibrosis and function in rats of hypertensive CKD in addition to other models. Therefore, the LPAR1 siRNA-LNP could be a potential therapeutic for kidney fibrosis.
SA-PO443
Targeting Lysophosphatidic Acid Receptor 1 (LPAR1) with siRNA-Lipid Nanoparticles (siRNA-LNP) Is a Potential Therapeutic Approach for CKD -Associated Kidney Fibrosis

Background: LPAR1 plays an important role in tissue fibrosis. Its expression is upregulated in kidneys (K) of different injuries. To explore if siRNA inhibition of its expression could be a therapeutic approach for K fibrosis, we developed a K-targeting LPAR1 siRNA-LNP.

Methods: A series of LPAR1 siRNAs were designed and screened in vitro. The activity of the selected lead siRNA was confirmed in vivo. A series of LNP formulations for delivery of siRNA to K were designed and screened in vivo. Cell distribution of siRNA in K was analyzed with different approaches. The selected lead LPAR1 siRNA-LNP was used to treat mice of DKD or rats of Adriamycin-induced CKD. LPAR1 gene knockdown, serum creatinine, uACR, K hydroxyproline (HP) and histological changes were determined.

Results: In vitro screen identified a lead LPAR1 siRNA of an IC50 ~10pM. The activity was confirmed in vivo. A lead LNP formulation was identified by showing >50% LPAR1 mRNA reduction in mouse K after a dose of 4 mpk and a higher siRNA accumulation in K than in liver or other tissues 24 hr after dosing. FACS analysis found that siRNA was delivered to majority of K cells including podocytes, mesangial cells, endothelial cells in glomeruli, and epithelial and non-epithelial cells in non-glomerular part. Treatment (Tx) of mice with a single dose of a podocin siRNA-LNP significantly reduced podocin mRNA. Further demonstrating the siRNA was delivered into podocytes. RNAseq analysis found that LPAR1 siRNA reduced LPAR1 mRNA level in different K cells. Tx of STZ-diabetic mice with LPAR1 siRNA at 4 mpk once a week for 4 wks lowered K HP levels, and improved K fibrosis and tubular degeneration. Tx of BTBR db/db mice caused ~20% and 45% reduction in uACR after 3 and 9 wks of Tx, respectively. Tx of rats of Adriamycin-induced CKD at 2 mpk/wk for 4 wks normalized serum creatinine lowered uACR by 60%, improved glomerulocarcinosis, stopped worsening of glomerular atrophy, and reversed glomerular effacement and tubular dilation. The Tx effect lasted for >11 wks.

Conclusions: Above data demonstrated that siRNA inhibition of LPAR1 expression improves K fibrosis accompanied by an improved K function in multiple CKD models. Therefore, the siRNA-LNP could be a potential therapeutic for K fibrosis.

SA-PO444
Renal Cell Type-Associated Therapeutic Effects of Semaglutide in a Mouse Model of Hypertension-Accelerated Diabetic Kidney Disease

Background: Obesity, hyperglycemia and hypertension are critical risk factors for development of diabetic kidney disease (DKD). While emerging evidence suggests that glagon-like-peptide-1 receptor (GLP-1R) agonists improve cardiovascular and renal outcomes in type 2 diabetes patients, their mode of action is presently unclear. Using paired bulk and single-nucleus RNA sequencing (RNAseq), we profiled renal transcriptome signatures of the long-acting GLP-1R agonist semaglutide alone and in combination with the ACE inhibitor lisinopril in a model of hypertension-accelerated, diabetic kidney disease (DKD) to determine the renal outcomes in type 2 diabetes patients, their mode of action is presently unclear.

Methods: Seven weeks after Renin AAV administration and six weeks post-UNx, db/db UNx-ReninAAV mice were administered (q.d) vehicle, semaglutide (30 mg/kg, s.c) or semaglutide (30 mg/kg, s.c) + lisinopril (30 mg/kg, p.o) for 11 weeks. Endpoints included blood pressure, urine biochemistry, kidney histopathology as well as paired bulk and single-nucleus RNA seq. Cell type deconvolution was performed by referencing expression of treatment-affected genes across all major kidney cell types using single nuclei RNAseq.

Results: Semaglutide robustly reduced hyperglycemia, hypertension and albuminuria compared with reduction in glomerulosclerosis severity. Co-administration of lisinopril further ameliorated hypertension and glomerulosclerosis. Gene expression affected by both semaglutide mono- and combination treatment were primarily associated with the immune system and extracellular matrix remodeling. Semaglutide promoted discrete renal gene expression changes in db/db UNx-UNx-UNx-ReninAAV mice with notable suppression of macrophage-associated genes. Combined semaglutide and lisinopril administration resulted in more widespread transcriptome changes in several renal cell types, including macrophages, mesangial cells, podocytes and proximal tubule cells.

Conclusions: Semaglutide improves disease hallmarks in the db/db UNx-ReninAAV mouse model of advanced DKD and improves renal transcriptome signatures. Outcomes were further improved by combined anti-hypertensive standard-of-care.

Funding: Commercial Support - Gubra

SA-PO445
Effects of Nonsteroidal Mineralocorticoid Antagonist (Finerenone) in Western Diet-Induced Kidney Diseases
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Background: Nonsteroidal mineralocorticoid receptor (MR) overactivation plays a crucial role in the pathogenesis of chronic kidney disease, several cardiovascular and arterial diseases. Recently the non-steroidal MR antagonist Finerenone (FN) was shown to have highly beneficial cardiac and renal protective effects. The purpose of these studies was to determine the mechanisms of the beneficial effects FN in kidney disease in a mouse model of western diet induced obesity and insulin resistance.

Methods: 2-month old C57BL/6 mice fed on low fat (LF) or western diet (WD) were treated with vehicle or FN for 6-months (prevention studies) or after 3 months on the LF or WD for 5 months of age, mice treated with vehicle or FN for 3 months (intervention studies) until they were 8 months old.

Results: Mice fed a Western diet (WD) had increased body weight and kidney weight, whereas Finerenone reduced kidney weight ratio without affecting body weight and blood glucose levels remained unchanged. WD-fed mice had higher plasma levels of TG and TC, reduced by FN. The WD fed mice exhibited significantly increased albuminuria and KIM1 which was decreased with FN. Kidneys of WD-fed mice showed increased expression levels of pro-inflammatory cytokines (MCP1, TGFβ), innate immunity pathways (TLR2, STING, STAT3), and fibrosis marker fibronectin and PAI-1, which were significantly reduced by FN. Interestingly, kidney cholesterol and ceramide levels were markedly increased in WD-fed mice, which were reduced by FN. Electron microscopy revealed glomerular basement membrane disruption, podocyte foot process loss, and mitochondrial structural abnormalities in WD-fed mice, all improved by FN.

Conclusions: Our data shows that administration of Finerenone exhibits a renal protective role and prevents the progression of kidney disease in a mouse model of western diet induced obesity and insulin resistance.

Funding: Commercial Support - Bayer

SA-PO446
Linagliptin Increases Urinary Sodium Excretion via Activating Renal Epithelial Sodium Channel (ENaC) in Diabetic Rodents and Patients with Diabetes Mellitus
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Background: About half of patients with diabetes mellitus (DM) develop hypertension, leading to further organ damage. ENaC activation is linked to hypertension. Whether SGLT2 inhibitors in patients with DM-N can become a potent to prevent the progression of DM-N remains unknown.

Methods: [1] SDT-fatty rats, an obse DM model, were given high salt water and categorized into four groups as followings; Sham, DM-N, DM-N treated with Empagliflozin (EMP) or Linaizin (LINA), DM-N treated with 6-week EMPA followed by 6-week LINA treatment with linagliptin (ELPA + LINA). [2] DOCA/salt mice, an ENaC-activated hypertensive model, were treated with EMPA or LINA + LINA to investigate if ENaC regulates ENaC activation. [3] Cultured distal tubules were treated with high sodium and glucose in the presence of EMPA, LINA, or GLP-1. [4] Urine samples were collected from patients with DM treated with LINA, EMPA, or the combination to investigate urinary sodium excretion.

Results: Tubular injury and renal fibrosis in SDT-fatty rats were improved by EMPA or LINA + LINA. Along with lowered glucose level, renal dysfunction was attenuated by EMPA or LINA alone. Renal sodium excretion was increased by combination of the two when compared to EMPA alone. Renal ENaC was reduced with upregulation of Nedd4-2 by EMPA + LINA. Also, combination of the two attenuated hypertension with increase in urinary sodium excretion in DOCA/salt mice. Upregulation of Nedd 4-2 in PAAs’ mouse was prevented by the combination, but not EMPA alone. High sodium and glucose medium increased ENaC expression and suppressed Nedd4-2 expression, both of which were reversed by co-incubation with GLP-1 or LINA. Among the patients with DM, urinary sodium excretion was increased by combination of the two even when compared to EMPA or LINA alone.

Conclusions: LINAG can become a potent to differentiate diabetic nephropathy from non-diabetic kidney disease in patients with type 2 diabetes mellitus. This study was conducted to investigate the...
Dysregulated miR-936 as a Novel Diagnostic Marker for Diabetic Nephropathy: Meta-Analysis and Validation Study

Gantsetseeg Garmaa,1,2 Stefania Budnuc,1,2 Tamás Köi,1,3 Gabor Kokeny,1 Semmelweis Egyetem, Budapest, Hungary; 2Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; 3Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 4Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; 5Department of Stochastics, Institute of Mathematics, Budapest University of Technology and Economics, Budapest, Hungary.

Background: miRNAs are short non-coding ribonucleic acid molecules that bind to target messenger RNAs, resulting in their degradation and translational repression. They could be used as a diagnostic marker and nucleic acid therapy in chronic kidney disease (CKD).

Methods: We used two consecutive methods to validate miR-936 in diabetic nephropathy (DN). First, investigating potential miRNAs in CKD is explored from a meta-analysis of 32 miRNA profiling studies. The enrichment analysis was performed for target genes and molecular pathways utilizing DIANA miPath v.3 and Reactome. Finally, for the first time, miR-936 was validated by qRT-PCR in kidney biopsy of DN patients and high glucose-induced HK-2 cells.

Results: Urinary miR-936 was one of the most down-regulated from a meta-analysis (Figure 1). The enrichment analysis found dysregulated miRNAs affecting fatty acid biosynthesis and metabolism pathways. MiR-936 was over-expressed in DN patient kidney biopsies (DN, n=3) compared to control kidney tissue (CTL, n=3) but did not reach statistical significance (Mann-Whitney test). HK-2 cells in high glucose (24 hours, 25 mmol/L, n=3) medium increased miR-936 expression by 2-fold (p<0.05 by Kruskal Wallis test), while mannitol, osmotic control (20 mmol/L, n=3) had no effect.

Conclusions: The dysregulation of miR-936 expression in diabetic nephropathy is investigated, which will provide further research on the molecular mechanism of dysregulated miR-936 in diabetic nephropathy.

Funding: Government Support - Non-U.S.

SA-PO448

Dysregulated miR-936 as a Novel Diagnostic Marker for Diabetic Nephropathy: Meta-Analysis and Validation Study

Gantsetseeg Garmaa,1,2 Stefania Budnuc,1,2 Tamás Köi,1,3 Gabor Kokeny,1 Semmelweis Egyetem, Budapest, Hungary; 2Mongolian National University of Medical Sciences, Ulaanbaatar, Mongolia; 3Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; 4Division of Pancreatic Diseases, Heart and Vascular Center, Semmelweis University, Budapest, Hungary; 5Department of Stochastics, Institute of Mathematics, Budapest University of Technology and Economics, Budapest, Hungary.

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Funding: Government Support - Non-U.S.

SA-PO448

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Background: miRNAs are short non-coding ribonucleic acid molecules that bind to target messenger RNAs, resulting in their degradation and translational repression. They could be used as a diagnostic marker and nucleic acid therapy in chronic kidney disease (CKD).

Methods: We used two consecutive methods to validate miR-936 in diabetic nephropathy (DN). First, investigating potential miRNAs in CKD is explored from a meta-analysis of 32 miRNA profiling studies. The enrichment analysis was performed for target genes and molecular pathways utilizing DIANA miPath v.3 and Reactome. Finally, for the first time, miR-936 was validated by qRT-PCR in kidney biopsy of DN patients and high glucose-induced HK-2 cells.

Results: Urinary miR-936 was one of the most down-regulated from a meta-analysis (Figure 1). The enrichment analysis found dysregulated miRNAs affecting fatty acid biosynthesis and metabolism pathways. MiR-936 was over-expressed in DN patient kidney biopsies (DN, n=3) compared to control kidney tissue (CTL, n=3) but did not reach statistical significance (Mann-Whitney test). HK-2 cells in high glucose (24 hours, 25 mmol/L, n=3) medium increased miR-936 expression by 2-fold (p<0.05 by Kruskal Wallis test), while mannitol, osmotic control (20 mmol/L, n=3) had no effect.

Conclusions: The dysregulation of miR-936 expression in diabetic nephropathy is investigated, which will provide further research on the molecular mechanism of dysregulated miR-936 in diabetic nephropathy.

Funding: Government Support - Non-U.S.
increase of 1 μg/m² in SO₂ (1.06, 1.00–1.13) concentration were also positively associated with ESRD. Apart from NO₂, all the above air pollutants have additional predictive value for ESRD in patients with T2DM and CKD, with PM₁₀, performing best.

Conclusions: In patients with T2DM and CKD, long-term exposure to PM₁₀, PM₂.₅, CO, and SO₂ was positively associated with the risk of ESRD.

Funding: Government Support - Non-U.S.

Figure 1. Association between air pollutants and ESRD

Figure 2. Subgroup analysis of follow-up time and prognostic efficacy of air pollutants

SA-PO452
Improving CKD Screening in Spanish-Speaking Patients with Poorly Controlled Type 2 Diabetes at a Rural Community Health Center
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Background: The American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO) consensus recommendations advise that patients with type-2 diabetes (T2DM) undergo annual screening with urine microalbumin creatinine ratio and estimated glomerular filtration rate. Less than half of patients with T2DM receive the recommend screening. This project aimed to increase screening in Spanish-Speaking patients with poorly controlled T2DM (A1c≥9) by 5% over 2 months at a community health center in rural North Carolina and evaluated secondary patient-centered outcomes of initiation of sodium glucose cotransporter 2 inhibitors (SGLT2i) and diagnosis with CKD.

Methods: We performed chart review querying for Spanish-speaking patients at SCCHC with T2DM with A1c≥9 without a diagnosis of CKD (n=134). We then created a pop-up alert for patients without any CKD screening in the past year. We performed patient outreach to schedule appointments, offer counseling on CKD screening, and end labs. Finally, we generated a flyer for providers summarizing ADA and KDIGO guidelines for CKD screening and initial management.

Results: Only 43% of patients received full screening at baseline. Overall, the number of patients screened for CKD increased by 7%. 85% of patients with alerts in their charts who showed up for appointments received full screening. 50% of patients continued through patient outreach, scheduled an appointment and all patients who were seen in clinic following outreach received full screening. Only 29% of patients for whom the only intervention was provider education received complete screening. No diagnoses of CKD were made as a result of screening. There was an increase in prescription of an SGLT2i from 35% to 69% in patients receiving any CKD screening.

Conclusions: The improvement in CKD screening resulting from this project supports the need for pre-visit planning tools that highlight CKD screening, for patient education efforts, and for a one click ‘Kidney Profile’ lab order. The increased use of SGLT2i in improving screening full screening supports a correlation between screening and increased risk reduction therapy. Future efforts to increase appropriate CKD diagnosis and patient counseling following screening will be important for empowering patients to prevent disease progression.

SA-PO453
HbA1c-Dependent Projection of Long-Term Renal Outcomes
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Background: Diabetes mellitus is a major risk factor for the development of chronic kidney disease (CKD). An association between glycated hemoglobin (HbA1c) and decline of kidney function is well established. There is limited data addressing the prognostic value of baseline HbA1c to predict long-term renal outcomes regardless of diabetes status or anti-diabetic therapies.

Methods: In this single-center retrospective observational study, we analyze the effect of glycemic status on renal outcomes in a study population of N=19,285 subjects over a median follow-up time of 69 months. The primary endpoint was defined as time to manifestation of moderate CKD (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²) in subjects with unconstrained kidney function (eGFR > 60 ml/min/1.73 m²) at baseline. The secondary endpoint was defined as time to progression of CKD (eGFR ≤ 30 ml/min/1.73 m²) in subjects with CKD stage III (eGFR 30 - 60 ml/min/1.73 m²) at baseline. Endpoints were individually analyzed using interval- and right-censored datasets. For univariate time-to-event analysis, subjects were grouped into four cohorts by median HbA1c at baseline (HbA1c < 5.7, 5.7 – 6.5, 6.5 – 8.5, > 8.5%). Covariate-adjusted hazard ratios were estimated applying multivariate parametric regression models on continuous HbA1c measures. A Cox proportional hazard based model was established to predict decline of kidney function based on discrete baseline HbA1c levels.

Results: Lowest baseline HbA1c levels were associated with the lowest decline of kidney function, highest baseline HbA1c levels with the fastest decline of kidney function. The primary endpoint for HbA1c < 5.7%: 16 years [95% CI: 13.6-17.8] for HbA1c 5.7 – 6.5%: 14 years [95% CI: 12.4-15.4]; for HbA1c 6.5 - 8.5%: 9 years [95% CI: 8.6-11.7] for HbA1c 8.5%: 2 years [95% CI: 7.8, 8.8]; P = 0.0001). Similar trends were observed for the secondary endpoint. Covariate-adjusted time-to-event analysis confirms a concentration-dependent effect of HbA1c at baseline on both endpoints.

Conclusions: HbA1c is a strong predictor for kidney function decline, regardless of preexisting diabetes status or CKD stage. Lower HbA1c levels are associated with a lower risk of manifestation or progression of CKD.

Funding: Government Support - Non-U.S.
Impact of SGLT2 Inhibitor on All-Cause Mortality Among Patients with Type 2 Diabetes with and Without CKD

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Background: SGLT2 inhibitors have been shown to improve survival among patients with chronic kidney disease (CKD) with and without diabetes. The long-term mortality benefit remains unclear. In addition, the existence of CKD among type 2 diabetes mellitus (DM) who are on SGLT2 inhibitor can influence its mortality benefit. In this study, we wanted to compare mortality benefit among type 2 DM who are taking SGLT2 inhibitors and CKD to patients with normal renal function. We hypothesize that SGLT2 inhibitor should be started prior to the development of renal impairment among patients with type 2 DM.

Methods: In this retrospective study, we included all type 2 diabetes patients who presented to Dasmam Diabetes Institute for follow up from 2015 until 2022. The patients were divided based upon whether they were taking SGLT2-inhibitor or not and their CKD status. The main outcome was all-cause mortality.

Results: A total of 3569 patients were included. The all-cause mortality unadjusted hazard ratio (HR) for patients who were on SGLT2-inhibitor was 0.61 (95% CI, 0.41-0.89). After Adjusting for Age, gender, BMI and CKD stage, the adjusted HR ratio was 0.67 (95% CI, 0.45-0.99). The all-cause mortality HR for patients who were on SGLT2-inhibitor was 0.64 (95% CI, 0.43-0.95) which was adjusted for renal impairment. The HR for patients who had renal impairment who did not receive SGLT2 inhibitor was 4.41 (95% CI, 2.94-6.608). Whereas for patients who were on SGLT2 inhibitor and had renal impairment the adjusted HR was 2.82 (95% CI, 1.60-4.99) and 2.37 (95% CI, 1.31-4.27).

Conclusions: Over period of 8 years follow up, SGLT2-inhibitors were associated with lower all-cause mortality. The presence of CKD is associated with reduced survival suggesting that SGLT2 inhibitor should be started prior to the development of renal disease to improve survival. More research required to assess the optimal time to start SGLT2 inhibitor.

SA-PO456

Preventing Hypoglycemia in ESRD Patients with Diabetes Mellitus: The Great Challenge

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Background: Patients with end stage renal disease who have coexisting diabetes mellitus are at an increased risk of developing hypoglycemia. With renal failure, patients have decreased renal gluconegenesis, glucose reabsorption, and insulin clearance. ESRD patients accounted for about one third of all severe hypoglycemia episodes in hospitalized diabetics. Inadequate dose-adjustment of insulin could be a significant factor contributing to higher rates of hypoglycemia in these patients. In this study, we propose to add a text-based warning for physicians when ordering insulin in order to prevent overcorrection of hypoglycemia in these patients. Our long term goal is to create a sliding scale for patients with ESRD in order to prevent hypoglycemia and its sequelae.

Methods: We conducted an analysis on 1,178 hospitalized patients to evaluate the incidences of hypoglycemia in patients with co-existing diabetes mellitus and end stage renal disease. Our study aimed at understanding whether administering a lower average dose of insulin would decrease the overall number of episodes of hypoglycemia in these patients. The intervention was a text-based electronic reminder for physicians when they ordered insulin. The 2 groups studied were the pre-intervention group from October 2021 to June 2022 and post-intervention group from July 2022 to March 2023. There were 703 patients studied in the pre-intervention period and 474 patients in the post-intervention period.

Results: Upon analysis of the results, it was noted that there was no statistically significant difference between pre and post intervention groups in the number of hypoglycemic episodes. Although not statistically significant, we do see a reduced amount of total hypoglycemic episodes in patients post-intervention who had at least one prior hypoglycemic episode recorded. It should be noted that the cut off for hypoglycemia classification was changed during the course of this study which could have contributed to the lack of statistically significant results.

Conclusions: This study raises attention towards an important complication of end stage renal disease. Recurrent hypoglycemia can further complicate the course of acute illnesses. With the number of hypoglycemic episodes noted to be higher in the pre-intervention group, it is worthwhile to adjust insulin administration for these patients inpatient.

SA-PO455

Higher Glycemic Variability Increased the Risk of All-Cause Mortality in Patients with Diabetes Mellitus on Hemodialysis

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Background: Glycemic (HbA1c) variability has been recognized as an important predictor for the risk of cardiovascular events and all-cause mortality in patients with diabetes mellitus (DM) with and without renal failure. The aim of this study was to examine the association between HbA1c variability, as a measure of long-term glycemic control and the risk of all-cause mortality in patients with DM and HD.

Methods: Data of 2001 patients (collected between 2008 and 2018) with DM type 1 and 2 and HD were divided into groups based on HbA1c variability before and after HD was divided into tertiles as the coefficient variation (CV), which was calculated as the ratio between the standard deviation (SD) and the mean of HbA1c. The relationships between HbA1c variability and mortality were examined by Cox models to estimate hazard ratios (HR) with and 95% confidence intervals (CI) in univariate and multivariate analyses, which was adjusted for demographics, laboratory findings and comorbidity. The patients were divided in seven groups, and we used the lowest CV group (CV≤0.5) as the reference group.

Results: During follow-up, 1071 (52%) deaths occurred. Through entire time of study each one unit increase of CV was associated with higher risk of mortality (HR 1.11, CI 1.02-1.23). Data before HD-start showed that 969 (47%) patients had HbA1c variability CV>4.6, which increased to 1188 (58%) in the group with the lowest CV<0.5. The best survival and 169 (8%) of these patients died. In a sub-analysis before HD-start, 597 (29%) of the patients had CV<0.5, but during HD, 405 (20%) of the patients had CV<0.5. The two groups with highest CV>2.8 had the highest risk of mortality with 305 (15%) of these patients died. In a sub-analysis before HD, 268 (13%) of the patients had CV>2.8, but during HD, 449 (22%) of the patients had CV>2.8. In the multivariate Cox analyses, the groups with highest CV (2.8-4.6 and >4.6) were associated with increased risk of mortality (HR 1.98, CI 1.54-2.47 and HR 1.99, CI 1.54-2.57) compared with the reference group.

Conclusions: Glycemic variability should be considered an important risk factor for mortality in patients with DM and HD. In patients with DM and HD, we highly recommend consistent monitoring of glucose homeostasis and regular evaluation of DM treatment.
SA-PO458

Efficacy of Continuous Glucose Monitoring (CGM) in People with Diabetes on Dialysis


Background: Patients with diabetes on dialysis (DM) experience wide variations in glucose levels leading to increased risk of hypoglycaemia. Due to the inaccuracies of HbA1c in dialysis patients, JBDS-IP and KDIGO Diabetes Work Group recommend the use of CGM. We conducted a systematic review to examine current evidence for CGM use and its impact on clinical outcomes.

Methods: Search of MEDLINE and Embase databases was conducted. Clinical or observational trials in adults with DM on dialysis and CGM intervention reporting glycaemic outcomes were included. Data collected included patient characteristics, intervention and glycaemic outcome. Quality was evaluated using the NHLBI assessment tool.

Results: Of the 936 citations identified, 49 duplicates were removed. 887 screened by title and abstract, 9 full texts reviewed and a further 7 excluded due to duplications and failure to meet to selection criteria. Data was extracted for 2 studies (table 1), both ‘good’ quality, prospective before-and-after interventional studies with no control group. Joubert et al, (2015) showed mean CGM glucose level was 8.3 at baseline and 7.7mmol/L, at the end of the CGM period (p<0.05). HbA1c decreased from 6.9 to 6.5% at the end of 12 weeks (p<0.05). Number of insulin adjustment was higher during the CGM compared to the SMBG period (2.1 vs 1.4, p<0.05). Mean CGM was lower on dialysis days (7.6 vs 8.9mmol/L, p<0.05). Képénékian et al, (2014) reported after 3 months with CGM-adapted insulin regimen, HbA1c decreased from 8.4 to 7.6% (p<0.01). Mean CGM values decreased from 9.9 to 8.9mmol/L (p<0.05). The frequency of glucose values >10mmol/L decreased from 41 to 30% (p<0.05), without significant increase in hypoglycaemia frequency. Insulin requirements increased from 70 to 82IU/d (p<0.01), without significant weight gain.

Conclusions: Evidence demonstrating impact of CGM on glycaemic outcomes in patients with DM on dialysis is lacking. Further trials with bigger sample size and longer follow up are needed to ascertain the benefits of CGM in these patients.

SA-PO459

Association of Peripheral Neutrophil Count with Risk of Cardiovascular Mortality Among Adults with Diabetic Kidney Disease: Evidence from NHANES 2005-2010

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Background: Accumulating data shows that chronic inflammation has crucial pathogenic contributions in CKD patients with diabetes, but the contribution of neutrophils count in diabetic kidney disease (DKD) remains elusive.

Methods: We performed a cross-sectional study of 44,494 participants in the National Health and Nutrition Examination Surveys (NHANES) from 2005 to 2020. The prevalence of CKD and diabetes were calculated. The association of peripheral neutrophil count levels with kidney functions in DKD and cardiovascular disease (CVD) mortality were further explored using logistic regression and Cox proportional hazards models.

Results: Among the 2,643 patients with DKD from NHANES, the weighted mean of peripheral neutrophil count level was 4.97. When compared with patients with DKD in the lowest neutrophil count quintile, The highest quintile had the positively association with uACR and negatively relationship with estimated eGFR. During 2,215 person-years of eligible follow-up, 766 deaths (n = 237 deaths from CVD) occurred. In comparison to those in the those in the lowest neutrophil count quintile group, the highest quintile group had the HRs of 1.77 for all-cause mortality and 2.24 for CVD mortality in the fully adjusted model. A linear count-response relationship of peripheral neutrophil count with CVD mortality were also demonstrated (P<0.002).

Conclusions: Higher peripheral neutrophil count was significantly associated with an increased risk of cardiovascular mortality and poor kidney function among patients with DKD.

Funding: Private Foundation Support

SA-PO460

Diagnosis of Renal and Cardiovascular Injuries in Type 1, Type 2, and Prediabetic Patients Using an Ensemble of Machine Learning and Deep Learning Methods

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Background: Diabetes is a growing global pandemic with serious complications such as renal and cardiovascular injuries. Diabetic nephropathy, characterized by decreased glomerular filtration rate (GFR) and albuminuria, is a microvascular complication of...
Diabetic Kidney Disease: Clinical - II

**SA-PO461**

**Differentiating Non-Diabetic Kidney Diseases from Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients with Nephrotic Syndrome**

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**Background:** Nephrotic syndrome (NS) in patients with type two diabetes mellitus (T2DM) encompasses both diabetic nephropathies (DN) and non-diabetic kidney diseases (NDKD). This study aims to investigate kidney biopsies in T2DM patients who had NS to determine the prevalence of NDKD and analyze characteristic features that are associated with NDKD. The objective is to develop a clinical prediction score that can differentiate any NDKD cases from DN alone.

**Methods:** This study was done as a single-center, retrospective, cross-sectional observational design, patients diagnosed with T2DM who underwent kidney biopsy due to NS at Vajira Hospital between 2013-2021. All patients received diagnoses of either DN, isolated NDKD, or NDKD superimposed on DN, which were confirmed through pathological examinations. To identify factors correlated with NDKD, a multiple logistic regression analysis was performed. Additionally, a clinical prediction score was developed by assigning weights to the predictors’ coefficients in a multivariable logistic model.

**Results:** A total of 273 patients were enrolled in this study, with 89 patients (32%) DN alone, 69 patients (25%) NDKD superimposed on DN, and 115 patients (42%) NDKD alone. The most prevalent NDKD causes were IgA nephropathy. The absence of diabetic retinopathy (DR) (adj.OR 2.26; 95% CI 1.29-3.93; p=0.004), duration of DM < 6 years (adj.OR 2.02; 95% CI 1.14-3.57; p=0.015), and absence of hypertension (adj.OR 2.058; 95% CI 1.08-3.89; p=0.026) significant associations with NDKD. From these 4 predictors, a prediction score was derived, wherein a score ≥5 indicated a higher likelihood of NDKD (AUCORC of 0.75; 95% CI 0.63-0.86).

**Conclusions:** The prevalence of any NDKD in T2DM with NS is 67%. No DR, Age > 50 years, duration of DM < 6 years, and absence of hypertension have significant association with NDKD. A new clinical prediction score for distinguishing any NDKD from DN alone can defer kidney biopsy.

**Algorithm using Clinical Prediction score**

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**SA-PO462**

**Progression to ESKD in Type 2 Diabetes by Histological Findings: A Retrospective Cohort Study**

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**Background:** The risk of progression to end-stage kidney disease (ESKD) varies among individuals with type 2 diabetes (T2D). This study aims to investigate if the risk of progression to ESKD differs by biopsy-proven type of kidney disease.

**Methods:** We conducted a retrospective cohort study including all adults with T2D in Denmark from 1996-2020 who had a kidney biopsy performed. The included individuals were previously classified as having diabetic nephropathy (DN) (n=599), non-diabetic nephropathy (NDN) (n=703), mixed disease (n=165), normal histopathology (n=49), or could not be classified (NC) (n=743). Using high-quality national registry data, the cohort was described with demographic, clinical, and laboratory data and comorbidity. Stratified analysis of progression to ESKD within the type of kidney disease was performed.

**Results:** The cohort consisted of 68% men with mean age 64.1±11.2 years at biopsy. At the time of biopsy, the DN group had systolic blood pressure (SBP) 144±20 mmHg and a body mass index (BMI) of 30.9±6.2 kg/m². They had a median and interquartile range [IQR] estimated glomerular filtration rate (eGFR) 39 [24.0, 59.2] ml/min/1.73m² and median [IQR] urine albumin-creatinine ratio (UACR) 2373 [980.2, 4183.5] mg/g. The NDN group had SBP 138±21 mmHg, a BMI of 30.8±6.5 kg/m², eGFR 29 [15.0, 50.0] ml/min/1.73m² and UACR 766 [59.5, 2384.5] mg/g. The mixed disease group had SBP 147±21 mmHg, a BMI of 31.7±6.1 kg/m², eGFR 25 [11.0, 48.0] ml/min/1.73m² and UACR 1863 [583.0, 3400.0] mg/g. We found a significant difference in the rate of renal progression (p<0.001). During a median follow-up of 12.8 years, progression to ESKD occurred in 52% with DN, 42% with NDN, 53% with mixed disease, 25% with normal histopathology, and 41% with NC. Time to ESKD from diagnosis of T2D was significantly different within the type of kidney disease (p<0.001): 13.2 [8.0, 17.9] median [IQR] years in DN, 7.8 [4.5, 12.8] years in NDN, 13.0 [7.6, 17.3] years in mixed disease, 13.1 [11.1] years in normal pathohistology, and 9.2 [5.1, 14.6] years in NC.

**Conclusions:** In people with T2D, we found the highest rate of ESKD in DN and mixed disease, but with the slowest time to progression. Analyses suggest that the risk of and time until progression to ESKD differs significantly within types of biopsy-proven diabetic kidney disease.

**Funding:** Private Foundation Support

**SA-PO463**

**Progression to ESKD in Type 1 Diabetes by Histological Findings**

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**Background:** Kidney disease in diabetes is a heterogeneous disease. To improve personalized medicine in people with diabetes, it is crucial to identify people at risk of progressing to end-stage kidney disease (ESKD). This study aims to investigate if progression to ESKD differs by biopsy-proven type of kidney disease in people with type 1 diabetes (T1D).

**Methods:** In this retrospective registry study, we included all Danish adults with T1D from 1996-2020 who had a kidney biopsy performed. The included individuals had diabetic nephropathy (DN) (n=132), non-diabetic nephropathy (NDN/n=73), mixed disease (n=39), normal histopathology (n=5), or could not be classified (NC/n=78). Demography, clinical presentation, laboratory values, and prevalence of comorbidity were described by compiling unified national registry data. Within the type of kidney disease, we analyzed progression to ESKD.

**Results:** The DN group consisted of 71% men with systolic blood pressure (SBP) of 146±21 mmHg and a body mass index (BMI) of 25.1±5.5 kg/m². In DN and mixed disease groups 66% and 56%, respectively, were men. In NDN, mean SBP was 137±18 mmHg and they had a BMI of 24.6±6.2 kg/m². Those with mixed disease had a mean SBP of 135±21 mmHg and a BMI of 24.7±3.7 kg/m². Median and interquartile range [IQR] estimated glomerular filtration rate (ml/min/1.73m²) and urine albumin-creatinine ratio (mg/g) were 37 [22.6, 54.1] and 2670 [935.4, 4390.7] in DN, 41 [14.0, 85.0] and 837 [304.5, 3860.5] in NDN, 27 [16.4, 71.8] and 1240 [435.0, 3472.0] in mixed disease, 29 [20.6, 36.5] and 201 [118.8, 984.7] in normal histology, and 35 [12.5, 62.5] and 436 [40.0, 2281.0] in NC, respectively. During a median [IQR] follow-up time of 22.6 [14.5, 30.0] years, 61% with DN advanced to ESKD, compared to 52% with NDN, 59% with mixed disease, and 46% with NC. There were no significant differences between groups.

Likewise, there was no significant difference in median [IQR] time to progression of ESKD, 17.4 [12.0, 21.9] years in DN, 14.9 [9.1, 23.0] years in NDN, 19.6 [17.1, 27.4] years in mixed disease, 24.1 [19.3, 26.0] years in normal histopathology, and 18.5 [11.3, 24.8] years in NC.

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

**Underline represents presenting author.**

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Conclusions: In people with T1D, retrospective analysis of registry data did not find a significant difference in risk of progression to ESKD or time to ESKD within biopsy-proven type of kidney disease.

Funding: Private Foundation Support

SA-PO464

Preliminary Results from iBeat Ancillary Study: A Novel Bar Vari Clini of Renal Damage in Diabetic Patients with CKD

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Background: Renal damage in diabetes is heterogeneous, kidney biopsy remains the gold standard for diagnosis. In this iBEAT substudy, within the BEAT-DKD project (https://www.beat-dkd.eu/), we aimed to correlate imaging, clinical, molecular and histopathological data to dissect renal damage phenotypes.

Methods: We enrolled 83 patients to perform kidney biopsy (carried out in 64 patients), US and MRI, biofluids and clinical data collection.

Results: According to KDIGO 13 patients were in stage A1, 26 in A2 and 25 in A3, all ranging from G1 to G4. Histological classification by Mazzuco et al (PMID: 11920336) identified 31% of patients with class 1 (diabetic nephropathy-DN); 36% with class 2 (vascular and ischemic glomerular changes); 4% with class 3a (glomerular diseases and DN) and 31% with class 3b (other glomerulopathies in the absence of DN). Since we observed heterogeneous histological lesions, we here propose a novel classification for diabetic patients with CKD. We recognized 3 different classes (DKD, NDKD, DKD+NDKD) and 6 different phenotypes including: a) in DKD (33%): pure metabolic (7%) and vascular (26%); b) in NDKD (63%): pure vascular (35%), immunological vascular (IgA, FSGS, MN; 9%), pure immunological (IgAN, FSGS; 19%); c) in DKD+NDKD overlapping phenotypes (4%). We observed differences of uACR (p=0.02) and proteinuria (p=0.005) among the different phenotypes of DKD and NDKD. PAS staining confirmed the increased mesangial expansion in DKD phenotype (p=0.04); vascular wall-to-lumen ratio discriminated vascular vs metabolic (p=0.04) and immune-related damage (p=0.05); renal resistive index discriminated among the phenotypes (p=0.02). We also performed single-cell RNASeq analysis of kidney biopsies mapping more than 61000 nuclei in different cell types, identifying differences between classes and phenotypes along the nephron and the vasculature (i.e. TNNT2 expression in podocytes was associated with vascular damage).

Conclusions: The integration of renal pathology, imaging and molecular data from the same patient has the potential to unlock new diagnostic criteria to address the heterogeneity of renal pathologies, providing a new classification of renal damage in diabetes.

SA-PO465

Globerular Crescents Are Associated with the Risk of Kidney Progression in Type 2 Diabetic Kidney Disease

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Background: Type 2 diabetic kidney disease (T2DKD) is the leading cause of chronic kidney disease and end-stage kidney disease. The heterogeneous phenotype of T2DKD complicates the approach to treating patients. While kidney biopsy is the gold standard for diagnosis, it is not perfect in predicting progression to end-stage kidney disease. Herein, we addressed whether the presence of glomerular crescents was associated with the outcomes in biopsy-proven T2DKD.

Methods: A total of 360 patients who were diagnosed as biopsy-proven DKD in the setting of type 2 diabetes but did not have other crescentic glomerulonephritis from 9 medical centers were reviewed. Hazard ratios (HRs) were calculated using a Cox regression model to evaluate the risk of kidney progression (i.e., ≥50% of decrease in estimated glomerular filtration rate) according to the presence of glomerular crescents.

Results: 11 patients (3.1%) had glomerular crescents in the biopsied tissues. During the follow-up period (median 18 months; maximum, 18 years), the crescent group had a higher risk of kidney progression than no crescent group with adjusted HR of 2.71 (1.22–6.03) (P=0.014). The relationship with kidney progression was more prominent in patients with high proportion of crescents than in those with low proportion.

Conclusions: The presence of glomerular crescents is associated with progression of T2DKD. Accordingly, histological monitoring of glomerular crescents may be needed to treat patients intensively.

Fig 1. Kidney outcome curves for patients with and without crescents in the biopsied tissues. Kaplan-Meier curve depicted for patients without crescents versus those who had glomerular crescents in the biopsied tissues.

SA-PO466

Diversity of Kidney Biopsy Findings Among Diabetic Patients in the Cleveland Clinic Kidney Biopsy Epidemiology Project

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Background: Patients with a clinical diagnosis of diabetes without other criteria to prompt kidney biopsy are often treated and managed as diabetic kidney disease (DKD). We sought to describe the spectrum of kidney biopsy findings among patients with diabetes and identify factors associated with finding DKD and non-DKD (NDKD).

Methods: We identified patients with a history of diabetes from the Cleveland Clinic Kidney Biopsy epidemiology project from January 2015 to September 2021 using available ICD-10 code data.

Results: Of 4128 patients with native kidney biopsies, 3503 had ICD-10 code data. We identified 1271 (36.3%) with an ICD-10 coded diabetes. Of these, 462 (36.3%) had DKD alone and 678 (53.3%) had NDKD alone, 105 (8.3%) had both DKD and NDKD and 26 (2.0%) were either non-diabetic or non-diagnostic. The most common diagnoses among those with NDKD were FSGS (23.6%), global glomerulosclerosis NOS (12.8%), ATN (8.9%) IgA nephropathy (8.0%) and ANCA vasculitis (7.4%) and membranous nephropathy (4.9%). When comparing types of NDKD between NDKD alone (n=678) and DKD+NDKD (n=105), global glomerulosclerosis NOS was more prevalent in NDKD alone group (13.9%, 5.7%). Oxalate nephropathy and PIGN were more prevalent in DKD+NDKD patients (4.8%, 0.9% and 11.4%, 3.5%, respectively). Aging and White race were positively associated with NDKD compared to DKD alone. (Table)

Conclusions: Of diabetic patients who underwent kidney biopsy, only 36.4% had DKD alone and 63.6% had additional diagnoses on biopsy. Aging had positive association with NDKD than DKD alone. Global glomerulosclerosis NOS, oxalate nephropathy and PIGN had different prevalence in NDKD versus DKD+NDKD. Further analysis is required and ongoing to determine factors associated with alternative diagnoses other than DKD among diabetes patients to guide the use of kidney biopsy in this setting.

Funding: Private Foundation Support

Factors associated with NDKD among diabetes patients in CCKBEP

SA-PO467

Diabetic Kidney Disease Phenotypes and Cardiovascular Outcomes

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Background: Adults with diabetic kidney disease (DKD) have high risk of major adverse cardiovascular events (MACE) and cardiovascular disease (CVD). However, variation in cardiovascular risk across DKD phenotypes remains poorly understood.

Methods: This is a longitudinal analysis of adults with diabetes from two cohorts, the National Health and Nutrition Examination Survey (NHANES, N=5,126) and the UK Biobank (N=27,059). We defined four distinct clinical phenotypes: no DKD, DKD, DKD+NDKD and non-DKD (NDKD). We sought to describe the spectrum of kidney biopsy findings among patients with diabetes and identify factors associated with finding DKD and non-DKD (NDKD).

Results: Of 4128 patients with native kidney biopsies, 3503 had ICD-10 code data. We identified 1271 (36.3%) with an ICD-10 coded diabetes. Of these, 462 (36.3%) had DKD alone and 678 (53.3%) had NDKD alone, 105 (8.3%) had both DKD and NDKD and 26 (2.0%) were either non-diabetic or non-diagnostic. The most common diagnoses among those with NDKD were FSGS (23.6%), global glomerulosclerosis NOS (12.8%), ATN (8.9%) IgA nephropathy (8.0%) and ANCA vasculitis (7.4%) and membranous nephropathy (4.9%). When comparing types of NDKD between NDKD alone (n=678) and DKD+NDKD (n=105), global glomerulosclerosis NOS was more prevalent in NDKD alone group (13.9%, 5.7%). Oxalate nephropathy and PIGN were more prevalent in DKD+NDKD patients (4.8%, 0.9% and 11.4%, 3.5%, respectively). Aging and White race were positively associated with NDKD compared to DKD alone. (Table)

Conclusions: Of diabetic patients who underwent kidney biopsy, only 36.4% had DKD alone and 63.6% had additional diagnoses on biopsy. Aging had positive association with NDKD than DKD alone. Global glomerulosclerosis NOS, oxalate nephropathy and PIGN had different prevalence in NDKD versus DKD+NDKD. Further analysis is required and ongoing to determine factors associated with alternative diagnoses other than DKD among diabetes patients to guide the use of kidney biopsy in this setting.

Funding: Private Foundation Support

Factors associated with NDKD among diabetes patients in CCKBEP
Albuminuria Is Associated with Higher Carotid Plaque Volume Quantified by Novel 3D Ultrasound in Type 1 Diabetes

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Background: Carotid atherosclerosis is associated with progression of kidney disease. Novel 3D ultrasound (3DUS) methods to quantify carotid plaque volume (CPV) may potentially provide more accurate information on carotid atherosclerosis compared to conventional ultrasound methods. We investigated the association between CPV and albuminuria in individuals with type 1 diabetes (T1D) and healthy controls.

Methods: Total CPV (ICPV) was quantified using a novel 3DUS transducer (XL14-3, Philips Healthcare) and calculated as the sum of CPV bilaterally. Individuals with T1D were stratified based on historic albuminuria: normal (30 < mg/g), moderately (30-299 mg/g), or severely increased (>300 mg/g). ICPV was transformed in all analyses. Association between ICPV and albuminuria groups was analyzed using linear regression with healthy controls as reference and adjusted for age, sex, systolic blood pressure, smoking, eGFR and LDL-cholesterol. Analyses were repeated solely including the T1D cohort.

Results: A total of 120 individuals with T1D and 20 healthy controls were included. 48% were female and mean (±SD) age was 54±15 years. Of the individuals with T1D, 30 had normal, 45 moderately and 45 severely increased albuminuria. Median (IQR) ICPV in each group was: healthy controls 11.6 (6.0-41.6) mm³, normal 13.0 (1.4-60.9) mm³, moderately increased 29.2 (17.8-106.1) mm³, and severely increased 46.3 (10.6-175.7) mm³ albuminuria. Participants with moderately and severely increased albuminuria had higher ICPV compared to healthy controls after adjustment (0.42, CI [0.01-0.83], p=0.05) and (0.60, CI [0.13-1.06], p<0.01), respectively. Among T1D, individuals with moderately (0.38, CI [0.03-0.72], p=0.03) and severely increased (0.53, CI [0.13-0.94], p=0.01) albuminuria had higher ICPV than individuals with normal albuminuria. Individuals with T1D and moderately or severely increased albuminuria had higher ICPV, measured with a novel 3DUS method, compared to individuals with normal albuminuria and healthy controls.
Conclusions: Our study provides evidence supporting the safety and efficacy of GLP-1RAs among T2DM patients with advanced CKD and ESKD. While GLP-1RAs may have GI side effects, they demonstrate significant improvement on cardiovascular outcomes, blood glucose control, and weight reduction.

SA-PO473
Effects of Ertugliflozin by Uric Acid Quintile: Observations from VERTIS CV
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Background: The sodium–glucose cotransporter 2 inhibitor ertugliflozin (ERTU) lowers serum uric acid (UA) levels. Using data from the VERTIS CV trial (NCT01986881), the impact of ERTU on eGFR and albuminuria was investigated in patients by baseline serum UA levels.

Methods: Patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomized (1:1:1) to ERTU 5 mg, 15 mg (doses pooled for analyses), and placebo (PBO). Patients were categorized by baseline UA quintile (Table). UA over time, eGFR slopes (chronic from Weeks 2 to 260), and the time to first event of progression of albuminuria were analyzed for ERTU versus PBO.

Results: At baseline, there were notable differences by UA subgroup, such as sex, UA, eGFR and diuretic use (Table). ERTU was associated with reductions in UA over time in all baseline UA subgroups (Fig. A). Treatment with ERTU resulted in a significantly slower rate of yearly eGFR decline in all UA subgroups compared with PBO (p<0.001; Fig. B). ERTU was associated with a reduced risk of albuminuria progression in all UA subgroups compared with PBO (Fig. C; Pannu et al. 0.34).

Conclusions: In VERTIS CV, ERTU reduced UA while attenuating eGFR decline and progressing albuminuria progression, irrespective of baseline UA quintile.

Funding: Commercial Support - The study and this analysis were funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in collaboration with Pfizer Inc., New York, NY, USA. Medical writing and/or editorial assistance was provided by Moamen Hammad, PhD, and Melissa Ward, BA, both of Scion, London, UK. This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Pfizer Inc., New York, NY, USA.

SA-PO472
Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) Among Patients with Type 2 Diabetes Mellitus (T2DM) and Advanced Chronic Kidney Disease (CKD): A Systematic Review and Meta-Analysis
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Background: Evidence supporting the use of GLP-1RAs in T2DM patients and advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD) is scarce.

Methods: A literature search was conducted using MEDLINE, EMBASE, and Cochrane Database from inception through February 2023. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (CRD 42022384585). ClinicalTrials.gov was searched for studies reporting safety or efficacy outcomes of GLP-1RAs in adult patients with T2DM and advanced CKD (stage 5 CKD and ESKD) were included. Outcome measures included mortality, cardiovascular, blood glucose, and weight. Adverse events were assessed for safety. Estimates were pooled using random-effects methods meta-analysis.

Results: Eight studies (5 trials and 3 cohort studies) consisting of 27,639 patients with a median follow-up of 3 months (IQR 3, 12) were included in this meta-analysis. There was no difference in one-year mortality outcomes, but one cohort study found a significant long-term reduction in all-cause mortality with GLP-1RAs (HR 0.7; 95% CI 0.6, 0.9).

Table: Demographic and clinical characteristics by uric acid quintile (Q).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
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<th>Q2</th>
<th>Q3</th>
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</thead>
<tbody>
<tr>
<td>UA (mg/dl)</td>
<td>5.4 (4.7)</td>
<td>5.7 (5.0)</td>
<td>6.1 (5.4)</td>
<td>6.7 (5.9)</td>
<td>7.4 (6.7)</td>
<td>5.4 (4.7)</td>
<td>5.7 (5.0)</td>
<td>6.1 (5.4)</td>
<td>6.7 (5.9)</td>
<td>7.4 (6.7)</td>
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<tr>
<td>Mean body mass index (BMI) (kg/m²)</td>
<td>28.3 (5.4)</td>
<td>28.9 (5.6)</td>
<td>29.4 (5.8)</td>
<td>30.2 (6.0)</td>
<td>30.9 (6.2)</td>
<td>28.3 (5.4)</td>
<td>28.9 (5.6)</td>
<td>29.4 (5.8)</td>
<td>30.2 (6.0)</td>
<td>30.9 (6.2)</td>
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<td>Mean glycated hemoglobin (% HbA1c)</td>
<td>7.8 (1.5)</td>
<td>8.1 (1.6)</td>
<td>8.3 (1.7)</td>
<td>8.7 (2.0)</td>
<td>8.7 (2.1)</td>
<td>7.8 (1.5)</td>
<td>8.1 (1.6)</td>
<td>8.3 (1.7)</td>
<td>8.7 (2.0)</td>
<td>8.7 (2.1)</td>
</tr>
<tr>
<td>Median UACR (mg/g creat)</td>
<td>119 (10.8)</td>
<td>161 (19.2)</td>
<td>191 (23.2)</td>
<td>216 (27.4)</td>
<td>249 (31.4)</td>
<td>119 (10.8)</td>
<td>161 (19.2)</td>
<td>191 (23.2)</td>
<td>216 (27.4)</td>
<td>249 (31.4)</td>
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<tr>
<td>Mean eGFR (ml/min/1.73m²)</td>
<td>73.8 (23.1)</td>
<td>69.7 (22.4)</td>
<td>65.5 (21.7)</td>
<td>61.3 (20.9)</td>
<td>56.9 (20.3)</td>
<td>73.8 (23.1)</td>
<td>69.7 (22.4)</td>
<td>65.5 (21.7)</td>
<td>61.3 (20.9)</td>
<td>56.9 (20.3)</td>
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<td>Median systolic blood pressure (mmHg)</td>
<td>133 (22)</td>
<td>135 (25)</td>
<td>137 (28)</td>
<td>140 (30)</td>
<td>143 (33)</td>
<td>133 (22)</td>
<td>135 (25)</td>
<td>137 (28)</td>
<td>140 (30)</td>
<td>143 (33)</td>
</tr>
<tr>
<td>Median diastolic blood pressure (mmHg)</td>
<td>81 (16)</td>
<td>82 (17)</td>
<td>83 (18)</td>
<td>84 (19)</td>
<td>85 (20)</td>
<td>81 (16)</td>
<td>82 (17)</td>
<td>83 (18)</td>
<td>84 (19)</td>
<td>85 (20)</td>
</tr>
</tbody>
</table>

Conclusions: DPI sUCR is applicable in CKD stage 1-4 patients and DKD cohorts. Patients with DPI sUCR ≥1.0 g/kg.d generally have a better prognosis. Our study reveals DPI sUCR equation identifies patients with LDL effectively in CKD and NHHANES cohort.

Funding: Private Foundation Support

SA-PO471
Effects of Probiotics and Fibers on Markers of Nephropathy and Endothelial Dysfunction in Persons with Type 1 Diabetes and Albuminuria
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Background: Recent data have pointed towards a link between gut microbiota and chronic kidney disease. Deficits in the intestinal barrier due to microbial imbalance affect bacterial toxins to pass and cause systemic inflammation damaging the endothelium. Fibers serve as substrate for the beneficial bacterial strains, together with probiotics they have a positive effect on the gut environment, reestablish the microbial symbiosis and thereby strengthen the gut barrier in experimental models. We hypothesized that a supplement of fructo-oligosaccharides and probiotics would strengthen the gut barrier and protect the endothelium and kidneys.

Methods: A randomized, double blind, placebo controlled, crossover study including 41 patients with type 1 diabetes and albuminuria (urinary albumin-to-creatinine ratio (UACR) >30 mg/g) on renin-angiotensin-system blockade. Participants received synbiotic mix and matched placebo for 12 weeks in a random order with 6 weeks of washout. The primary endpoint was change from baseline to end of period in UACR (3 month urine samples per visit). Secondary endpoints: Change from baseline to end of period in endothelial glycoalxly thickness (perfused boundary region) and in inflammatory markers; end-of-period glomerular filtration rate (GFR) and ambulatory systolic blood pressure measured after each treatment period with synbiotic mix versus placebo.

Results: A total of 41 participants were randomized and 35 completed the study. Mean age was 58 (SD 10) years, 73% (n=30) were male, median UACR was 134 (30) ml/min/1.73m². There was no significant difference in UACR between the two groups. Percentage changes in UACR (UACR × 100 / UACRbaseline) were: -25.2% (95% CI -38.4: -12.0% in the synbiotic group and -18.4% (95% CI -29.6: 9.6) % in the placebo group with no significant difference between treatment periods (9.37 (-25.2; 44.0) percentage points; p = 0.60). No significant difference in the secondary end points was demonstrated.

Conclusions: Twelve weeks treatment with a supplement of synbiotic mix had no effect on UACR, perfused boundary region, inflammatory markers, GFR or ambulatory systolic blood pressure in subjects with type 1 diabetes and albuminuria.

Funding: Commercial Support - Novo Nordisk Foundation (Grant number: NNF OC0013659) and DSM Nutritional Products Ltd. Kaiseraugst, Private Foundation Support
SA-PO474

Effects of Sotagliflozin on Anemia in Patients with Type 2 Diabetes (T2D) and Stages 3 and 4 CKD

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Background: Anemia is frequent in advanced diabetic kidney disease. Sodium-glucose cotransporter inhibitors (SGLTis) consistently increase hemoglobin (Hb) through multiple mechanisms. We examined the effects of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, on Hb in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) stages 3 and 4 with and without anemia.

Methods: This was a pooled patient-level data analysis from two studies evaluating the efficacy and safety of sotagliflozin (200 and 400 mg) vs. placebo in patients with T2D and CKD 3 or 4 over 26 weeks. The effect of sotagliflozin on Hb, hematocrit, serum albumin, systolic blood pressure (SBP), body weight and estimated glomerular filtration rate (eGFR) was assessed in patients with anemia (defined as baseline Hb <13 mg/dL for men and <12 mg/dL for women) and without anemia.

Results: In the entire cohort, baseline mean Hb was 12.7 g/dL and sotagliflozin increased Hb from baseline to week 26 by 0.39 g/dL (200 mg; 95% CI 0.21-0.56) and 1.75 g/dL (400 mg; 95% CI 1.21-0.25) vs. placebo (p<0.0001). Of the 1064 patients randomized, 493 (46.3%) patients had anemia at baseline. The effect on Hb with sotagliflozin relative to placebo was more pronounced in patients without anemia over 26 weeks (Figure [doses pooled]). Sotagliflozin (doses pooled) increased odds of anemia resolving (odds ratio 1.95, p=0.017), with a trend towards decreased odds of anemia developing (odds ratio 0.75, p=0.41) over 26 weeks. The effect of sotagliflozin on serum albumin, SBP, body weight, and eGFR was generally consistent between patients with and without anemia. Sotagliflozin was generally well tolerated with similar safety profiles between anemia subgroups.

Conclusions: Sotagliflozin increased Hb in a rapid and sustained manner in patients with T2D and moderate-severe CKD over 26 weeks, and reversed anemia in a population at high risk of anemia.

Funding: Commercial Support - Lexicon Pharmaceuticals, Inc., The Woodlands, TX

SA-PO475

SGLT2 Inhibitor Therapy Ameliorates Anemia in Diabetic Kidney Disease

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Background: Sodium glucose cotransporter 2 inhibitor (SGLT2i) is a standard treatment for kidney and cardiovascular protection in diabetic kidney disease (DKD). Recent evidence suggests that SGLT2i may enhance erythropoietin production. We perform a retrospective cohort study to determine the effect of SGLT2i on the hemoglobin level in patients with DKD.

Methods: We reviewed 670 DKD patients started on SGLT2i. Their hemoglobin level and estimated glomerular filtration rate (eGFR) were evaluated 6 months before the use of SGLT2i, immediately before, and 6 months after the use of SGLT2i were reviewed.

Results: The hemoglobin level had a small but significant increase 6 months after SGLT2i inhibitor treatment from 12.89 ± 1.75 to 13.08 ± 1.94 g/dL (p = 0.0001). The absolute increase in hemoglobin level was 0.19 ± 1.06 g/dL, 274 patients (40.9%) had hemoglobin increase ≥ 0.5 g/dL, and 117 (17.5%) had an increase ≥ 1.0 g/dL. In contrast, the average hemoglobin level was 13.01 ± 1.75 g/dL 6 months before SGLT2i, which showed a significant decline to the pre-treatment level (p<0.0001). The increase in hemoglobin after SGLT2i was most marked in CKD stage 3b (12.26 ± 1.81 to 12.68 ± 1.98 g/dL, p < 0.0001). There was no significant correlation between the change in hemoglobin level and the severity of albuminuria or HbA1c level.

Conclusions: SGLT2i has a small but significant beneficial effect on DKD-related anemia. The clinical impact of this effect deserves further studies.

Funding: Clinical Revenue Support

SA-PO476

ESKD-Free Survival Time in Patients with CKD and Type 2 Diabetes (T2D) in FIDELITY

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Background: End-stage kidney disease (ESKD) is a major health and economic burden; patients with reduced quality of life are at high risk of cardiovascular mortality. FInerenone significantly reduced the risk of cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in FIDELITY, a prespecified pooled analysis of the FIDELITY-DKD and FIGARO-DKD trials. Here, we estimated the ESKD-free survival time of patients treated with finerenone vs placebo.

Methods: Patients with T2D and CKD (albuminuria and estimated glomerular filtration rate [eGFR] a25-90 mL/min/1.73 m²) and on optimized renin–angiotensin system (RAS) inhibition were randomized (1:1) to finerenone or placebo. To estimate the population-level effect of finerenone, the restricted mean survival time for ESKD after 4.5 years of treatment in FIDELITY was extrapolated to 6,425,196 US patients with T2D and CKD according to the US National Health and Nutrition Examination Survey. The cumulative incidence and treatment effects of finerenone vs placebo for time to eGFR <0.5 g/dL, ≥1.0 g/dL, and ≥1.0 g/dL to 1.5 g/dL were also analyzed using a patient-based two-slope model extrapolated to 20 years.

Conclusions: FInerenone significantly reduced the risk of cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in FIDELITY, a prespecified pooled analysis of the FIDELITY-DKD and FIGARO-DKD trials. Here, we estimated the ESKD-free survival time of patients treated with finerenone vs placebo.

Funding: Clinical Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Results: In FIDELITY, finerenone significantly reduced the risk of ESKD vs placebo (hazard ratio [HR] 0.70; 95% confidence interval [CI] 0.54-0.99; p = .0400). After 4.5 years of treatment with finerenone, the overall estimated time saved from ESKD for the US patient population vs placebo was 103,260 years (95% CI â340 to 210,556). Using extrapolations based on 5000 Monte-Carlo simulations for the individual eGFR patient slopes, the cumulative incidence for time to eGFR <10 mL/min/1.73 m² showed a risk difference between treatments of â4.5%, â7.6%, â6.7% and â5.6% for 5, 10, 15 and 20 years, respectively, corresponding to a number needed to treat of 22, 13, 15 and 18 patients for finerenone. Treatment effects of finerenone vs placebo for time to eGFR <10 mL/min/1.73 m² showed a relative risk reduction of 21% (HR=0.79; 95% CI 0.76-0.82).

Conclusions: Treatment with finerenone and optimized RAS therapy was associated with a delay in time to ESKD in patients with CKD and T2D and may provide patient and healthcare cost-saving benefits.

Funding: Commercial Support - Bayer AG

SA-PO477
Discrepancy Between Lifetime vs. Five-Year Risk Estimates for ESKD in US Adults with Diabetes
Yoohitatsu Ohi,1 Xiaoqian Zhu,1 Maria Clarissa Tio,1 Timothy E. Yen,1 Neville R. Dossabhoy,2 Tatjana Shafi,3 The University of Mississippi Medical Center, Jackson, MS; 4 Houston Methodist Hospital, Houston, TX.

Background: The Kidney Failure Risk Equation (KFRE) estimates the short-term (2- or 5-year) risk of ESKD. Misinterpretation of this short-term risk as lifetime risk may lead to patient misunderstanding and suboptimal shared decision-making.

Methods: We analyzed data from 972 US adults aged 35-84 years with diabetes and eGFR 30 to <60 mL/min/1.73 m² who participated in the 1999-2019 NHANES. Each sample was weighted to represent the general US population. We used the KFRE to calculate 5-year ESKD risk, and the Swedish National Diabetes Register prediction model (Östergaard, CJASN 2022) to estimate the lifetime ESKD risk where we calibrated baseline hazards for mortality and ESKD based on the national databases. We compared the distribution of lifetime risk across KFRE categories, further stratified by age groups.

Results: The mean age of the study cohort was 71 years, 52% were female, the median HbA1c was 6.8%, and the median duration of diabetes was 15 years. The mean eGFR was 49 mL/min/1.73 m², and 55% and 43% had moderate and severe albuminuria, respectively. The 5-year risk of ESKD by KFRE (median 1.2% [IQR, 0.6% to 3.1%]) was consistently lower than the lifetime ESKD risk (median 22% [IQR, 12% to 42%]). This discrepancy was more pronounced in younger patients (Figure). For example, within the KFRE 1% to 5% risk category, the median estimated lifetime risk was 21% for age ≥70 years, 43% for age 60-69 years, and 53% for those <60 years.

Conclusions: The KFRE, a short-term ESKD risk estimate, substantially underestimates the lifetime risk of ESKD in patients with diabetes at every risk interval, particularly in the younger populations. Clinicians should consider lifetime ESKD risk estimates, rather than just short-term ESKD risk, when counseling patients with diabetes.

Funding: Other NIH Support - National Institute of General Medical Sciences

SA-PO478
Overall and Interindividual Effect of Four Different Drug Classes on Soluble Urokinase Plasminogen Activator Receptor Expression in Albuminuric Type 1 and Type 2 Diabetes
Viktor Rotbaum Curovic,3 Morton B. Houlihan,1,2 Maryjoleen Kroonen,2 Niels Jongs,1 Tine Hansen,1 Emilie Zobel,1 Juliette Tavenier,1 Jesper Eugen-Olsen,1 Gozewijn D. Laverman,3 Frederik Persson,2 Peter Rosslie,3 Elloed J. Heerspink1,5 Leuven Diabetes Center Copenhagen, Heerlen, Denmark; 2 University Medical Center Groningen, Groningen, Netherlands; 3 Københavns Universitet, København, Denmark; 4 Copenhagen University Hospital - Amager and Hvidovre, Hvidovre, Denmark; 5 Ziekenhuisgroep Twente, Almelo, Netherlands.

Background: Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker active in multiple inflammatory processes and a risk factor of diabetic nephropathy. We evaluated the effect of four different drug classes on suPAR in type 1 and type 2 diabetes with albuminuria.

Methods: Post hoc analyses of a randomized, open-label, crossover trial including 26 adults with type 1 and 40 with type 2 diabetes with urinary albumin-creatinine ratio (UACR) ≥30 and ≤500 mg/g assigned to 4-week treatments with telmisartan 80mg, empagliflozin 10mg, linagliptin 5mg, and baricitinib 2mg separated by 4-week washouts. Plasma suPAR was measured before and after each treatment. SuPAR change after each treatment was calculated and, for each individual, the best suPAR-reducing drug was identified. Subsequently, the effect of the best individual drug was compared against the mean of the other three drugs. Repeated measures linear mixed-effects models were employed. Finally, treatment effect on UACR was correlated against treatment effect on suPAR, for each treatment and participant, assessed using Pearson’s R.

Results: Baseline median (IQR) plasma suPAR was 3.5 (2.9, 4.3) ng/mL. No overall effect on suPAR levels was observed for any one drug. The individual best-performing drug was identified for 20 (30%) participants, followed by empagliflozin for 19 (29%), linagliptin for 16 (24%), and telmisartan for 11 (17%). The individual best-performing drug reduced suPAR by 13.3% (95% CI: 3.7, 22.8; p=0.007). Difference in suPAR response between the individual best-performing drug and the other drugs was −19.7% (−23.1, −16.3; p<0.001). Baseline levels of suPAR and UACR were significantly correlated (R=0.28, p=0.029), but changes in UACR and suPAR after treatment were not correlated for any drug.

Conclusions: We demonstrated no overall effect of 4-week treatment with telmisartan, empagliflozin, linagliptin, or baricitinib on suPAR. However, individualization of treatment might significantly reduce suPAR levels and this mechanism is independent of UACR response.

Funding: Private Foundation Support

SA-PO479
Early Use and Effectiveness of Finerenone in US Patients with CKD and Type 2 Diabetes: A FOUNTAIN Platform Analysis
Nikolaus G. Oberprieler,1 Csaba P. Kovesdy,1 J. Bradley Layton,1 Alain Gay,1 Alfredo E. Farajta,1 Fangfang Liu,1 Catherine B. Johannes,1 Manel Pladevall-Vila,1 David Vizcaya,12 Bayer AG, Leverkusen, Germany; 3 University of Tennessee, Memphis, TN; 4 RTI Health Solutions Research Triangle Park, Research Triangle Park, NC; 5 RTI Health Solutions Barcelona, Barcelona, Spain.

Background: Based on evidence from clinical trials, finerenone reduces the risk of cardiovascular and renal complications among patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Evidence from finerenone use in real-world clinical practice is lacking.

Methods: Longitudinal (from July 2021 to latest data available) cohort study using existing US electronic health record and insurance claim databases. Among individuals with both CKD and T2D, a single cohort of new users of finerenone is described (patient characteristics, comorbidities, comedinations, and incidence rates of cardiovascular and renal outcomes, including eGFR and UACR changes over time).

Results: Preliminarily, among an initial cohort of 662 new users of finerenone who had a mean (SD) age of 72.1 (8.3) years with 46.6% being female. The most common comorbidities at baseline were hypertension (98.3%), hyperlipidemia (87.5%), peripheral vascular disease (66.8%), neuropathy (53.7%), retinopathy (35.5%), and congestive heart failure (34.8%). 9.9% of individuals had acute coronary syndrome and 6.5% experienced a stroke prior to finerenone initiation. Baseline comorbid use was common with 70.5% of individuals using an angiotensin-converting enzyme inhibitor (ACE) or an angiotensin receptor blocker (ARB), 60.2% a beta-blocker, and 50.6% calcium channel blockers (CCB). Furthermore, 90.9% of finerenone users were on anti-hyperglycemic medications, including insulin (46.6%), metformin (42.9%), sodium-glucose cotransporter-2 (SGLT2) inhibitors (42.3%), and glucagon-like peptide-1 (GLP-1) receptor agonists (35.2%). Complete results from the full Optum EHR and OM1 Real-World Data Cloud databases, including incidence rates of cardiovascular and renal outcomes, will be presented as part of the conference presentation.

Conclusions: Early evidence from patients who receive finerenone as part of clinical practice in the US suggests that finerenone is used independently of demographic and clinical characteristics. Furthermore, this analysis of early adopters suggests that finerenone is used as a complementary treatment option to other renal and cardiovascular protective medication classes recommended for patients with CKD and T2D.

Funding: Commercial Support - Bayer AG

SA-PO480
Comparative Kidney and Cardiovascular Effectiveness of Empagliflozin Compared to Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus
Daniel E. Dumenston,1,2 Hillary Mulder,1 Elizabeth Lyndon,1 Karen Chiswell,1 Zachary Lamprown,1 Christina M. Shay,1 Keith A. Marsolo,1 Hayden Bosworth,1,2 Neha Pagidipati,1,2 Duke Clinical Research Institute, Durham, NC; 3 Duke University School of Medicine, Durham, NC; 4 Boehringer Ingelheim International GmbH, Ingelheim, Germany.

Background: Placebo-controlled trials of sodium-glucose cotransporter-2 inhibitors (SGLT2i) demonstrated kidney and cardiovascular benefit for people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). We used real-world data to compare the effectiveness and safety of empagliflozin to dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with T2DM, with and without CKD.

Methods: We used electronic health record data from 20 large US health systems participating in PCORnet®. Using propensity overlap weighting, we compared the effectiveness of empagliflozin vs DPP4i in patients with T2DM among those newly prescribed these medications between 2016-2020. Primary composite endpoint included first occurrence of 40% eGFR decline, incident ESKD, or all-cause mortality (ACM) through 2 years. We also assessed cardiovascular and safety outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
Results: Among 62,197 patients, 32% initiated empagliflozin and 68% initiated DPP4i. Median follow-up was 1.1 years. Empagliflozin was associated with lower risk of the primary outcome compared to DPP4i (Table). For risk of ACM and a cardiovascular composite of stroke, myocardial infarction, or AC were also lower in patients prescribed empagliflozin overall and in those with CKD. The difference in heart failure hospitalization risk between groups did not reach statistical significance. Genital mycotic infections and diabetic ketoadiposis were the only safety events more common in patients prescribed empagliflozin. Differences in risk for primary composite, 40% eGFR decline and ACM were also significantly lower in patients with CKD.

Conclusions: In a real-world population with T2DM with and without CKD, empagliflozin is associated with significantly lower risk for kidney and cardiovascular outcomes compared with DPP4i.

Funding: Commercial Support - Boehringer Ingelheim and Lilly

Table: Comparative kidney and cardiovascular outcomes and differences in empagliflozin exposure compared to DPP4i in patients with T2DM with and without chronic kidney disease (POC01405) 3

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Empagliflozin (%)</th>
<th>DPP4i (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome (ACM)</td>
<td>2.3</td>
<td>3.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Invasive Infection</td>
<td>1.2</td>
<td>1.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Heart Failure Hospitalization</td>
<td>9.8</td>
<td>11.6</td>
<td>0.001</td>
</tr>
<tr>
<td>All-Cause Death</td>
<td>13.1</td>
<td>13.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular Death</td>
<td>5.4</td>
<td>6.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular Hospitalization</td>
<td>9.9</td>
<td>11.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Cardiovascular Event Without Hospitalization</td>
<td>11.7</td>
<td>12.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Noncardiovascular Death</td>
<td>0.0</td>
<td>0.0</td>
<td>NA</td>
</tr>
<tr>
<td>Noncardiovascular Hospitalization</td>
<td>1.5</td>
<td>1.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Total Adverse Event Rate</td>
<td>12.6</td>
<td>13.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean UACR (mg/g)</td>
<td>827 (273)</td>
<td>1,150 (295)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Mean eGFR (mL/min/1.73 m^2) SD is 53 (23). Uptake of agents acting on the RAAS decreased in the real-world setting. In general, the uptake of guideline-recommended therapies for CKD associated with T2D is low (RAAS inhibitors and statins). Advocacy for greater adherence to standard of care could improve patient outcomes.

Funding: Commercial Support - The study and this analysis were funded by Bayer AG, Leverkusen, Germany. Medical writing and/or editorial assistance was provided by Moamman Hammad, PhD, and Melissa Ward, BA, both of Scion, London, UK. This support was funded by Bayer AG, Wuppertal Germany according to Good Publication Practice guidelines.

SA-PO481

Interim Results from FINE-REAL: A Prospective Study Providing Insights into the Use of Finerenone in Routine Clinical Settings Susanne S. Nicholas,1 Ricardo Correa-Rotter,2 Nihar Desai,3 Lixin Guo,4 Sankar D. Navaneethan,5 Kevin M. Pantalone,6 Christopher Wanner,7 Stefanie Hamacher,8 Alain Gay,9 David C. Wheeler,10 David Geffen School of Medicine at UCLA, Los Angeles, CA; 1Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; 2Section of Cardiovascular Medicine, Yale School of Medicine, Yale New Haven Hospital, New Haven, CT; 3Department of Endocrinology, Beijing Hospital, National Center of Gerontology, Institute of Geriatric Medicine, Chinese Academy of Sciences, Beijing, China; 4Section of Nephrology, Baylor College of Medicine, Houston, TX; 5Department of Endocrinology and Metabolism Institute, Cleveland Clinic, Cleveland, OH; 6Department of Medicine, Division of Nephrology, University Hospital Würzburg, Würzburg, Germany; 7ClinStat GmbH, Huerth, Germany; 8Medical Affairs & Pharmacovigilance, Pharmaceuticals, Bayer AG, Berlin, Germany; 9Department of Renal Medicine, University College London, London, United Kingdom.

Background: Finerenone is a selective, nonsteroidal mineralocorticoid receptor antagonist, which improved kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D) in phase 3 trials. Finerenone is approved in the European Union, US, China, and several other countries. FINE-REAL (NCT03438733) aims to provide insights on characteristics and treatment patterns of patients treated with finerenone in clinical practice.

Methods: FINE-REAL is a prospective, single-arm, non-interventional study of finerenone in routine clinical settings. The study included patients with CKD stages 3-4 who were prescribed finerenone. The study population was identified from the Veterans Affairs Corporate Data Warehouse from 2005-2022. Individuals who had an incident prescription for a GLP-1 RA were included, with the date of prescription used as the index date for the analysis. The primary outcome was treatment discontinuation, defined as an interruption in GLP-1 RA prescription for at least 90 days. Cox proportional hazards regression identified factors associated with time to treatment discontinuation and the association of treatment discontinuation with time to all-cause death, treating GLP-1 RA discontinuation as a time-varying covariate.

Results: Of 60,020 individuals who received a GLP-1 RA, 95% were male, 75% were White, 20% were Black, 63% were of age ≥ 70, and 80% had CKD stage 3a. Discontinuation (at least once) occurred in 28,467 (47%) GLP-1 RA users over a median (IQR) of 1.41 (0.72, 2.59) years of follow up. Black or unreported race, younger age, and concomitant vascular disease were associated with GLP-1 RA discontinuation (Figure). There were 9628 deaths. GLP-1 RA discontinuation, included as a time-varying covariate, was associated with all-cause death (HR 2.22 [95% CI 1.21, 3.44], P=0.0005) independent of age, sex, race, CKD stage, medical comorbidities, and concomitant medication use.

Conclusions: In CKD population, discontinuation of GLP-1RA is common and was associated with an increased risk of death. Additional studies exploring the reasons for short-term and long-term discontinuations of these agents are needed.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

SA-PO482

Predictors and Outcomes of Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) in CKD J. Parker Greco,1,2 Peter Richardson,3 Vijay Nambi,3,4 Michael E. Matheny,5,6 Salim S. Virani,3,7 Sankar D. Navaneethan,1,2 Baylor College of Medicine, Houston, TX; 1Michael E DeBakey VA Medical Center, Houston, TX; 2Vanderbilt University Medical Center, Nashville, TN; 3VA Tennessee Valley Healthcare System, Nashville, TN; 4The Aga Khan University, Karachi, Pakistan.

Background: GLP-1 RAs improve cardiovascular and kidney outcomes in patients with CKD but are underutilized. We aimed to study treatment discontinuation and its associations with patient-level characteristics and death among those with CKD.

Methods: Adults with CKD stages 3-4 were identified from the Veterans Affairs (VA) Corporate Data Warehouse from 2005-2022. Individuals who had an incident prescription for a GLP-1 RA were included, with the date of prescription used as the index date for the analysis. The primary outcome was treatment discontinuation, defined as an interruption in GLP-1 RA prescription for at least 90 days. Cox proportional hazards regression identified factors associated with time to treatment discontinuation and the association of treatment discontinuation with time to all-cause death, treating GLP-1 RA discontinuation as a time-varying covariate.

Results: Of 60,020 individuals who received a GLP-1 RA, 95% were male, 75% were White, 20% were Black, 63% were of age ≥ 70, and 80% had CKD stage 3a. Discontinuation (at least once) occurred in 28,467 (47%) GLP-1 RA users over a median (IQR) of 1.41 (0.72, 2.59) years of follow up. Black or unreported race, younger age, and concomitant vascular disease were associated with GLP-1 RA discontinuation (Figure). There were 9628 deaths. GLP-1 RA discontinuation, included as a time-varying covariate, was associated with all-cause death (HR 2.22 [95% CI 1.21, 3.44], P=0.0005) independent of age, sex, race, CKD stage, medical comorbidities, and concomitant medication use.

Conclusions: In CKD population, discontinuation of GLP-1RA is common and was associated with an increased risk of death. Additional studies exploring the reasons for short-term and long-term discontinuations of these agents are needed.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

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

857
SA-PO483
Increased Risk of Serious Hypoglycemia with Insulin Glargine in Veterans with Type 2 Diabetes: An Emulated Clinical Trial Observational Study

**Background:** Serious hypoglycemic events needing medical attention are significant complications of anti-glycemic therapy in type 2 diabetes (T2D), particularly in those with CKD. Therefore we examined the risk of serious hypoglycemic events with insulin glargine (IG) use compared to glucagon-like-peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i) in a national cohort of veterans.

**Methods:** We conducted an active comparator, new user design study of veterans (N = 30165) with T2D with CKD (eGFR < 60) on metformin who then initiated on IG or SGLT2i or GLP1-RA for the first time between 01/01/2018 to 12/31/2021. Those with any previous use of these agents were excluded. Administrative censor date was 03/31/2023. Serious hypoglycemic events needing medical attention were identified from EU/urgent care visits or hospital discharge diagnosis with ICD10 codes using a validated algorithm. Inverse probability weights (IPW) were developed using propensity scores for the three drug classes. In IPW Cox models, the study drug classes were related to the risk of serious hypoglycemic events.

**Results:** 38.2% were initiated on IG, 12.7% on GLP1-RA and 49.1% on SGLT2i. Mean eGFR was 79.5±20.1 mL/min/1.73m². There were 972 events over 78594 years follow-up. In IPW Cox regression, compared to GLP1-RA, the IG group had higher risk whereas the SGLT2i group had lower risk (Table 1).

**Conclusions:** IG is associated with higher serious hypoglycemia risk in CKD. The safety of IG in CKD needs to be reevaluated.

**Table 1. Risk of hypoglycemia by drug class and CKD**

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Event Rate</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noe (N=12874)</td>
<td>0.71</td>
<td>1.00</td>
</tr>
<tr>
<td>GLP1-RA (N = 60755)</td>
<td>0.92</td>
<td>1.00</td>
</tr>
<tr>
<td>Insulin Glargine (N = 48921)</td>
<td>1.09</td>
<td>1.39 (1.38, 1.42)</td>
</tr>
<tr>
<td>SGLT2i (N = 25258)</td>
<td>0.62</td>
<td>0.70 (0.65, 0.76)</td>
</tr>
<tr>
<td>CRT (N = 30661)</td>
<td>1.74</td>
<td></td>
</tr>
<tr>
<td>GLP1-RA (N = 17871)</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Insulin Glargine (N = 10901)</td>
<td>1.00</td>
<td>1.49 (1.42, 1.56)</td>
</tr>
<tr>
<td>SGLT2i (N = 15377)</td>
<td>0.74</td>
<td>0.67 (0.60, 0.69)</td>
</tr>
</tbody>
</table>

SA-PO484
Increased Mortality Risk with Insulin Glargine in Veterans with Type 2 Diabetes: An Emulated Clinical Trial Observational Study

**Background:** Insulin glargine (IG) is one of the most commonly used anti-glycemic agents in advanced CKD. However, there is a paucity of data in head to head comparisons of IG with newer agents such as glucagon-like-peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i). Therefore we examined the risk of mortality with insulin glargine use compared to GLP1-RA and SGLT2i use in a national cohort of veterans.

**Methods:** We followed the active comparator, new user design to emulate a trial to compare the effect of initiating on IG or SGLT2i or GLP1-RA among veterans with T2D on metformin who initiated any one of these three between 01/01/2018 to 12/31/2021 (N = 158,939). Those with previous use of these agents were excluded. Administrative censor date was 03/31/2023. Generalized propensity score based inverse probability weighting (IPW) was employed to control confounding in the observational data and facilitate comparisons among the three drug classes. In IPW Cox models, the study drug classes were related to the risk of mortality in those without and with CKD (eGFR < 60).

**Results:** 38.2% were initiated on IG, 12.7% on GLP1-RA and 49.1% on SGLT2i. There were 972 events over 196,977 years follow-up. In IPW Cox regression, compared to GLP1-RA, the IG group had higher mortality risk whereas the SGLT2i group had lower mortality in the CKD subgroup (Table). **Conclusions:** IG is associated with higher mortality risk in both non-CKD and CKD subgroups. These results suggest that the routine clinical use of IG needs to be reconsidered.

SA-PO485
Major Adverse Kidney Disease Events in a Real-World Population with Diabetes

**Background:** Assessing risk for major adverse kidney disease events (MAKDE) helps target populations who could benefit from improved chronic kidney disease (CKD) awareness, detection, and intervention. In a real-world population with diabetics, we evaluated the frequency of MAKDE and Kidney Disease Improving Global Outcomes (KDIGO) risk categories during 2013-2020.

**Methods:** The study population was derived from electronic health records data in the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry at Providence and UCLA Health systems. Demographic and clinical characteristics were obtained for patients aged ≥18 years with diabetes. CKD was defined by eGFR <60 mL/min/1.73 m², UACR ≥30 mg/g or UPCR ≥0.15 g/d. MAKDE was defined as a composite of 40% eGFR decline from baseline, eGFR <15 mL/min/1.73 m², dialysis, or kidney transplant. Frequency of MAKDE was evaluated by baseline CKD status and KDIGO risk categories.

**Results:** Among patients with diabetes (N=285,036), 51% (n=144,016) were women and mean age was 61±16 years. At baseline, 21% (n=66,672) had CKD with mean eGFR of 56±24 mL/min/1.73 m² and median UACR of 58 (interquartile range [IQR] 33-164) mg/g. Frequency of MAKDE was 28% (16,180/60,672) in those with CKD and 14% (32,112/224,364) in those without CKD. Median follow-up was 2.3 (IQR 1.0-4.0) years. Among patients with CKD who had baseline eGFR and UACR/UPCR measurements, 37% were classified as high or very high KDIGO risk. MAKDE frequency increased by higher KDIGO risk categories (Figure). **Conclusions:** MAKDE occurred commonly in a real-world population with diabetes. Compared to those without CKD, prevalence of MAKDE was twice as high in patients with CKD and more than one-third of them were in high or very high KDIGO risk categories when both eGFR and UACR/UPCR were measured.

**Funding:** Other U.S. Government Support
with frailty and advanced illness, or ≥81 with frailty were excluded. Auto ordering of Scr and CKD in the United States

**Results:**

Patients with CKD had either SGLT2 or GLP1a within the Service plans, were found to be significant predictors of using SGLT2i and GLP1a (Table).

**Conclusions:** We document low use of SGLT2i and GLP1a among diabetic patients with CKD in 2020. Given encouraging results from several recent, large randomized clinical trials, our study suggests an ongoing need for investigating barriers and disparities in the real-world use of these medicines.

**Funding:** Other U.S. Government Support

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**SA-PO487**

**Prescribing of Sodium Glucose Co-Transporter 2 Inhibitors Among Hispanic/Latino Individuals Within Duke University Health System**

Matthew R. Sinclair,1,2 Yixuan Feng,1 Clarissa J. Diamantidis,1 Benjamin A. Goldstein,3 Duke University School of Medicine, Durham, NC; 3Duke Clinical Research Institute, Durham, NC; 2Duke University Department of Biostatistics and Bioinformatics, Durham, NC.

**Background:** Type 2 diabetes (T2D) is a risk factor for cardiovascular disease, chronic kidney disease, and death. Lifetime prevalence of T2D in Hispanic/Latino individuals is 10.1% and 15.3% respectively. One medication class, the sodium-glucose co-transporter-2 inhibitors (SGLT2is), improve cardiovascular and kidney outcomes among patients with T2D. Unfortunately, recent national evidence shows that racial and ethnic minority individuals with T2D, including Hispanics/Latinos, are less likely to receive SGLT2is compared to non-Hispanic White individuals. Among Hispanic/Latino individuals, using SGLT2is within Duke University Health System (DUHS) are currently unknown. We examined prescribing rates and likelihood of SGLT2i prescribing among Hispanic/Latino individuals with T2D within DUHS compared to other races and ethnicities.

**Methods:** Exclusion criteria from the DUHS electronic health record system to identify adults with T2D eligible to receive an SGLT2i. Starting in January of 2017, we defined eligibility as having a diagnosis code for T2D and an outpatient encounter with a hemoglobin A1C >6.5%. Patients were followed until either receiving an SGLT2i, losing eligibility, eGFR <30 or A1C <6.5%, death, or follow-up through December 31, 2022. We assessed time to SGLT2i prescribing based on race/ethnicity, accounting for competing risks in a subdistribution hazard model.

**Results:** Among adults with T2D (n = 6,653), Hispanic/Latino individuals had a lower cumulative incidence of SGLT2i prescriptions (10.1%) compared to both non-Hispanic Black (16.3%) and non-Hispanic White (17.5%) individuals (p = 0.12). After adjusting for age, sex, type of health insurance, area deprivation index, and comorbidities, there was suggestion of a decreased likelihood of prescribing among Hispanic/Latino individuals when compared to both non-Hispanic Black (adjusted hazard ratio (aHR) 0.77 (95%CI:0.53-1.11)) and non-Hispanic White (aHR 0.77 (95%CI:0.53-1.12)) individuals.

**Conclusions:** SGLT2is are prescribed at low rates among patients with T2D within DUHS, consistent with national trends. Likelihood of prescribing was lowest among Hispanic/Latino individuals, even after adjustment for key demographics and clinical comorbidities, when compared to their non-Hispanic Black and White counterparts.

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**SA-PO488**

**Use of Medicines to Protect Kidney Function Among Patients with Type 2 Diabetes (T2D) in the United States**

Yun Han,1 Miao Yu,1 Michael Heung,1 William H. Herman,1 Joseph A. Vassalotti,2 Fang Xu,2 Rajiv Saran,1 University of Michigan, Ann Arbor, MI; 2Centers for Disease Control and Prevention, Atlanta, GA; 1Icahn School of Medicine at Mount Sinai, New York, NY.

**Background:** Newer classes of diabetes, kidney, and cardioprotective medicines, such as SGLT2i and GLP1a, have shown better outcomes among diabetic patients. We examined the use of SGLT2i and GLP1a among patients with T2DM and CKD in the US.

**Methods:** We identified 425,879 patients aged ≥20 years diagnosed with T2DM and CKD (mean age: 73.9 years) from Optum Clinformatics® data. Medical history and specialist visits in 2019 were defined by ICD codes and provider ID (nephrology, cardiology, and endocrinology). We examined specific medicine use(SGLT2i, GLP1a, ACE-inhibitors, ARBs) and CKD progression among adults with T2D.

**Results:** SGLT2i use was observed among 5.5% of patients with type 2 diabetes and CKD, with higher usage in CKD stage G1–2 (6.2%) compared with other stages (G1: 1.6%, G2: 2.1%, and G3: 2.8%, P < .0001). About 8.6% of patients used GLP1a with a higher usage in CKD stage G3 (7.9%) compared with early stages and advanced stages (G1–2: 7.5%, G3: 7.1%, and G5: 5.7%, P < .001). After adjusting for demographics and other covariates, having endocrinologist visits, being covered by Exclusive Provider

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**SA-PO489**

**Treatment Utilization and Disease Burden Associated with CKD Progression in Patients with Type 2 Diabetes**

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**Background:** Effective management of type 2 diabetes (T2D) is important for preventing/delaying complications, such as chronic kidney disease (CKD). This real-world, retrospective cohort study examined clinical characteristics and antidiabetic treatment utilization, particularly sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), in patients with CKD and T2D.

**Methods:** Data were obtained from the Merative™ MarketScan® Explorys Claims Electronic Health Record Database (January 1, 2016, to September 30, 2020). Patients were aged ≥18 years and had ≥2 estimated glomerular filtration rate (eGFR) values between 15 and 89 ml/min/1.73 m² within 2 years of follow-up (range of 16-24 months). First eGFR value qualifying for inclusion was the index date, and patients were continuously enrolled for 6 months pre-index and 12 months post-index. Patients had diagnoses of CKD and T2D in the pre-index period. Treatment utilization was reported by CKD stages 2–5; all analyses were descriptive.

**Results:** A total of 7,261 patients were included (mean ± SD age, 72.4 ± 10.6 years; 56.4% male). Patients had CKD stage 2 (28.0%), 3a (27.4%), 3b (29.5%), or 4 (15.1%). At pre-index, 4.2% and 7.8% of patients received SGLT2is and GLP-1RAs, respectively. At post-index, an average, 43.3% of patients across CKD stages 2–5 received metformin, 10.4% received GLP-1RAs, and 7.3% received SGLT2is; decreasing use of these agents was observed with CKD progression (Figure). In a subset of patients with poor glycemic control (glycated hemoglobin >7%; n=9,321), metformin, SGLT2i and GLP-1RA utilization was low; 18.2–30.1% received SGLT2is or GLP-1RAs (Figure).

**Conclusions:** Despite a large number of patients with comorbid CKD and T2D having poor glycemic control, SGLT2i and/or GLP-1RA utilization was low. Improved diabetes management is needed in this patient population.
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Limitations to the use of Guideline-Directed Medical Therapy (GDMT) in Patients with CKD and Type 2 Diabetes Mellitus (DM) in the Primary Care Setting at an Inner-City Hospital in Bronx, New York

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Background: In 2022, KDIGO modified its GDMT for CKD and Type 2 DM patients to include SGLT-2 inhibitors (SGLT2i’s) along with angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) as first-line therapy. However, many patients are discontinued due to adverse effects of an initial decline in estimated glomerular filtration rate (eGFR), frequent yeast infections, urinary tract infections, and euglycemic ketoacidosis. We aimed to study which limitations affect practice patterns in our hospital.

Methods: We conducted a retrospective analysis of patients with CKD and Type 2 DM from the primary care clinics from North Central Bronx Hospital, a community hospital in Bronx, NY, from July of 2019 to July of 2022. Statistical analysis was performed using the SPSS program where dichotomous variables and their relationships were analyzed using Chi square and binary logistic regression.

Results: Out of 419 patients recruited, 66.8% were found to be prescribed an ACEI/ARB, while 20.5% were prescribed SGLT2i’s. A history of hyperkalemia showed a decreased odds ratio (OR) (0.460, 0.28-0.73 CI 95%, P=0.04), whereas a microalbuminuria check showed an increased OR (1.923, 1.2-1.9 95% CI, P=0.04) of an ACEI/ARB prescription respectively. CKD stage was also found to affect ACEI/ARB prescription with more patients being prescribed in stages 2, 3a, 3b (78.2%, 68.6%, 67.9%) and less in patients with CKD stages 4, 5 (55.6%, 47.6%), respectively, P= 0.015. In the regression model, the only independent variable found to affect SGLT2i prescriptions was microalbuminuria, where patients who had a microalbuminuria check within last year were more likely to have been prescribed an SGLT2i OR=2.5, 1.11-3.12 CI 95%, p= 0.019.

Conclusions: A history of hyperkalemia and advanced CKD stage are limiting factors to prescribing ACEI/ARB, while not checking microalbuminuria are limiting factors to prescribing ACEI/ARB and SGLT2 inhibitors.

SA-PO491

Change in Urine Albumin-to-Creatinine Ratio (UACR) and Health Care Resource Utilization (HRU) and Costs in Patients with Type 2 Diabetes (T2D) and CKD

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Background: UACR is an important measure of kidney damage, but the impact of changes in UACR on HRU and costs in patients with T2D and CKD is unclear.

Methods: We used the Optum electronic health records database (01/2007-09/2021) to identify adult patients with albuminuria, measured by UACR ≥30 mg/g (initial test) after diagnosis of T2D and CKD. UACR change was categorized as increased (>30% change), stable (<30% to 30%), or decreased (<30%) based on the percent change between the initial test and the last test (between 183-730 days after the initial test). All-cause inpatient (IP) admissions, emergency room (ER) visits, outpatient (OP) visits, and total medical costs were evaluated during the 1 year after the last test. The association of UACR change with HRU was evaluated using Poisson regression, adjusting for key baseline characteristics. Medical costs (2022 USD) were estimated using a unit cost approach based on HRU frequencies.

Results: Among 144,814 patients eligible for the study, 81,084 (56%) had decreased, 31,766 (22%) had stable, and 31,964 (22%) had increased UACR. Compared with patients with stable UACR (IP admissions: 0.18 per person-year [PPY]; ER visits: 0.31 PPY; OP visits: 19.13 PPY; costs: $12,521), those with decreased UACR had similar HRU (IP: 0.17 PPY; ER: 0.31 PPY; OP: 19.90 PPY) and annual medical costs ($12,329), while those with increased UACR had higher HRU (IP: 0.24 PPY; ER: 0.35 PPY; OP: 21.20 PPY) and costs ($15,013). Compared with patients with stable UACR, those with decreased UACR had adjusted incidence rate ratios of 0.97 (95% CI: 0.93-1.01) for IP, 0.97 (0.94-1.01) for ER, and 1.02 (1.01-1.03) for OP. Patients with increased UACR had adjusted incidence rate ratios of 1.22 (1.17-1.28) for IP, 1.10 (1.05-1.15) for ER, and 1.07 (1.05-1.08) for OP compared with patients with stable UACR.

Conclusions: Among patients with T2D and CKD who had albuminuria, increases in UACR were associated with higher HRU and costs compared to patients with stable UACR, while decreases in UACR were associated with similar HRU and costs. Mitigating increases in UACR could yield economic benefits for this patient population.

Funding: Commercial Support - Bayer U.S. LLC

SA-PO492

Cost-Effectiveness Analysis of Dapagliflozin vs. Finnerone for Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage chronic kidney disease (CKD) worldwide. CKD carries a health problem public health associated with high morbidity, mortality, high costs and low quality of life. It is necessary to implement risk reduction strategies, such as the use of selective sodium-glucose cotransporter inhibitors 2 (SGLT2) and selective nonsteroidal mineralocorticoid receptor antagonist (MRA), reducing the risk of 20-40% of time to first onset of kidney failure, sustained decrease in eGFR, and renal or cardiovascular death.

Methods: A probabilistic economic model (Markov model) was developed to evaluate the cost-effectiveness of dapagliflozin versus finerenone for CKD. The model compared patients with dapagliflozin 10 mg per day versus finerenone 20 mg per day, added to standard treatment, in a cohort analyzed at 100 years of age. The states of CKD, progression to CKD with renal replacement therapy (RRT) requirement, renal and cardiovascular death were structured. The effect of dapagliflozin was estimated based on DAPA-CKD trial (HR 0.56; 95% CI, 0.45 - 0.68; p < 0.001) and the effect of finerenone based on FIDELITY trial (HR 0.77; 95% CI, 0.67–0.88; P = 0.0002). Probabilities, benefits, and costs of previous studies reported in literature were collected; to finally calculate the total costs, years of life gained adjusted for quality of life and the cost-effectiveness ratio.

Results: The total difference in cumulative life years was 3,979 for CKD in favor of dapagliflozin use. An incremental cost-effectiveness ratio, expressed in quality-adjusted life years, of $8,907 dollars was estimated with dapagliflozin versus $14,451 dollars with finerenone.

Conclusions: Dapagliflozin is cost-effective treatment versus finerenone for CKD, total difference $5,544 dollars for quality-adjusted life year.
SA-PO493

Overcoming Recruitment Obstacles in a Trial Examining Intradialytic Plantar Electrical Nerve Stimulation in Diabetic Hemodialysis Patients

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Background: Recruitment of patients on hemodialysis (HD) into a clinical trial is challenging. We examined the feasibility and scalability of using functional plantar electrical nerve stimulation (iPENS) during every HD for 12 weeks. Our original target was to recruit 100 patients over 4 year study period.

Methods: Our study design is a double-blind, randomized controlled trial. We used iPENS to improve gait, balance and mobility (assessed using wearable sensors) among diabetic patients undergoing HD. Patients received either 1-hour active iPENS or non-functional iPENS during every HD for 12 weeks. Our original target was to recruit 100 patients over 4 year study period.

Results: We screened 540 HD patients in 2018-23. 410 (76%) patients were excluded (mostly non-diabetic and non-anamnestic patients). 130 (24%) patients met the inclusion criteria, but 19 (14.6%) refused to participate (not interested in any extra tasks during HD). 111 patients consented, but 18 (16.2%) dropped (mostly due to COVID-19 criteria, but 19 (14.6%) refused to participate (not interested in any extra tasks during HD). In the end, 92 patients (17% of the total screened patients) completed the study. Our study faced 11 months interruption related to COVID-19 pandemic. No patients discontinued the study because of extra burden or side effects. Most patients reported positive feedback and experience, with many requesting to continue the intervention beyond the study duration.

Conclusions: Our study was successful in recruiting its target despite its complexity and the challenges it faced. Creating an innovative study design that suits patients’ schedules was essential to our success.

Funding: Government Support - Non-U.S.

SA-PO494

Systolic Blood Pressure Modifies the Relationship Between Coronary Artery Calcification and Adverse Kidney Outcome: Results from KNOW-CKD

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Background: Previous studies have shown that elevated BP and coronary artery calcification (CAC) are risk factors for adverse kidney outcomes. However, the interaction between CAC and BP in relation to CKD progression has not well been studied. In this observational study, we aimed to evaluate whether systolic blood pressure (SBP) could modify the association between CAC and CKD progression in patients with CVD.

Methods: We analyzed 1698 participants with CKD stages G1 to G5 from the Korean cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD). Participants with kidney failure with replacement therapy (KFR) and those with missing data for CAC and SBP were excluded. We censored the participants according to their 1-year-mean systolic BP as controlled (SBP <120 mmHg) or uncontrolled (SBP ≥120 mmHg) and the CAC status (Agatston score=0 or >0 AU). CKD progression was defined as a composite of halving eGFR from baseline value or onset of KFR.

Results: During 10,023 person-years of follow-up (median 6.2 years), the composite outcome occurred in 689 (40.7%) participants. We found a significant interaction between the Agatston score and SBP for CKD progression (P=0.02). There were 90 (27.5%), 67 (37.0%), 219 (39.5%), and 313 (49.7%) composite outcome events in participants with controlled BP without CAC (group 1), uncontrolled BP without CAC (group 2), uncontrolled BP without CAC (group 3), and uncontrolled BP with CAC (group 4), respectively. In multivariable cause-specific Cox model, the corresponding hazard ratios (95% confidence interval) for groups 2, 3, and 4 were 1.25 (0.88-1.77), 1.44 (1.12-1.87), and 1.78 (1.35-2.34), respectively, compared with group 1. Sensitivity analysis using a different SBP cutoff of 130 mmHg yielded similar results.

Conclusions: The clinical implication of CAC for CKD progression may be influenced by the status of controlled SBP, and CAC is more strongly associated with adverse kidney outcome when SBP is not adequately controlled.

Funding: Government Support - Non-U.S.

SA-PO495

Are We Dismissing Type 2 Myocardial Infarction (MI) in ESRD? A Serious Note of Concern

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Background: Patients with ESRD and elevated troponin (cTn) have increased morbidity and mortality. The cTn elevation is often overlooked and categorized as chronic cTn elevation or demand ischemia. We aim to evaluate 30-day readmission and mortality at one year among hospitalized ESRD patients.

Methods: Adult patients with ESRD and elevated cTn admitted from 4/2020 to 4/2022 were included. The 4th Universal Definition of MI and cTn change ≥20% in patients with elevated cTn on admission were used to identify type 1 MI in ESRD. Patients were stratified into 2 groups: type 1 and type 2 MI. 30 days readmission rate and mortality during admission & 1 year were analyzed.

Results: Of the 376 patients hospitalized, 168 were classified as Type 1 or 2 MI and the rest were determined to have chronic elevation of cTn. 24 were classified as type 1 and 144 as type 2. Baseline characteristics were similar between groups. 30 days readmission rate was 21% in the type 1 group vs 18% in the type 2 (p=0.745). Mortality during hospitalization was 21% for type 1 vs 9% for type 2 (p=0.083). Mortality was comparable at 1 year: 29% for type 1 vs 17% in Type 2. Risk of mortality in type 2 MI was higher with heart failure (OR 4.121, p=0.041), AFib (OR 6.684, p=0.031) and hemoglobin <8 (OR 9.023, p=0.007). Patients with CVA (OR 0.080, p=0.010), chest pain on admission (OR 0.097, p=0.006), and atypical symptoms (OR 0.079, p=0.016) had better survival.

Conclusions: Type 2 MI is more common among hospitalised ESRD patients. It has comparable outcomes at one year to type 1, highlighting the importance of strategies to accurately diagnose and risk stratify for better outcomes. Further research in this area, including the role of intervention, will enhance our understanding and improve clinical practices for this vulnerable population excluded in the ISCHEMIA/CKD trial.

Funding: Government Support - Non-U.S.

SA-PO496

Are We Closing the Loop in Patients with ESRD Too Soon?

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Background: Cardiovascular (CV) disease remains the leading cause of death in ESRD patients. Myocardial infarction (MI) is associated with poorer outcomes compared to the general population. A recent consensus by the Standardized Nomenclature in Nephrology Hemodialysis (SOUND-HD) group defines MI type 1 in ESRD patients if they have changes in EKG, symptoms, and a rise or fall of troponin (cTn) within 6 to 12 hours.
hours of more than 20% if elevated or more than 50% if normal on admission. We aimed to
study the outcomes of patients with ESRD and elevated troponin according to this new
consensus.

Methods: This retrospective single center study included patients with ESRD admitted with elevated troponin from April, 2020 to 2022. Patients with a single cTn on admission treated cTn less than 6 hours apart from the initial, admitted for cardiac arrest or trauma were excluded. Patients that met criteria for type I MI according to the SONG-HD group consensus were included for the study. Baseline characteristics and mortality up to 1 year were analyzed using descriptive statistics.

Results: According to inclusion and exclusion criteria a total of 24 ESRD patients were admitted during this period for type I MI. 4 patients received ACS protocol (ACSP) and PCI within 30 days with a mortality of 0%, 12 patients only ACSP with a mortality of 25% and 8 patients no intervention with a mortality of 50%. 14 patients were documented type I MI and 10 patients were not due to the lack of guidelines at that time. Out of the 14 patients, 3 received ACS/PCI and PCI within 30 days, with a mortality rate of 0%, 9 only ACSP with a mortality of 11% and 2 received no intervention with a mortality rate of 50%. Out of the 10 patients not identified as type 1 on hospitalization, mortality was 50%.

Conclusions: To date there are no clinical trials about the benefit or harm of reverasulavascularization in patients with ESRD. The ISCHEMIA-CKD study reports no benefit in initial invasive strategy when compared to conservative strategy in patients with CKD stage 3 and 4. Though our sample size is small, it brings to light the recurrent question about the role of early cardiac catheterization/PCI among patients with type 1 MI with ESRD while highlighting the importance of early and accurate recognition of type 1 MI in this high risk population.

SA-PO497
Etelcalcetide Use Affects Changes in Agatston Coronary Artery Calcium (CAC) Score in Maintenance Dialysis Patients
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Background: Dialysis patients are known to be at high cardiovascular risk, and the Agatston CAC score, a measure of coronary artery calcification, has been associated with cardiovascular events. Recently, calcimetics such as etelcalcetide have been used to manage secondary hyperparathyroidism, but their effect on vascular calcification is unknown. Therefore, the present study investigated whether etelcalcetide use affects changes in Agatston CAC scores in maintenance hemodialysis patients.

Methods: This historical cohort study included 192 patients undergoing maintenance hemodialysis who had Agatston CAC score of 100 or higher and were not using calcimetics other than etelcalcetide. Propensity score matching was performed by age, gender, diabetes mellitus, Ca, iP, and intact PTH. In addition, we examined whether there was a difference in etelcalcetide use and the rate of change in Agatston CAC score after one year.

Results: In the two groups of patients matched for background factors by propensity scores (18 patients each), the Agatston CAC score change was significantly lower in the etelcalcetide use group (p=0.0284).

Conclusions: Etelcalcetide use in maintenance dialysis patients may reduce coronary calcification.

SA-PO498
Empagliflozin in Patients with Acute Heart Failure and Diuretic Resistance: Preliminary Data from the DRIP-AHF-1 Trial
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Background: Diuretic resistance is common in acute heart failure and associated with poor clinical outcomes. Chronic kidney disease (CKD) is a major determinant of diuretic resistance. Association of furosemide with sodium-glucose co-transporter 2 inhibitors can potentially overcome diuretic resistance in acute heart failure patients with CKD.

Methods: This is a prospective, single-arm, observational, open-label clinical trial. Patients admitted with acute heart failure with estimated glomerular filtration rate (eGFR) of 15-45mL/min/1.73m2 and diuretic resistance, defined as a urinary output (UO)=300mL in the 2 hours post 1-1.5mg/kg IV furosemide, were recruited. These patients received a 25mg of empagliflozin 2 hours post a second IV furosemide bolus of 1-1.5mg/kg, administered at least 5 hours after the initial furosemide bolus. Primary outcome is the 3-hour UO post furosemide/empagliflozin on the first day of the study, compared with furosemide alone. Secondary outcomes include fractional excretion of sodium (FENa) and total urinary sodium excretion.

Results: From 32 patients screened, 6 patients met inclusion criteria and consented to participate. Median age was 80 (75-84) years, 67% were male, median ejection fraction was 40 (40-55) % and median baseline of eGFR 18 (17-25) mL/min/1.73m2. All patients had a strong response to furosemide after empagliflozin administration (Table)

Conclusion: Our preliminary data shows that empagliflozin at a dose of 25mg, when added to high dose IV furosemide in patients with acute heart failure, low eGFR and diuretic resistance, is capable of increasing urinary output and urinary sodium excretion.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: At 6 months of follow-up, RDN produced a clinically meaningful blood pressure reduction independent of concomitant antihypertensive medications. The application of RDN in patients undergoing maintenance hemodialysis is efficacy and safety.

Funding: Government Support - Non-U.S.

SA-PO501
Poolled, 12-Month Renal Safety and Blood Pressure (BP) Reductions Using the Symplicity Spyral Radiofrequency Renal Denervation Catheter
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Background: Renal denervation (RDN) targets the sympathetic nervous system to lower blood pressure (BP). Impact on long-term renal function after RDN is less well known. We report the 12-month BP reductions and renal safety after RDN from the largest existing database, using the latest generation, multi-electrode, radiofrequency (RF) Symplicity Spyral™ catheter.

Methods: A broad spectrum of patients with hypertension were enrolled in the SPYRAL HTN Global Clinical Program, consisting of 4 major studies; SPYRAL First-In-Man, SPYRAL HTN-OFF MED, -ON MED and Global SYMPLECTIC Registry (GSR). GSR is an all-comer registry for patients with uncontrolled hypertension, including chronic kidney disease (CKD), whereas patients enrolled in the SPYRAL HTN-OFF and -ON MED trials required to have OSBP ≥150 and <180 mmHg and ODBP ≥90 mmHg. OFF MED patients were required to have a drug washout period prior to treatment and did not take drugs for the first 3 months. ON MED patients were on a stable 1-3 antihypertensive drug regimen for 6 months. All were treated with RF RDN using the Spyral catheter. We pooled reductions in office and 24-h ambulatory BP, safety outcomes include changes in the estimated glomerular filtration rate (eGFR) and renal artery stenosis incidence (>70% confirmed by angiography).

Results: As of March 2023, 1,539 patients received RF RDN using the Spyral catheter. Patients at baseline were 58±12 years old, 38.2% female, 30.1% had type 2 diabetes, eGFR was 64±24 ml/min/1.73m². 21.6% had CKD stage 3 or more, ODBP 164±22 mmHg and ASBP was 152±17 mmHg. 12 months after RDN, OSBP changed by -15.9 ± 23.2 (p=0.001) and ASBP changed by -10.0 ± 15.7 (p=0.001). Significant diastolic BP reductions were also observed, eGFR changed minimally by <2.0 ml/min/1.73m² (p=0.001). There was no incidence of renal artery stenosis (>70%).

Conclusions: In this large, pooled population of patients receiving RF RDN using the Spyral catheter, there were significant and consistent BP reductions through 12 months. There was no incidence of renal artery stenosis (>70%).

SA-PO502
Mineralocorticoid Receptor Antagonist (MRA) Use Among CKD Patients Before and After the Transition to Dialysis: A Real-World Observation from an Integrated Health System
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Background: MRAs may improve outcomes in the end-stage kidney disease (ESKD) population, but their use has been limited due to potential side effects and concerns. Among a large, diverse real-world population of incident ESKD patients, we evaluated MRA use prior to and post transition to dialysis and its associations with short-term and all-cause hospitalizations and mortality.

Methods: A retrospective cohort study within Kaiser Permanente Southern California was performed among CKD patients (eGFR<60) who transitioned to dialysis between 1/1/2007 and 12/31/2017. MRA (spironolactone and eplerenone) use was defined as two or more pharmacy dispensations. MRA use was evaluated as ever, within 3, 2, and 1 year before dialysis, at dialysis initiation, and 1 year after dialysis. Multivariable logistic regression was performed to assess the patients’ characteristics related to the use of MRA. Among 128,612 CKD patients who transitioned to dialysis, 18.3% used an MRA at any time before dialysis and decreased prior to the initiation of dialysis (Figure 1). Among 5,655 ESKD patients who survived, MRA use was 1.9% at 1 year after dialysis. Dialysis patients on MRA were more likely to be non-Hispanic White (OR: 1.87; 95% CI: 1.12-3.12), African American (OR: 1.82; 95% CI: 1.07-3.09), on peritoneal dialysis (OR: 1.67; 95% CI: 1.10-2.55), and have uncontrolled hypertension with higher hypertensive medication use. The 1 year RR for hospitalization (1.00; 95% CI: 0.52-1.88) was not significant among MRA vs. non-MRA users.

Conclusions: MRA use was low (1.9%) after transitioning to dialysis. Uncontrolled hypertension but not heart failure was associated with MRA use. Given potential benefits, MRA use in dialysis may represent an area of focus in managing the dialysis population.

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

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Methods: The study was approved by the Nazareth Hospital EMMS Human Research Review Committee and carried at Nazareth Hospital. All patients provided informed consent. Thirteen chronic diastolic patients with HRHF (FE≥40%) were recruited. All patients received conventional diuretic regimens (3 sessions a week for HD, daily diuresis for PD) and all received conventional treatment for CHF and other background illnesses. Patients were treated with Sacubitril/Valsartan at incremental doses 2X50 up to 2X200 mg/day and blood samples were collected and ECHO was performed at baseline and after 3 and 6 months after treatment. Also, quality of life was assessed by Cardiomyopathy Questionnaire (Kansas City KCCQ-12) before and after life after Sacubitril/Valsalan administration.

Results: Administration of Sac/Val to diastolic patients with HF/EF for 6 months gradually improved EF independently of morphological changes in cardiac geometry, as was assessed by echocardiography, and hemodynamic alterations. Specifically, EF was 32±1±115% at baseline and increased to 41±5±178% at 6 months and 48.6±4±72 (P<0.005) following 3 and 6 months of treatment with Sacubitril/Valsalan, respectively. This improvement was associated with significantly reduced pulmonary artery systolic pressure (PASP). Interestingly, the quality of life significantly improved after Sacubitril/ Valsartan treatment. No major adverse effects were reported in the present study, supporting the safety of Sacubitril/Valsalan at least in these patients and for the applied follow up period.

Conclusions: Collectively, these findings support the use of Sac/Val as a cardio protective agent in diastolic patients with HF/EF.

Funding: Private Foundation Support

SA-PO507
Heart Failure (HF) in the SGLT2 Inhibitor (SGLT2i) and GLP1 Receptor Agonist (GLP1-RA) Era: Does Hypertension (HTN) Matter? 
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Background: Whether uncontrolled HTN modifies the potential protective effects of SGLT2-I and GLP1-RA on HF is unknown.

Methods: We conducted an active comparator, new user design study in a national cohort of veterans (N = 129,186) with type 2 diabetes (T2D) on metformin without HF at baseline and initiated on an SGLT2i, GLP1-RA or insulin glargine (IG) for the first time between 1/1/18 and 12/31/21 and followed until 3/31/23. In Cox models, we examined whether the associations of SBP categories with HF risk modified by the drug class.

Results: 13.1% were initiated on GLP1RA, 38.9% on IG and 47.9% on SGLT2i. There were 8,850 HF events over 355,990 person-years. Within each of the drug classes, those with SBP 110 to 130 mmHg had the lowest and > 150 mmHg the highest incidence of HF (Fig). In a multivariable Cox model adjusted for SBP levels, demographics, comorbidity, CKD stages and other variables, compared to GLP1RA, IG had higher risk of HF but SGLT2i had similar risk (Table). In the same model, there was a graded association of SBP levels with the risk of HF (Table). The product interaction term of drug class and SBP categories was not significant (p = 0.65).

Conclusions: HTN remains a significant risk factor for HF in veterans with T2D initiated on SGLT2i or GLP1RA.

HF risk by Drug Class and SBP groups

<table>
<thead>
<tr>
<th>SBP Group</th>
<th>Reference Hazard Ratio</th>
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<tbody>
<tr>
<td>&lt;110</td>
<td>1.0 (1.0 - 1.2)</td>
</tr>
<tr>
<td>110 to 130</td>
<td>1.20 (1.03 - 1.38)</td>
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<tr>
<td>130 to 140</td>
<td>1.03 (0.87 - 1.20)</td>
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<tr>
<td>&gt;140</td>
<td>1.21 (1.13 - 1.32)</td>
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</tbody>
</table>

Product interaction term = 0.65

SA-PO506
Sacubitril/Valsartan Improves Cardiac Function in Dialysis Patients
Zaher Arnaly, Nazareth Hospital EMMS, Nazareth, Israel.

Background: Heart failure is a common disease characterized by activation of adverse neurohormonal systems and high mortality and mortality rate. Noteworthy, cardiovascular diseases are well known complication of CKD, especially in ESRD, where dialysis patients are 7- 8 times more likely to encounter cardiac arrest than the general population. Sacubitril/Valsalan (Sac/Val) is a dual inhibitor/blocker of nephrilysin and angiotensin II receptor, which exert cardioprotective effects among patients with reduced and preserved ejection fraction (HFrEF & HfPEF). Unfortunately, the drug is not approved for subjects with advanced CKD and dialysis patients due to safety concern. The current study examined cardiac and renal effects of Sac/Val in dialysis patients.

Figure: Mean change from baseline (before MTX, Wk -6) in BP during biweekly pegloticase (8 mg) treatment.

SA-PO505
Blood Pressure Changes with Intensive Urate-Lowering in Uncontrolled Gout Patients with and Without CKD
Brad A. Marder,1 Richard J. Johnson,2 Hyon Choi,1 Katie L. Obermeyer,1 Brian LaMoreaux,1 Peter E. Lipsky,3 Horizon Therapeutics plc. Deerfield, IL; 1University of Colorado, Aurora, CO; 2Massachusetts General Hospital, Boston, MA; 3AMPEL Biosolutions LLC, Charlottesville, VA.

Background: Hyperuricemia is high in uncontrolled gout (UGG) patients (pts) and associated with gout and hyperuricemia. In adults, allopurinol had little effect on BP, but intensive urate-lowering with pegloticase reduced systolic (SBP) and diastolic (DBP) BP. BP changes during pegloticase use (MIRROR RCT trial) were examined.

Methods: UCG pts (SU7mg/dL, oral ULT failure/intolerance, and a1 gout symptom) were randomized 2:1 to oral MTX (15mg wk) or pegloticase to pegloticase (8mg biweekly, 52wks). After 2wk MTX tolerance period and 4wk MTX/PHO Run-in, pts began pegloticase+MTX/PHO (Day 1). Sitting BP was measured before MTX (baseline [BL, Wk -6]) and pegloticase (Wk –4, Day 1) exposure and every 2wks thereafter. Preinfusion, on-treatment BP data were included. Mean(SD) change from BL (CFB) was examined for treatment groups and BL eGFR (<60, ±0.60±1.73mL/min).

Results: 152pts (89% men, 55±13yrs, 14±11yr gout history, 76% tophi, 11% flares/yr) were randomized (100 MTX, 52 PBO). Groups were similar at BL, including SBP (MTX vs PBO: 133±16 vs 131±15mmHg), and DBP (82±9 vs 83±7mmHg). SBP initially decreased in both groups but more in MTX pts by Wk24 (CFB: -6±16 vs -1±18mmHg). CFB was sustained in MTX pts thru Wk52, but fluctuated after Wk24 in PBO pts (n=19; Figure). In MTX pts, DBP was below BL thru Wk52 (CFB: -2±8mmHg). In PBO pts, DBP first declined, but returned to BL by Wk52 (CFB: +1±12mmHg). Pts with BL eGFR<60 (13% vs 23%) and DBP ≥79 (4.0; SMD=0.2). Mean baseline serum creatinine was 1.3±0.9 for PRNBP vs 1.2±0.8 for those without PRNBP (SMD<0.09).

Conclusions: The highly sensitive and specific algorithm to identify PRNBP use in VA hospitals found that inpatient PRNBP use was very common and occurred among those with higher admission BP. This cohort is the largest to date to study PRNBP use and will be the basis of future study to examine the clinical outcomes of PRNBP use in VA hospitals.

Funding: Other NIH Support - T35, Veterans Affairs Support
Hypertension and CVD: Clinical - II

Effect of Baroreflex Activation Therapy on Blood Pressure: A Randomized Sham Clinical Pilot Trial on Behalf of the BAT Team

Daniel Gordin,1,2 Johan R. Simonsen,1 Pirkka Vikatma,1 Ilkka T. Tikkanen,1,2 On Behalf of the BAT Team. HUS Helsingin yliopistollisen sairaala, Helsinki, Finland;1 Minerva Foundation Institute for Medical Research, Helsinki, Finland.

Background: Baroreflex activation therapy (BAT) is a promising treatment option for individuals with resistant hypertension. No randomized sham controlled trials have been done thus far.

Methods: This investigator-initiated randomized, double-blinded sham-controlled pilot trial included five Finnish patients with resistant hypertension. Participants were found eligible if they were 18-70 years old with a daytime systolic ambulatory blood pressure (ABP) of ≥145 mmHg, and/or a diastolic ABP ≥95 mmHg. Patients were on ≥2 antihypertensive drugs including a diuretic. A witnessed drug intake prior to ambulatory blood pressure measurement (ABPM) was implemented. The Barostim Neo System was implanted for modulation of the autonomic nervous system by direct electrical stimulation of the carotid baroreceptors. One month after implantation, all participants were randomized to either 8 months BAT-system on or BAT-system off followed by continuous BAT for all participants (Figure). ABPM was performed per protocol. The primary outcome was defined as a change in systolic ABP after 8 months of BAT, compared to pharmacotherapy.

Results: BAT decreased mean daytime systolic blood pressure by 11.8 mmHg in three participants randomized to BAT, while in the two remaining participants randomized to continuous pharmacotherapy mean systolic daytime blood pressure increased by 8.7 mmHg. When pooling daytime systolic 24-hour ABP, BAT was associated with a 9.2 mmHg lower mean blood pressure (143.5 mmHg [95% CI:142.2-144.9] vs 152.7 mmHg [151.1-154.2], <0.0001). In linear mixed models with the BAT-system's status as a fixed effect, daytime SBP at baseline and after 8 months of follow-up were compared between individuals on BAT and continuous pharmacotherapy. BAT was associated with a reduction in mean daytime SBP of -11.7 mmHg (P=0.0001).

Conclusions: BAT may lower systolic blood pressure in individuals with resistant hypertension. Large-scale studies are needed to support this assumption.

Funding: Private Foundation Support, Government Support - Non-U.S.
SA-PO511
Apelin Offers Cardiovascular and Renal Benefits in Health and CKD
Fiona A. Chapman, David E. Newby, Neeraj Dhaun. The University of Edinburgh Centre for Cardiovascular Science, Edinburgh, United Kingdom.

Background: Chronic kidney disease (CKD) affects 1 in 10 people and cardiovascular disease is its commonest endpoint. Despite standard-of-care, outcomes remain poor and new therapies are needed. Apelin, an endothelium-dependent vasodilator and inotrope, is a potential novel treatment. We examined the cardiovascular and renal actions of apelin in health and CKD.

Methods: Patients with stable, non-diabetic CKD and age- and sex-matched healthy volunteers were recruited to a randomized, double-blind, placebo-controlled study. Subjects received pyroglutamated apelin-13 (Pyr[13]apelin-13 (1 nmol/min and 30 nmol/min) or placebo on two study visits. Blood pressure, impedance cardiography and pulse wave velocity were measured. Iohexol and para-aminohippurate clearances determined glomerular filtration rate (GFR) and effective renal blood flow (ERBF), respectively. Tubular function was assessed via urinary electrolyte and free water excretion.

Results: Twelve patients with CKD and 12 healthy volunteers were recruited. Baseline characteristics are shown in Table 1. Compared to placebo, in health and CKD 30 nmol/min [Pyr[13]apelin-13 reduced mean arterial pressure by ~3% and systemic vascular resistance index by ~10-15%, and increased cardiac index by ~10-15% (p<0.05 for all comparisons). In health and CKD, 1 nmol/min and 30 nmol/min [Pyr[13]apelin-13 had similar effects on renal endpoints. ERBF increased by ~15% (p<0.01 compared to placebo in both groups). In CKD only, GFR fell by ~4 mL/min, filtration fraction by ~3% and proteinuria by ~25% (p<0.01 compared to placebo for all). [Pyr[13]apelin-13 promoted natriuresis and free water clearance in health and CKD. Overall, the effects of apelin were prolonged in CKD.

Conclusions: Apelin has cardiovascular and renal benefits in CKD. If maintained long-term these would improve cardiovascular and renal outcomes. Clinical trials of long-acting oral apelin analogues are justified in CKD and other conditions with impaired salt and water balance.

Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Healthy volunteers (n=12)</th>
<th>Chronic kidney disease (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49.4±9</td>
<td>48.4±11</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>8 (67)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>80±9</td>
<td>93±15</td>
</tr>
<tr>
<td>Systolic vascular resistance index, dyne<em>s</em>cm<em>2/m</em>2</td>
<td>254±92</td>
<td>301±192</td>
</tr>
<tr>
<td>Pulse wave velocity, m/s</td>
<td>5.0±0.2</td>
<td>6.6±0.3</td>
</tr>
<tr>
<td>Glomerular filtration rate, mL/min</td>
<td>96±8</td>
<td>41±5</td>
</tr>
<tr>
<td>Protein excretion rate, mg/g/m</td>
<td>0 (0)</td>
<td>384±12 (0-1271)</td>
</tr>
</tbody>
</table>

SA-PO512
Apelin Increases Forearm Blood Flow in CKD
Fiona A. Chapman, David E. Newby, Neeraj Dhaun. The University of Edinburgh Centre for Cardiovascular Science, Edinburgh, United Kingdom.

Background: Chronic kidney disease (CKD) is a global health emergency. It is independently associated with cardiovascular disease. Despite current treatment patients still suffer from cardiovascular disease and kidney failure and/or due to cardiovascular causes. There is an unmet need for newer therapies and apelin, an endothelium-dependent vasodilator and potent inotrope, is an attractive therapeutic target. Clinical studies find apelin improves endothelial function in health and heart failure. We examined the local vascular actions of apelin in CKD.

Methods: Patients with stable, non-diabetic CKD and age- and sex-matched healthy volunteers were recruited to a randomised, placebo-controlled study. Baseline blood pressure and pulse wave velocity were measured. Gold-standard venous occlusion plethysmography was used to examine endothelial function in response to incremental intra-arterial doses of acetylcholine (7.5, 15 and 30g/min, endothelium-dependent vasodilation), sodium nitroprusside (1, 2 and 4g/min, endothelium-independent vasodilation), and pyrogulamated apelin-13 (Pyr[13]apelin-13; 0.3, 1, 3, 10 and 100nmol/min). Circulating tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) assessed endogenous fibrinolysis.

Results: Fifteen patients with CKD (mean age 55±4 years; 53% male) and 15 healthy volunteers (mean age 51±3 years; 67% male) were recruited. In comparison to health, patients with CKD had a higher blood pressure (mean arterial pressure: 120mmHg versus 93mmHg, p<0.05) and increased pulse wave velocity (7.5±2.2 m/s versus 6.0±0.9 m/s, p<0.01). Similar dose-dependent vasodilation to acetylcholine and sodium nitroprusside was seen in both groups. [Pyr[13]apelin-13 dose-dependently increased forearm blood flow to a maximum of ~30% in both health and CKD (p<0.01 compared to baseline for both). Net tPA antigen release increased 20-70 fold in both groups, with a trend to a greater release in CKD.

Conclusions: In optimally managed patients with CKD, apelin promotes vasodilation and may regulate fibrinolysis. If maintained longer-term with systemic treatment, apelin would reduce cardiovascular risk. Systemic studies are needed to investigate the haemodynamic and renal effects of apelin in CKD.

SA-PO513
Relationship Between Iron Deficiency and QTc Prolongation in Japanese Maintenance Hemodialysis Patients
Kichiro Fujisaki,1 Sho Sasaki,2 Toshiaki Nakano,2 Nobuhiko Joki,1 Hizuka Hospital, Iizuka, Japan; 1Kyushu University, Fukuoka, Japan; 2Toho University Ohashi Medical Center, Tokyo, Japan; 3Kyoto University Hospital, Kyoto, Japan.

Background: QT interval prolongation is a risk factor for fatal arrhythmias and other cardiovascular complications. Causes of QT interval prolongation in hemodialysis (HD) patients is not fully understood. It has also recently been reported that lower transferrin saturation (Tsat), one of the marker for iron deficiency, is associated with cardiovascular complications in patients with CKD. We hypothesize that iron deficiency may be associated with QT interval prolongation in HD patients.

Methods: We identified 175,448 eligible patients from a nation-wide database receiving thrice-weekly HD in Japan. The cross-sectional study was conducted on adult maintenance HD patients enrolled in the 2019 Japanese Society for Dialysis Medicine Annual Survey. Logistic regression analysis was performed with serum ferritin (S-ferr) and TSat as explanatory variable and QTc prolongation (QTc >500 msec) as outcome, adjusted for possible confounding factors.

Results: A total of 175,448 patients were included in the analysis of this study. The mean QTc (standard deviation) was 451.7 (36.1) msec. 13,343 (7.6%) of subjects have suffered from QTc >500 msec. On multivariate analysis, the adjusted odds ratios [95% confidence interval] for QTc prolongation in the groups with Tsat >20% and S-Ferr ≤100 ng/mL, Tsat >20% and S-Ferr >100 ng/mL with the group with S-Ferr >100 ng/mL and Tsat >20% as the control group, were 1.12 [1.05, 1.20], 1.19 [1.14, 1.25] and 0.99 [0.95, 1.04], respectively. A J-curve relationship was observed between Tsat and QTc prolongation (Figure).

Conclusions: This study suggests that decreased TSat (≥20%) may be associated with QTc prolongation in maintenance HD patients. Iron deficiency may play some role for prolonging ventricular repolarization time independent of other risks in HD patients.

SA-PO514
Characteristics and Prediction of Tumor Recurrence in Patients with Pheochromocytoma and Paraganglioma: A Single-Center Experience in Taiwan
Yi-Ran Tu,1 Kun-Hua Tu,2,3 Chang Guang Memorial Hospital Linkou, Taoyuan, Taiwan; 2Chang Guang University, Taoyuan, Taiwan.

Background: Both pheochromocytoma and paraganglioma are rare catecholamine-producing neuroendocrine tumors. Surgical resection is the only curative treatment for these tumors. Patients receiving tumor resections, however, still probably encountered tumor recurrence. To our best knowledge, it’s still with unclear clinical presentation of these catecholamine-producing tumor and lack of useful parameters to predict recurrence after tumor resection. The aim of this study is to find predictors of tumor recurrence in patients with these two rare neuroendocrine tumors.

Methods: This study was conducted at a tertiary medical center in Taiwan retrospectively. Data collection by chart review was undertaken in a 2000-bed private university hospital in Taiwan between January 2000 and December 2021. In total, 310 patients with pathologic diagnosis of pheochromocytoma or paraganglioma were enrolled.

Results: The study subjects were grouped as PCC and PGL and then further classified to sympathetic PPGLs and parasympathetic PPGLs according to the tumor origin. This study include 156 patients of PCC and 154 patients of PGL which larger than 3 cm. Clinical characteristics of PCC and PGL were summarized in Table 1. The characteristics of PCC and PGL were listed in Table 2. The proportion of sympathetic PPGLs and parasympathetic PPGLs were 76% and 24% in PCC, and 94% and 6% in PGL, respectively.

Conclusions: The factors of tumor recurrence are summarized in Table 3. Tumor recurrence was significantly moderate higher in patients with sympathetic tumors (PCC and PGL) than parasympathetic tumors (PCC and PGL). The other factors, such as age, gender, and tumor size, were not significantly different between PCC and PGL.

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

866
recurrent, and 289 patients categorized as non-recurrent group. Comparing with non-recurrent group, recurrent group are younger (p=0.03407), and have more genetic ancestry (p=0.02062).

Conclusions: Our study demonstrates the characteristics of PCC and PGL, and several clinical parameters such as age and genetic ancestry are associated with tumor recurrence after tumor resection in patients with PCC or PGL. It will help clinicians to closely monitor disease status after tumor resection.

SA-PO515
Differences in Cardiovascular Phenotype and Pharmacotherapy Between Patients with ESKD Based on Transplant Eligibility
Sherna Bae,1 Mark Schnitzer,2 Krista L. Lentine,3 Mari McAdams-Decarlo,4 New York University Grossman School of Medicine, New York, NY; 3Saint Louis University, Saint Louis, MO; 2University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; 1Department of Population Health Sciences, Leicester, United Kingdom

Background: Cardiovascular disease (CVD) is a major cause of death in end-stage kidney disease (ESKD) patients, linked to traditional and non-traditional risk factors. The ISCHAEMIA-CKD trial indicated no benefit from early invasive treatment for coronary artery disease (CAD) in advanced kidney disease. Hence, optimizing conservative medical therapy is crucial. We conducted post-hoc analyses using CYCLE-HD trial data to compare structural and functional heart disease and pharmacotherapy in patients active and not active on the transplant waiting list.

Methods: 130 hemodialysis patients underwent cardiac MRI for comprehensive cardiovascular phenotyping (2015-18). Appropriate comparison tests were used depending on data distribution. If initial testing revealed a significant difference, ANCOVAs were used to adjust for age.

Results: 71/110 patients were active and 59/130 were not active on the transplant list. The ‘active’ group were younger (53 (40, 61) vs 66 (57, 75) years), 68% vs 79% were male, 69% vs 64% had hypertension, 20% vs 10% had dyslipidemia, 30% vs 48% had diabetes. There were no significant differences in medication use: 15% vs 8% on an ACE inhibitor or ARB, 48% vs 41% on a beta blocker, 50% vs 37% on a calcium channel blocker, 28% vs 32% on aspirin, 45% vs 61% on a statin. After adjusting for age, left ventricular (LV) ejection fraction, global longitudinal, and circumferential strain were significantly lower in the ‘not active’ group and LV mass index was higher (Table 1).

Conclusions: In this analysis, pharmacotherapy to mitigate CVD was poor irrespective of transplant listing status. CV phenotype was different between those listed and those not listed. Greater attention must be paid to optimizing CV pharmacotherapy in both groups of patients to improve CV outcomes.

Table 1: Cardiac MRI characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Active, n=71</th>
<th>Not active, n=130</th>
<th>p-value</th>
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<tbody>
<tr>
<td>LV mass index (g/m²)</td>
<td>58 (48, 77)</td>
<td>50 (40, 65)</td>
<td>F=1.8</td>
</tr>
<tr>
<td>LV mass index (g/m²)</td>
<td>58 (48, 77)</td>
<td>50 (40, 65)</td>
<td>F=1.8</td>
</tr>
<tr>
<td>Global left ventricular (LVEF)</td>
<td>66 (59, 69)</td>
<td>61 (53, 67)</td>
<td>F=3.8</td>
</tr>
<tr>
<td>Global left ventricular (LVEF)</td>
<td>66 (59, 69)</td>
<td>61 (53, 67)</td>
<td>F=3.8</td>
</tr>
<tr>
<td>Global longitudinal strain</td>
<td>26 (12, 32)</td>
<td>22 (9, 35)</td>
<td>F=3.8</td>
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<tr>
<td>Global longitudinal strain</td>
<td>26 (12, 32)</td>
<td>22 (9, 35)</td>
<td>F=3.8</td>
</tr>
<tr>
<td>Global circumferential strain</td>
<td>23 (12, 34)</td>
<td>20 (8, 30)</td>
<td>F=3.8</td>
</tr>
<tr>
<td>Global circumferential strain</td>
<td>23 (12, 34)</td>
<td>20 (8, 30)</td>
<td>F=3.8</td>
</tr>
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</table>

SA-PO516
Comparative Safety and Effectiveness of Statins in Kidney Transplant Recipients: Immediate-Release vs. Extended-Release Tacrolimus
Cheol Ho Park,1 Hyung Woo Kim,1 Jung Tak Park,1 Tae ik Chang,2 Tae-Hyun Kang,1 Seung Hyeok Han,1 Monica G. Stain,1 Matthew L. Lentine,1 for PREDICT (Pre-emptive Renal Donor Evaluation to Investigate Clinical Trials)

Background: Tacrolimus (Tac) is a first-line anti-rejection medication with immediate-release (Tac IR) and extended-release (Tac ER) versions. Hypertension is a common adverse effect of Tac, but the longitudinal blood pressure control between kidney transplant recipients receiving Tac ER and Tac IR has never been studied.

Methods: A retrospective, single-center cohort study used data from the University of Pittsburgh Health System. Adult patients aged 18+ who started tacrolimus immediately after kidney transplantation between January 1st, 2016, and December 31st, 2019, were included. The primary outcome was time-varying systolic and diastolic blood pressure (SBP and DBP) documented through December 31st, 2021. Baseline and time-varying variables were collected, and the secondary outcome was the incidence of hypertensive crisis. Sensitivity analysis was performed using time-constant exposure based on the type of Tac patients received at four months post-transplant. A logistic regression model, a 3-step marginal structural model, and a 2-tailed Fisher’s exact test were used for analysis.

Results: 654 patients with 16,382 BP entries were analyzed. Black patients were 2.32 times more likely to receive Tac ER (p=0.001). Patients taking Tac ER had a 1.87 mmHg lower SBP than those taking Tac IR (p=0.009), but no difference in SBP in the sensitivity analysis with a time-constant exposure at a 4-month cutoff. No significant differences were observed in DBP in both the main and sensitivity analyses. A total of 9 patients experienced a hypertension crisis; 8 were on Tac IR, and 1 was on Tac ER. No statistical difference in the occurrence of hypertension crises between the two groups was found.

Conclusions: Post-transplant patients taking Tac ER show a slightly lower SBP than those on Tac IR, without a significant difference in hypertensive crisis incidence.

Funding: Other NIH Support - pharmacoepidemiology T32
Outcomes of CKD Stage 3-5 patients that underwent left heart catheterization

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Profile</th>
<th>Odds Ratio</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
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<tbody>
<tr>
<td>Mortality</td>
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<td>0.390</td>
<td>0.252</td>
<td>0.612</td>
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<tr>
<td>Acute Kidney Injury</td>
<td>&lt;0.001</td>
<td>0.651</td>
<td>0.426</td>
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<td>Acute Heart Failure</td>
<td>0.006</td>
<td>0.667</td>
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<td>Cardiac Arrest</td>
<td>&lt;0.001</td>
<td>0.732</td>
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<td>1.276</td>
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<tr>
<td>Length of Stay (Days)</td>
<td>&lt;0.001</td>
<td>1.080</td>
<td>1.218</td>
<td>0.942</td>
</tr>
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</table>

SA-PO519

Additive Risk for Pericardial Effusion of Exposure to Either Hydralazine or Minoxidil and Advanced CKD


Background: Vasodilatory antihypertensives hydralazine and minoxidil have been linked to the development of pericardial effusion. However, most of the available evidence comes from small cohort studies or case series. Furthermore, because advanced chronic kidney disease (CKD) is associated with uremic pericardial effusion, it is not clear whether hydralazine or minoxidil independently confer a risk for pericardial effusion in advanced CKD. We aimed to examine this question in a large patient database.

We retrospectively reviewed records of adult patients who underwent transthoracic echocardiography (TTE) between 2017 and 2022 to identify those diagnosed with pericardial effusion. Exposure to either hydralazine or minoxidil within 3 months prior to the TTE was probed, as well as demographic and clinical characteristics, including CKD status. Advanced CKD included stage 4 or 5 CKD or end-stage kidney disease. Cases of mesothelioma or tuberculosis were excluded.

Results: A total of 153,678 unique patients with TTE entered the analysis. Pericardial effusion was found in 1,442 (0.94%). By multivariate logistic regression, exposure to hydralazine [OR 1.58 (CI 1.4–1.8), p<0.0001], exposure to minoxidil [OR 4.48 (CI 2.8–7.2), p<0.0001], advanced CKD [OR 2.30 (CI 1.7–3.1), p<0.0001], coronary artery disease [OR 1.21 (CI 1.1–1.4), p=0.011], and female sex [OR 1.33 (CI 1.2–1.5), p=0.0001], were independently associated with increased risk of pericardial effusion, whereas age, race, diabetes mellitus and hypertension were not. The rate of pericardial effusion was greatest in those exposed to vasodilators: 1.4% of hydralazine users (n=24,650) compared to 0.8% of nonusers (n=121,118) (p<0.0001), and 5.4% of minoxidil users (n=354) compared to 0.9% of nonusers (n=153,414) (p=0.0001). Among those with advanced CKD (n=2,337), the incidence of pericardial effusion was overall higher and significantly associated with exposure to either hydralazine (3.6% vs 1.7% for nonusers, p=0.02) or minoxidil (6.5% vs 2.1% for nonusers, p=0.043).

Conclusions: Hydralazine and minoxidil confer an increased risk for pericardial effusion that augments the increased risk associated with advanced CKD. Because these agents are frequently prescribed in advanced CKD, close monitoring is advisable.

SA-PO520

Renalism: An Obstacle to Left Heart Catheterization in CKD Patients

Chapman Wei, Ahmad Mustafa, Fasih Sami Siddiqi, Radu C. Grovu, Shahriar Khan, Tuuj A. Rizvi, Jennifer Wahbah Makhoul, Joanne Ling, Nenindu Asogwa, Nawal Mustafa, Mitchell Weinberg, Elle El-Charabaty, Suzanne E. El Sayegh. Staten Island University Hospital, Staten Island, NY.

Background: “Renalism” is the reluctance of clinicians to conduct contrast-based studies such as left heart catheterization (LHC) on individuals with chronic kidney disease (CKD). Non-ST-elevation myocardial infarction (NSTEMI) often requires LHC and delay can lead to increased mortality and adverse cardiovascular outcomes.

Methods: The National Inpatient Sample Database 2016-2018 was used to sample patients presenting with NSTEMI. Baseline demographics and comorbidities were collected using ICD-10-codes. Patients less than 18 years old, missing data, and with end-stage renal disease were excluded. Patients were stratified into CKD 1-2 vs CKD 3-5 and propensity matching was performed to two cohorts. Mortality and cardiovascular outcomes were compared in CKD 3-5 patients who underwent LHC and those who did not.

Results: Of 427,593 NSTEMI patients, 79,284 had CKD 3-5. CKD 3-5 patients were less likely to have LHC and had increased mortality. After matching, CKD 3-5 was independently associated with less LHC. During regression analysis, CKD 3-5 patients that underwent LHC were 2.9 times less likely to have in-hospital mortality compared to patients that did not undergo LHC. Additionally, LHC in CKD 3-5 patients was also associated with decreased cardiovascular outcomes and acute kidney injury (p<0.001).

Conclusions: Alteration in practice-based guidelines due to risk of contrast-induced nephropathy leads to less LHC in CKD patients and increased mortality and adverse cardiovascular outcomes. Further studies are needed to evaluate the risks and benefits of contrast-based studies in this patient cohort.
showed increased risk of mortality were seen for valve replacement (vs CABG), urgent surgery, and patients admitted with greater Charlson score. Mortality at 24 months was 32 [29-35]% for the dialysis group and 16 [12-20]% for the transplant group.

**Conclusions:** Among KF patients requiring CS, early mortality rates are substantially increased, especially when other comorbidities are present or surgery is urgent. While the risks of not operating are not known for these cohorts, this data will inform and support careful consideration of the risks of cardiac surgery in this group.

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

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**SA-PO523**

**Association of CKD and Cardiovascular Disease Risk with All-Cause Mortality: A Mediation Analysis in Chinese Adults**

**Yang Li, Zhongshan Hospital Fudan University, Shanghai, China.**

**Background:** To evaluate the complex relationship of chronic kidney disease (CKD) and cardiovascular disease (CVD) risk with mortality in different age groups and the mediation effect of CVD risk among Chinese adults.

**Methods:** A total of 7533 participants from the China Health and Nutrition Survey (CHNS) cohort were included in this study. CKD was defined as eGFR <60 mL/min/1.73m². Framingham risk score (FRS) was used to assess CVD risk. The interaction, joint association of CVD risk and CKD on mortality, and subsequent mediation effect were evaluated using multivariable Cox regression.

**Results:** CHNS cohort recorded 266 deaths over a mean follow-up time of 5.04 years. The all-cause mortality rates among adults with CKD and high CVD risk were significantly higher than healthy controls (22.48 and 21.30 per 1000 person-years). The adjusted hazard ratios (aHR) were 1.70 (95% CI 1.27-2.28) and 1.62 (95%CI 1.26-2.09), respectively. There was a negative interaction between CKD and CVD risk on mortality. The association between CKD and mortality was stronger in low-medium CVD risk group (aHR=1.87, 95% CI 1.20-2.91). Besides, mortality hazard was highest in CKD patients with high CVD risk (aHR=3.14, 95% CI 1.92-5.14). Mediation analysis showed that CVD risk mediated 33.4% of the effect of CKD on all-cause mortality (p<0.001). After adjusting for the moderator of age, the mediation proportion was 7.2%-10.3%.

**Conclusions:** Comprehensive strategies including lifestyle modifications, diet restrictions, and cardio-nephrology multidisciplinary treatment for mitigating CVD risk in CKD patients should focus on middle-aged people and early disease detection.

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

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**SA-PO524**

**Constipation and Risk of Death and Cardiovascular Events in Hemodialysis Patients**

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**Background:** Constipation is common in dialysis patients and primary care. Recent studies have disclosed its independent associations with the increased risk of mortality or cardiovascular disease in the general population. In this study, we aimed to investigate the association of constipation with clinical outcomes using a large cohort of hemodialysis (HD) patients in Korea.

**Methods:** This retrospective, population-based cohort study used HD quality assessment data from the Korean Health Insurance Review and Assessment (HIRA) during the period between January 2015 and June 2021. Public medical insurance registration is mandatory in Korea, and HIRA is an independent agency that reviews and assesses healthcare benefit costs. Constipation was defined as the number of total prescribed laxatives between January 2015 and June 2021 during the baseline one year period. The primary endpoint was evaluated as the development of all-cause mortality and cardiovascular events including myocardial infarction (MI) and stroke. Each event was identified as the relevant International Classification of Disease (ICD)-10 diagnosis as the major diagnostic code and procedure codes of related insurance claims.

**Results:** A total of 35,230 patients over the age of 19 years old were included in the study, and the mean follow-up period was 54.2 months. Overall, 25.9% of HD patients were identified as having constipation, which seemed to be higher than the reported 15-20% in the general population. The most frequently prescribed laxatives were lactulose/lactitol.

In Cox proportional hazard model, constipation was associated with increased all-cause mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.09–1.23) and ischemic stroke (HR, 1.16; 95% CI, 1.0–1.32) after multivariable adjustment for demographics, prevalent comorbidities, and medications. Constipation was not significantly associated with MI and hemorrhagic stroke after multivariable adjustments although the crude cumulative incidence of each was higher in patients with constipation.

**Conclusions:** Constipation was associated with higher risk of all-cause mortality and incident ischemic stroke independently of known cardiovascular risk factors in prevalent HD patients. Further studies are needed to determine whether constipation serve as one of the indicators of poor health or is a possible causal factor to cardiovascular disease.

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**SA-PO525**

**The Role of Blood Pressure Load in Ambulatory Blood Pressure Monitoring in Adults: A Review of Current Evidence**

**Ophir Eyal,1,2 Iddo Z. Ben-Dov.1 Hadassah University Medical Center, Jerusalem, Israel.**

**Background:** In the field of ambulatory blood pressure monitoring (ABPM), the concept of the blood pressure load (BPL), defined as the percentage of readings above a certain threshold, has been in general use since the 1990s. However, the benefits of using this index in adults have not been clearly demonstrated, and accordingly it has not been integrated into the major blood pressure diagnosis and treatment guidelines. In this manuscript, we present the first comprehensive review of the current evidence regarding the possible associations of BPL with target organ damage and clinical outcomes, the major determinants for its role and utility in blood pressure measurement. We put a particular emphasis on studies exploring whether BPL has added benefit to the mean blood pressure indices.

**Methods:** Our review is based on a search of PubMed for all articles containing the combination of the MeSH term “Blood Pressure Monitoring, Ambulatory” and “blood pressure load” or “BP load”, last performed on April 13th, 2023. We also scanned the references from articles found on the PubMed search. We included all the articles for which we could find full text in English examining the associations of BPL as defined above with clinical outcomes or organ damage.

**Results:** While a couple dozen studies aimed to assess the association of the blood pressure load with target organ damage, the cumulative sample size is small. Almost all of the studies are retrospective, and none are interventional. Though the associations of the BPL with various measures of target organ damage are evident, the available literature fails to demonstrate a clear and consistent added value for the BPL over the mean blood pressure indices.

**Conclusions:** The BPL has been a part of the ABPM report for more than 3 decades worldwide. However, we have found no previous paper reviewing the evidence for its use. Based on our analysis, we summarize that while the associations of BPL with target organ damage are clear, it is inconclusive whether the addition of BPL to the mean blood pressure indices has any advantage. There is a clear need for further research in this field, including large-scale prospective trials with long-term follow-up to elucidate the possible benefits of incorporating BPL into clinical practice.

**Funding:** Veterans Affairs Support
SA-PO527

Health Care Utilizations and Costs in the Year Following an Incident Major Thrombotic Cardiovascular Event (MTCVE) in Patients with and Without ESKD

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Background: Patients with end-stage kidney disease (ESKD) are at higher risk of major thrombotic cardiovascular events (MTCVEs) and use more substantial healthcare resources than compared to patients without ESKD. There is limited information on costs following MTCVEs in patients with ESKD.

Methods: Cohorts of Medicare fee-for-service beneficiaries aged ≥66 years were created using data from the US Renal Data System (USRDS) for ESKD patients receiving in-center hemodialysis (HD) and a 20% sample of Medicare claims for non-ESKD patients. We included patients experiencing a new MTCVE (myocardial infarction, ischemic stroke, venous thromboembolism, or critical limb ischemia) between 2015-2018. Adjusted all-cause healthcare resource utilization (HCUR) and costs were assessed for 1 year following the index event.

Results: Table 1 and Figure 1 detail HCUR and costs, respectively, in the year following each type of MTCVE. Patients with ESKD had much higher rates of all-cause hospitalization than non-ESKD patients, with the largest magnitude of difference in patients with VTE. Rates of ICU admissions, inpatient days, emergency and outpatient encounters were significantly higher in ESKD patients even after demographic adjustment. Adjusted costs of care were higher in ESKD patients compared with non-ESKD patients across all encounter and MTCVE types, with some variation in costs attributable to specific encounter types.

Conclusions: In the year after an incident MTCVE, patients with ESKD had significantly higher all-cause HCUR and costs of care than non-ESKD patients who experienced the same type of MTCVE. These differences persisted even after adjustment. Adjusted costs of care were higher in ESKD patients compared with non-ESKD patients following each type of MTCVE. Patients with ESKD had much higher rates of all-cause hospitalization than non-ESKD patients, with the largest magnitude of difference in patients with VTE. Rates of ICU admissions, inpatient days, emergency and outpatient encounters were significantly higher in ESKD patients even after demographic adjustment. Adjusted costs of care were higher in ESKD patients compared with non-ESKD patients across all encounter and MTCVE types, with some variation in costs attributable to specific encounter types.

Funding: Commercial Support - Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

SA-PO528

Evaluation of Plasma Sphingolipids as Mediators of the Relationship Between Kidney Diseases and Cardiovascular Events

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Background: Patients with chronic kidney disease (CKD) are at higher risk for cardiovascular events. Sphingolipids are a family of circulating lipids with regulatory and signaling roles that are strongly associated with both eGFR and cardiovascular disease. We examined whether circulating sphingolipids partially mediate the associations between eGFR and cardiovascular events.

Methods: We measured the circulating concentrations of 4 ceramides and 4 sphingomyelins with the fatty acids 16:0, 20:0, 22:0, and 24:0, in plasma from 3,463 participants in the Cardiovascular Health Study without prevalent cardiovascular disease.

We tested the adjusted mediation effects by these sphingolipids of the associations between eGFR and incident cardiovascular disease via quasi-Bayesian Monte Carlo method with 2,000 draws, using a Bonferroni-corrected p value for significance of 0.00625.

Results: The mean (±SD) eGFR was 70 (±16) mL/min/1.73 m², and the mean age was 76 (±5) years. Lower eGFR was associated with higher plasma ceramide and sphingomyelin 16:0, and lower ceramides and sphingomyelins 20:0 and 22:0. Lower eGFR was associated with risk of incident heart failure and ischemic stroke, but not myocardial infarction. Five of eight sphingolipids partially mediated the association between eGFR and heart failure. The strongest mediators were ceramide-16:0 (proportion mediated 14%, 95% CI 8-23%) and sphingomyelin-16:0 (proportion mediated 10%, 95% CI 5-17%). No sphingolipids significantly mediated the association between eGFR and ischemic stroke (Table).

Conclusions: Plasma sphingolipids partially mediated the association between lower eGFR and incident heart failure. Altered sphingolipid metabolism may contribute to heart failure in patients with CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI: R01 HL128575, and R01 HL111375, Private Foundation Support.

SA-PO529

Plasma Uromodulin and Cardiovascular Outcomes in Adults with Hypertension and CKD

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Background: Uromodulin (UMOD) is an emerging kidney tubule biomarker that may improve identification of persons at elevated cardiovascular (CV) risk beyond conventional markers. We evaluated the association of plasma UMOD with CV outcomes in CKD.

Methods: This was a secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), in which an intensive systolic blood pressure (SBP) target reduced risk of CV events and mortality. We measured plasma UMOD at baseline in participants with eGFR >60 mL/min/1.73 m² (N = 2302) and evaluated its association with a composite primary outcome of nonfatal myocardial infarction (MI), acute coronary syndrome without MI, acute decompensated heart failure (HF), stroke or CV death. Hazard ratios (HR) were estimated using Cox proportional hazards models adjusted for demographic and clinical variables, including eGFR and albuminuria.

Results: Median follow-up was 3.9 years, mean eGFR was 46 (IQR: 36–55) mL/min/1.73 m² and median plasma UMOD was 17.2 (IQR: 12.3–23.2) mg/mL. In the lowest UMOD quartile, 105 out of 575 (18.3%) experienced the primary outcome compared to 57 out of 575 (9.9%) in the highest. After multivariable adjustment, higher UMOD was not significantly associated with the primary outcome in the overall cohort. Of the component outcomes, each SD higher UMOD was associated with 30% lower risk of stroke (HR 95% CI: 0.51–0.95, p <.01) only. The association of UMOD with the primary and HF outcomes differed by eGFR (p for each interaction <.05). Each SD higher UMOD was associated with 24% lower risk of the primary outcome (HR 95% CI: 0.63–0.91) and 33% lower risk of HF (HR 95% CI: 0.51–0.89) in those with eGFR >45 mL/min/1.73 m² (p <.01 for both), but not among those with eGFR ≤45 mL/min/1.73 m².

Conclusions: Higher plasma UMOD in hypertensive persons with CKD is associated with lower risk of stroke and, among those with lower eGFR, lower risk of CV and HF events.

Funding: NIDDK Support.
SA-PO530

Association of Serum Magnesium with Atrial Fibrillation in Patients Requiring Peritoneal Dialysis

Kenji Nakata, Tatsunori Toida, Noriaki Kuriita, Nobuhiko Joki. Toho Daigaku Iryo Center Ohashi Byoin, Meguro-ku, Japan; Kyushu Hoken Fukushima Daigaku, Nobeoka, Japan; Fukushima Kenritsu Ika Daigaku Igaku Daigakuin Igaku Senko, Fukushima, Japan; 4Fukushima Kenritsu Ika Daigaku Fuzoku Byoin, Fukushima, Japan.

Background: It has been known that morbidity of atrial fibrillation (AF) in chronic kidney disease is higher than in general population. Age, obesity, diabetes mellitus (DM), and cardiovascular disease, these are thought to be one of the risk factors of AF. Hypomagnesemia is also potential risk factor of AF in hemodialysis patients, while it has not been studied in peritoneal dialysis (PD) patients. Hence, we examined association between serum magnesium (sMg) level with AF.

Methods: A nation-wide, cross-sectional study was performed by using data from Japanese Renal Data Registry, which encompasses a nationwide population dialysis centers, corrected at the end of 2019. The inclusion criteria were as follows: only PD patients, aged≥20. The exclusion criteria were as follows: missing data for Mg and history of AF. Among 33259 dialysis patients, 2366 PD patients were enrolled into this study finally. They were divided three groups according to the lower and upper level of sMg general reference value of 1.8 and 2.6, named low-, normal-, and high-sMg group respectively. Odds ratio (OR) for AF was calculated in each group compared with normal-sMg group by logistic regression analysis. AF was diagnosed by rest 12-leads electrocardiogram.

Results: Mean age was 63±13 years, 65.1% of them were male, 47.8% had DM. Mean sMg level was 2.14±0.58, and 4.3% had AF. In unadjusted model, the odds ratio OR for AF in three groups divided by sMg level was 2.23 (95% CI 1.58-3.12), while high-sMg group did not show significant increment or decrement of OR for AF. After adjusting of confounding variables of age, sex, DM, current smoker, same trend had been seen between low and normal sMg groups.

Conclusions: Hypomagnesemia was closely associated with AF in PD patients. Preventing hypomagnesemia may reduce the incidence of AF in PD patients. We may need to monitor the sMg level regularly and pay attention more to hypomagnesemia to prevent AF in PD patients.

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mg, mg/dL</td>
<td>OR 95%CI p</td>
</tr>
<tr>
<td>1.8-2.2</td>
<td>2.23 (1.44-3.46) 0.0003</td>
</tr>
<tr>
<td>2.3-2.6</td>
<td>0.85 (0.43-1.75) 0.63</td>
</tr>
</tbody>
</table>

Adjusted factor: Model 1; unadjusted. Model 2; age, sex. Model 3; age, sex, diabetes mellitus, current smoker

SA-PO531

Biomarkers of Kidney Tubule Health and Retinal Microvascular Signs: The Multi-Ethnic Study of Atherosclerosis

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Background: Both the retina and kidney can be damaged by microvascular disease. Here, we examined the association between biomarkers for kidney tubule health and retinal microvascular signs in persons who participated in The Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: Among 470 MESA participants, we measured 6 plasma biomarkers of kidney tubule health: KIM-1, MCP-1, SupAR, TNFR 1 and 2, and YKL-40 and 6 urinary biomarkers of kidney tubule health: A-1MG, EGF, IL-18, KIM-1, MCP-1, and YKL-40. Retinal microvascular measurements were assessed from fundus photography: central retinal arteriolar and venular equivalents (CRAE and CRVE, respectively). We used multivariable linear regression models to test the associations between kidney tubule health markers and CRAE and CRVE. Final model was adjusted for age, race, gender, BMI, hypertension, LDL, HDL, smoking, urine albumin, urine creatinine and eGFR.

Results: Mean age was 60±10 years and mean eGFR was 92.1±31 ml/min/1.73m². The prevalence of HTN and current smoking was 36% and 14%, respectively. The mean CRAE and CRVE was 144±14 μm and 214±21 μm, respectively. In adjusted continuous models, each 1 SD higher plasma KIM-1, and urine KIM-1 concentrations were individually associated with narrower CRAE. Each 1 SD higher plasma SupAR concentrations were individually associated with wider CRAE and CRVE (Figure). There was no significant association between remaining biomarkers and CRAE and CRVE.

Conclusions: In this study of community-living individuals without CKD, diabetes, or CVD, selected kidney tubule health markers are associated with retinal microvascular changes. These findings suggest that microvascular disease may impact the kidney tubules, above and beyond the glomerulus.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Plasma</th>
<th>Unadjusted</th>
<th>Partially Adjusted</th>
<th>Fully Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>KIM-1 (pg/ml)</td>
<td>-5.14</td>
<td>-11.60</td>
<td>-9.50</td>
<td>-10.00</td>
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<tr>
<td>MCP-1 (pg/ml)</td>
<td>-9.38</td>
<td>-7.00</td>
<td>-6.00</td>
<td>-5.00</td>
</tr>
<tr>
<td>SupAR (pg/ml)</td>
<td>-9.30</td>
<td>-9.20</td>
<td>-8.00</td>
<td>-7.00</td>
</tr>
<tr>
<td>TNFR1 (pg/ml)</td>
<td>4.06</td>
<td>5.10</td>
<td>4.00</td>
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<tr>
<td>TNFR2 (pg/ml)</td>
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<td>1.00</td>
<td>0.00</td>
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<tr>
<td>YKL40 (pg/ml)</td>
<td>1.20</td>
<td>1.10</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>A-1MG (mg/mmol)</td>
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<td>1.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>EGF (ng/ml)</td>
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<td>2.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Adjusted for age, sex, race, BMI, hypertension, LDL, HDL, smoking, urine albumin, urine creatinine and eGFR.

SA-PO532

Subclinical Primary Aldosteronism and eGFR Decline

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Background: Primary aldosteronism (PA), characterized by renin-independent aldosterone secretion, is the most common and modifiable form of secondary hypertension. Overt PA predisposes to disproportionately high rates of cardiovascular and kidney disease, independent of blood pressure (BP). Growing evidence suggests that milder forms of renin-independent aldosteronism (ie, Subclinical PA) are highly prevalent yet their clinical significance remains uncertain.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Prospective study of 536 participants aged 40-69 yr and on no BP medications from the randomly sampled, population-based CARTaGENE cohort (Canada). Using aldosterone and renin levels from enrollment, we employed multivariable linear regression models to measure the association between the aldosterone-renin ratio (ARR) and eGFR (via the 2021 CKD-EPI_{eGFR} equation) measured at enrollment and after 5.7 years’ follow-up.

Results: The mean (SD) age, eGFR, and systolic BP were 55 (7) years, 107 (13) mL/min/1.73m², and 132 (11) mmHg, respectively. Higher ARR was successively associated with steeper annual eGFR decline with ARR Tertile 3 having a 74% steeper decline than ARR Tertile 1 (1.18 vs. 0.68 mL/min/1.73m²/yr, P=0.01; Fig. 1). On multivariable linear regression, higher ARR was associated with steeper annual eGFR decline (P=0.03; Fig. 2).

Conclusions: In a randomly sampled, population-based cohort of individuals on no antihypertensive medication, Subclinical PA was associated with steeper eGFR decline, independent of BP. Subclinical PA may serve as a potentially modifiable risk factor to prevent or slow CKD.

SA-PO533

Abstract Withdrawn

SA-PO534

Galectin-3 and Mortality in Relation to Vascular Calcification in Incident Hemodialysis Patients

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Background: Vascular calcification is a recognized risk factor for mortality in hemodialysis patients. Galectin-3 (Gal-3), a key regulator of fibrosis, inflammation, and cell proliferation, has been implicated in adverse outcomes in several pathological conditions such as heart failure and chronic kidney disease. The study aims to determine whether Gal-3 levels may affect vascular calcification and how these effects may contribute to mortality risk in hemodialysis patients.

Methods: Serum Gal-3 was measured in patients from the incident hemodialysis cohort (n=477, age 68.5 ± 12.6 years) and the cut-off value for predicting mortality was estimated by area under the receiver operating characteristic (ROC) curve (AUC). The extent of aortic arch calcification (AAC) was assessed by chest X-ray. We performed a causal mediation analysis to investigate the effect of Gal-3 on mortality via vascular calcification. Mortality data were obtained with a median follow-up of 42 months.

Results: Serum Gal-3 levels were closely associated with age (r=0.131, p=0.004), coronary artery disease history (r=0.117, p=0.010), brain natriuretic peptide levels (r=0.154, p=0.004), high-density lipoprotein (HDL) cholesterol (r=0.243, p<0.001), high-sensitivity C-reactive protein (hs-CRP) (r=0.183, p=0.002), and AAC score (r=0.249, p<0.001). At a cut-off level of 37.0 ng/mL, the AUC for predicting mortality was 0.718 with sensitivity and specificity of 60.2% and 74.7%, respectively. Multivariate Cox regression analysis showed that higher Gal-3 levels increased all-cause mortality by 2.2-fold (95% confidence interval [CI] 1.38-3.45, p<0.001). The results of the mediation analysis suggested that this association was partially mediated by vascular calcification. Both the indirect effect between Gal-3 and mortality through vascular calcification (β=0.068, bootstrapped 95% CI 0.0020-0.0138) and the direct effect of the Gal-3 on mortality (β=0.0370, bootstrapped 95% CI 0.0205-0.0594) were significant.

Conclusions: This study suggests a possible mechanism linking serum Gal-3 and increased mortality in hemodialysis patients, providing evidence for a significant role of Gal-3 in vascular calcification.

SA-PO535

Dialysis Transition in Patients with and Without Heart Failure in a CKD Population


Background: CKD and heart failure (HF) frequently coexist and are associated with worsened outcomes. We sought to compare CKD patients with and without HF who transitioned to dialysis.

Methods: Retrospective study between Jan 2007 and Dec 2018 among incident CKD adult patients who initiated dialysis within Kaiser Permanente. Incident CKD identified as ≥2 consecutive eGFR<60 prevalent HF determined by ICD coding for HF. Dialysis setting (inpatient vs outpatient) and dialysis access (among HD) at initiation were determined for patients with vs without HF. Multivariable logistic regression used to estimate odds ratios (OR) and 95% CI for inpatient dialysis initiation and catheter use.

Results: 6,812 CKD patients initiated dialysis. 2,498 had HF [71% preserved EF (HFrEF), 20% reduced EF (HFrEF), and 9% unknown EF]. Inpatient dialysis start occurred in 18.5% with HF vs 9.6% without HF. Catheter use at dialysis start occurred in 58.5% with HF vs 51.9% without HF. Inpatient dialysis start occurred in 18.5% with HF vs 9.6% without HF. Inpatient dialysis start occurred in 18.5% with HF vs 9.6% without HF. Multivariable logistic regression used to estimate odds ratios (OR) and 95% CI for inpatient dialysis initiation and catheter use.

Conclusions: HF patients were more likely to start dialysis inpatient. HFrEF was associated with inpatient and catheter at dialysis start. Our findings question whether CKD patients with HF may benefit from earlier and differential dialysis transition strategies.
SA-PO536
Association of Antihypertensive Medications with Cardiovascular (CV) Outcomes in Patients with CKD
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Background: Angiotensin converting enzyme inhibitors (ACEI) and receptor blockers (ARB) are first line for hypertension in patients with CKD. Whether the second agent prescribed is associated with CV events is less clearly established.

Methods: Using the Veterans Affairs Corporate Data Warehouse, we identified veterans with CKD stages 1-5 based on estimated glomerular filtration rate and albuminuria from 1/1/2010 to 12/31/2016. We selected individuals prescribed an ACEI/ARB as monotherapy for hypertension at or prior to the time of prescription of a second antihypertensive agent (index date), grouped by thiazide diuretics (TD), loop diuretics (LD), calcium channel blockers (CCB), and beta blockers (BB). The primary outcome was the composite of hospitalization for heart failure or fatal or non-fatal myocardial infarction or stroke, or revascularization. Inverse probability of treatment weights (IPTW) were generated using generalized boosted methods, and Cox proportional hazards regression assessed associations between medications and CV events.

Results: Of the 328,399 participants, 98,222 (30%) were prescribed TD, 39,202 (12%) LD, 71,091 (22%) CCB, and 119,884 (36%) BB. The mean age was 71 years, 97% were men, 72% were White, and 18% were Black. Compared to the other groups, TD users were younger, more likely to be female, and less likely to have CKD stages 4 or 5. Heart failure was more common among users of LD (36%) and BB (18%) compared to TD (3%). Weighted standardized differences demonstrated that characteristics were balanced between groups after IPTW. There were 111,124 composite CV events. Compared to TD, increased hazard of CV events was seen for LD, CCB, and BB users (Figure 1).

Conclusions: Although residual indication bias cannot be excluded, these data suggest that there may be an increased risk of CV events with LD, CCB, and BB compared to TD in those with CKD. Examination of the reasons to initiate these agents is warranted.

Funding: Veterans Affairs Support

SA-PO537
Kidney Function Predicts New-Onset Cardiorenal Events and Mortality in Primary Aldosteronism: Approach of the 2021 Race-Free eGFR Equation
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Background: Individuals with primary aldosteronism (PA) exhibit glomerular hyperfiltration, which may conceal underlying kidney damage. We aimed to investigate whether baseline estimated glomerular filtration rate (eGFR) is associated with cardiovascular outcomes in this population.

Methods: This observational cohort study enrolled 760 coronary artery disease-naive patients diagnosed with PA between January 1, 2007 and December 31, 2018 (male, 45%; mean age, 52.3 ± 11.9 years). The baseline eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which includes serum creatinine and cystatin C but omits the race variable. Outcomes were composite cardiovascular events (total death, non-fatal myocardial infarction, and coronary revascularization procedure), all-cause mortality, and adverse kidney events.

Results: Using a mean follow-up of 5.8 ± 3.2 years, new-onset composite cardiovascular events occurred in 47 patients, with a crude incidence rate of 10.9 per 1,000 person-years. Multivariable Cox proportional hazards analysis showed that baseline eGFR was independently associated with composite cardiovascular events (hazard ratio [HR], 0.98 [95% CI, 0.97–0.99]). Penalized splines smoothing in multivariable regression analysis demonstrated that the risk of composite cardiovascular events increased negatively and linearly when patients had a baseline eGFR less than 85 mL/min/1.73m². Patients with baseline eGFR <85 mL/min/1.73m² were independently associated with higher risks of composite cardiovascular events (HR, 2.39 [95% CI, 1.16–4.93]), mortality (HR 4.63 [95% CI, 1.59–13.46]), and adverse kidney events (subdistribution HR, 5.96 [95% CI, 3.69–9.62], with mortality as a competing risk). (Figure 1A-C)

Conclusions: Our data support interpreting baseline eGFR as a predictor for new-onset adverse cardiorenal events and emphasizes the importance of the early detection of kidney function impairment in hypertensive patients with PA. We also firstly point to the validity of the 2021 race-free CKD-EPI equation in patients with PA.

Funding: Government Support - Non-U.S.

SA-PO538
Blood Pressure Is Not Controlled to <130/80 mm Hg in Majority of Veterans with High Atherosclerotic Cardiovascular Disease (ASCVD) Prevention
Aseel Zghayvat,1,2 Meghan O’Halloran,3 Chipping Ho,3 Frances M. Weaver,3,5 Ashley M. Hughes,7 Kevin Stroupe,1,2 Talar Markosian,5 Holly J. Kramer,1,2 Loyola University Health System, Maywood, IL; 3University of Illinois Chicago, Chicago, IL; 4Edward Hines Junior VA Hospital, Hines, IL.

Background: Blood pressure (BP) control remains the most effective intervention to prevent cardiovascular disease (CVD). The American College of Cardiology/American Heart Association (ACC/AHA) hypertension guideline recommends a BP goal <130/80 mm Hg for adults with high CVD risk which includes individuals with existing ASCVD, diabetes mellitus (DM) or chronic kidney disease (CKD). Few studies have examined the proportion of Veterans with CVD, DM or CKD with BP controlled to <130/80 mmHg receiving care within Veterans Affairs patients aligned care teams (PACT).

Methods: Vital sign data were obtained from 98,433 Veterans aged 18 to 85 years with a hypertension diagnosis during a PACT visit within eight Veteran Integrated Service Network 12 medical centers from January 1, 2019, through March 1, 2020. BP control was examined by high CVD risk (age ≥65 years and/or CV, DM or CKD) and by presence of CV, DM, CKD based on ICD10 diagnosis codes, or estimated glomerular filtration rate <60 ml/min/1.73 m² on two occasions based 90 days apart prior to the end of the study period. BP control was defined as a systolic BP <130 mmHg and diastolic BP <80 mmHg based on BP recorded during the last PACT clinic visit during the study period.

Results: The mean age was 68.5 years (SD 12.7) and 93% were male. Among the 89,537/98433 Veterans with high CVD risk, BP was controlled to <130/80 mmHg in 37.5% and <140/90 mmHg in 76.5%. Among subgroups, BP was controlled to <130/80 mmHg in 42.8% (5313/12,414) with CKD, 39.8% (13,484/33,880) with diabetes, 45.3% with CVD (13,402/29,584) and in 47.1% (1810/3845) with CKD, DM and CVD. In contrast, BP was controlled to <140/90 mmHg in over 75% of Veterans with CKD, DM and/or CVD (Figure 1).

Conclusions: The majority of Veterans with high CVD risk did not have BP controlled to <130/80 mmHg. Strategies are needed to improve BP control in Veterans with high CVD risk.

Figure 1. Clinical outcomes of interest in patients stratified by the baseline kidney function.
SA-PO539
Association Between Birth Weight Z-Score and Blood Pressure in Young Adults
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Background: Low birth weight (BW) has been associated with increased risk of hypertension later in life. The aim of this study was to examine the association between BW z-score and blood pressure (BP) indices in young healthy adults.

Methods: Participants were recruited from a cohort of 970 adults aged 20-22 years who participated in a population-based study of BP in 9-10-year-old Icelandic children. All participants underwent 8 resting clinic BP measurements during two separate visits and an ambulatory BP (ABP) measurement. Birth weight and gestational age obtained from the Icelandic Birth Registry were used to calculate BW z-scores based on a standardized growth chart by Niklasson & Albertsson-Wikland. Pearson correlation coefficient and multivariable linear regression were used for analysis.

Results: Of 170 young adults who completed the follow-up study, 102 were women (60%). The mean clinic BP was 120/65 mm Hg in men and 112/66 mm Hg in women. The mean BW for men was 3625±736 g and 3646±592 g for women. A negative correlation was observed between BW z-score and both systolic and diastolic ABP (r=-0.14, p=0.026 and -0.10, p=0.20, respectively). When the sexes were analyzed separately, the correlation between BW z-score and systolic ABP was statistically significant only in women (r=-0.24, p=0.014). In women the association between BW z-score and diurnal systolic ABP was significant (r=-0.26, p=0.013) while the correlation with nocturnal systolic ABP was not (r=-0.16, p=0.097). When adjusted for body mass index a significant association was detected between BW z-score and both systolic and diastolic ABP in young women (beta=-1.7, p=0.02 and beta=-1.2, p=0.01, respectively). This association was stronger for both diurnal systolic and diastolic ABP (beta=-1.8, p=0.02, and beta=-1.4, p=0.02), than for nocturnal systolic and diastolic ABP (beta=-0.08, and beta=-0.1, p=0.2). In men, BW z-score did not have a significant association with either ABP (systolic, r=-0.002 p=0.9; diastolic, r=-0.1 p=0.4) or clinic BP (systolic, r=-0.07 p=0.4; diastolic, r=-0.02 p=0.8) at follow-up.

Conclusions: Low BW z-score has a strong association with systolic ABP in young women and this relationship is stronger for diurnal systolic ABP.

SA-PO540
Prevalence of Aldosterone Breakthrough in a Cardiometabolic Clinic and Association with Albuminuria

Background: Type 2 diabetes (T2D) and chronic kidney disease (CKD) patients have cardiovascular and renal benefits when treated with renin-angiotensin-system (RAS) blockers. Some of these patients are known to exhibit a rise in aldosterone levels while on RAS blockers, called aldosterone breakthrough. The aim of our study is to assess the prevalence of aldosterone breakthrough in our clinic and its association with albuminuria.

Methods: Patients from a cardiometabolic clinic with available plasma aldosterone concentration (PAC) levels were screened. Exclusion criteria included: not taking a RAS blocker for at least 10 months, current treatment with a mineralocorticoid receptor antagonist (MRA) and an Aldosterone to renin ratio suggestive of primary hyperaldosteronism. Patients with a PAC=400pmol/L were considered to have aldosterone breakthrough.

Results: 64 patients met the inclusion criteria with 21 (33%) showing aldosterone breakthrough. Patient characteristics are shown in the Table. No significant differences in patient characteristics were seen in patients with or without aldosterone breakthrough except for higher albuminuria in the breakthrough group. The prevalence of CKD was numerically higher in the breakthrough group. Similar trends were seen when aldosterone breakthrough was defined as a PAC level above the median of our sample.

Conclusions: Aldosterone breakthrough is prevalent in patients from a cardiometabolic clinic and is associated with higher albuminuria. Patients with aldosterone breakthrough can potentially draw more benefit when treated with an MRA.

Baseline characteristics based on the presence or absence of aldosterone breakthrough:

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No aldosterone breakthrough</th>
<th>Aldosterone breakthrough</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, median (IQR))</td>
<td>67 (64-77)</td>
<td>67 (60-75)</td>
<td>0.58</td>
</tr>
<tr>
<td>Sex, male (n, %)</td>
<td>49 (77)</td>
<td>33 (60)</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypertension, (n, %)</td>
<td>91 (69)</td>
<td>77 (56)</td>
<td>0.02</td>
</tr>
<tr>
<td>Type 2 Diabetes, (n, %)</td>
<td>70 (66)</td>
<td>42 (96)</td>
<td>0.73</td>
</tr>
<tr>
<td>Heart Failure, (n, %)</td>
<td>13 (12)</td>
<td>7 (14)</td>
<td>0.52</td>
</tr>
<tr>
<td>Chronic kidney disease, (n, %)</td>
<td>19 (14)</td>
<td>22 (51)</td>
<td>0.08</td>
</tr>
<tr>
<td>Scr (mg/dL, median (IQR))</td>
<td>16 (13)</td>
<td>20 (21)</td>
<td>0.65</td>
</tr>
<tr>
<td>Albuminuria, (median (IQR))</td>
<td>284 (79-1118)</td>
<td>36 (10-381)</td>
<td>0.42</td>
</tr>
<tr>
<td>PAC specific (median (IQR))</td>
<td>540 (499-689)</td>
<td>227 (153-289)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*defined as eGFR<60mL/min/1.73m²
IQR - Interquartile range; PAC - Plasma aldosterone concentration; SGLT2i - sodium-glucose transporter 2 inhibitors.

SA-PO542
Low-Grade Albuminuria and Cardiovascular Mortality Among Healthy Adults
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Background: Albuminuria is associated with cardiovascular events among adults with underlying cardiovascular disease and diabetes, even at low levels of urinary albumin excretion. We hypothesized that low-grade albuminuria is associated with cardiovascular death among healthy adults.

Methods: We included adults participating in the 1999-2014 National Health and Nutrition Examination Survey (N=18,606). We excluded those with urinary albumin-to-creatinine ratio (UACR) >300mg/g, baseline cardiovascular disease, hypertension, diabetes, estimated glomerular filtration rate <60ml/min/1.73m², those who were currently pregnant, and those who had received dialysis in the last year. We assessed the relationship between log-transformed UACR and cardiovascular and all-cause mortality using multivariable Cox proportional hazards models. Models were adjusted for age, sex, race or ethnicity, survey year, BMI, insurance, smoking, A1c, systolic blood pressure, total cholesterol, serum albumin, statin use, and eGFR.

Results: Mean age was 38.1 years (standard deviation 14.0) and 53.4% were female. The median length of follow up was 12.2 years (interquartile range 8.4-16.4 years). In adjusted models, each doubling of UACR was associated with a 34% higher risk of cardiovascular death [HR 1.34 (95% confidence interval (CI) 1.10-1.63)] and a 28% higher risk of all-cause mortality [HR 1.28 (95% CI 1.16-1.41)]. The highest tertile of UACR was associated with an 84% higher risk of cardiovascular death [HR 1.84 (95% CI 1.18-2.89)] and 59% higher risk of all-cause mortality [HR 1.59 (95% CI 1.29-1.97)], compared with the lowest tertile (Table 1).

Conclusions: Higher levels of albuminuria in the “normal” range < 30 mg/g in healthy individuals nevertheless predict cardiovascular and all-cause mortality.

Funding: Other NIH Support - Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R38HL143584

Table 1

<table>
<thead>
<tr>
<th>UACR (mg/g)</th>
<th>Cardiovascular Death (n, %)</th>
<th>All-Cause Mortality (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;15</td>
<td>48 (4.2)</td>
<td>80 (4.7)</td>
</tr>
<tr>
<td>15-30</td>
<td>60 (5.9)</td>
<td>102 (5.8)</td>
</tr>
<tr>
<td>31-100</td>
<td>110 (11.2)</td>
<td>208 (11.7)</td>
</tr>
<tr>
<td>&gt;100</td>
<td>250 (24.1)</td>
<td>500 (28.3)</td>
</tr>
</tbody>
</table>
SA-PO543

The Impact of Chronic Fluid Overload, Water Imbalance (Tonicity), and Sodium Toxicity on Mortality of Hemodialysis Patients

Jule Pinter, Bernd Genser, Nicholas C. Chesnaye, Stefan Pfeifer, Kaitlin J. Mayne, Stefano Stuard, Ulrich Moissl, Jeroen Kooman, Kitty J. Jager, Christoph Wanner, Brendan Smyth, and Bernhard J. Canaud.

European Clinical Database Study Group, Julius-Maximilians-Universität Würzburg Medizinische Fakultät, Würzburg, Germany; Universität Heidelberg, Heidelberg, Germany; Amsterdam Public Health Research Institute, Amsterdam, Netherlands; University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom; Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; Universität Maastricht Faculty of Health Medicine and Life Sciences, Maastricht, Netherlands; NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; Université de Montpellier Faculté des Sciences de Montpellier, Montpellier, France; Amsterdam UMC Locatie AMC, Amsterdam, Netherlands.

Background: Chronic fluid overload, water imbalance and plasma sodium toxicity (tonicity) contribute to high mortality in hemodialysis-dependent (HD) patients and the interplay remains unclear. In this retrospective cohort, we aimed to determine the dose-response relationship and interplay between cumulative burden of fluid overload (FO) as associated with FO increased with cumulative exposure burden, mild FO (≥1.1 Liter) showed a steeper increase pattern with HR peaking at 3.28 (95%CI: 3.00 to 3.59) than severe relative FO. 7% <- normal fluid status was defined as fluid depletion. Hazard Ratios (HR) for defined conditions were estimated from Cox regression frailty model and adjusted for clustering by country and clinics and potential confounding variables.

Results: A total of 115 patients were included, 9 (7.8%) died. Phase Angle (PA) (4.64±4.64° 1.11vs3.12°; p=0.02), Lean Tissue Index (LTI) (12.41Kg/m²±3.14vs9.75Kg/m² ±2.95; p=0.02), Intracellular Water (ICW) (15.26L±3.53vs13.23L±4.97; p=0.03) were related with survival. Correlation analysis found positive correlation of PA (r=0.001), LTI (p=0.02) and ICW (p=0.03) with survival. Age (53.98y±14.75y vs70.67y±7.14; p=0.001) and E/I ratio (0.97±0.14y vs1.17±0.16y; p=0.001) were related with mortality. Age (p=0.002) and E/I ratio (p=0.005) had positive correlation with mortality.

Conclusions: Phase Angle, Intracellular water, E/I ratio, and Lean Tissue Index of a single non-invasive BIA can be used as earlier predictors of survival and mortality in HD patients allowing premature identification and intervention in this group of patients to reduce mortality risk.

SA-PO544

Bioelectrical Impedance Parameters as Earlier Predictors of Mortality/Survival in Ecuadorian Hemodialysis Patients


Background: Bioelectrical impedance analysis (BIA) is a non-invasive test to assess body composition and water distribution. Nutritional and volume disturbances are related with mortality in hemodialysis (HD) population. Few is known about BIA parameters as mortality/survival predictors. The aim of the study was to study BIA parameters as mortality/survival predictors in HD patients.

Methods: Observational-prospective-cohort study from April 2021-2023 in one HD center. BIA analysis was performed in HD patients and parameters significatively related with mortality and survival were identified. ROC curves, regression and correlation analysis were performed in BIA parameters identified.

Results: A total of 875 patients were included. Age ≥67y (875 vs704; p=0.001), Lean Tissue Index (LTI) (12.41Kg/m²±3.14vs9.75Kg/m² ±2.95; p=0.02), Intracellular Water (ICW) (15.26L±3.53vs13.23L±4.97; p=0.03) were related with survival. Correlation analysis found positive correlation of PA (r=0.001), LTI (p=0.02) and ICW (p=0.03) with survival. Age (53.98y±14.75y vs70.67y±7.14; p=0.001) and E/I ratio (0.97±0.14y vs1.17±0.16y; p=0.001) were related with mortality. Age (p=0.002) and E/I ratio (p=0.005) had positive correlation with mortality.

Conclusions: Phase Angle, Intracellular water, E/I ratio, and Lean Tissue Index of a single non-invasive BIA can be used as earlier predictors of survival and mortality in HD patients allowing premature identification and intervention in this group of patients to reduce mortality risk.

Table 1. Baseline characteristics and variables with statistical significance of studied population.

<table>
<thead>
<tr>
<th>Variables studied.</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender (%)</td>
<td>56.5</td>
</tr>
<tr>
<td>Age (mean ±SD)</td>
<td>55.2±14.9</td>
</tr>
<tr>
<td>Body Mass Index (mean ±SD) kg/m²</td>
<td>25.61±1.16</td>
</tr>
<tr>
<td>CTX Tissue (g%)</td>
<td>- Diabetes</td>
</tr>
<tr>
<td>- Others</td>
<td>20.4</td>
</tr>
<tr>
<td>Comorbidities (%)</td>
<td>- Diabetes</td>
</tr>
<tr>
<td>- Hypertension</td>
<td>47.8</td>
</tr>
<tr>
<td>- Anemia</td>
<td>20.1</td>
</tr>
<tr>
<td>*HD vintage (months)</td>
<td>72 (26-108)</td>
</tr>
<tr>
<td>Deaths</td>
<td>9</td>
</tr>
<tr>
<td>Mortality prevalence</td>
<td>7.8%</td>
</tr>
</tbody>
</table>

Table 2. Variables with statistical significance with survival.

<table>
<thead>
<tr>
<th>Variables with statistical significance with survival</th>
<th>Cut-off (Sensitivity, Specificity %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase Angle (p=0.001)</td>
<td>≥3.26 (58.8, 96.4)</td>
</tr>
<tr>
<td>Lean Tissue Index (p=0.02)</td>
<td>≥30.35 (62.2, 53.3)</td>
</tr>
<tr>
<td>Intracellular Water (p=0.02)</td>
<td>≥13.15 (66.8, 53.3)</td>
</tr>
<tr>
<td>*Variables with statistical significance with mortality</td>
<td>≥66.5 (58.0, 52.7)</td>
</tr>
<tr>
<td>E/I ratio (p=0.001)</td>
<td>≥0.99 (75.2, 52.3)</td>
</tr>
</tbody>
</table>

*HD: Vintage values expressed in median and interquartile range (25% - 75%); Sensitivity, Specificity: Values obtained with student T-test in mortality and survival.
SA-PO545
Kidney Sodium MRI: Extending the Concept of Residual Kidney Function in Hemodialysis
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Background: It is widely recognized that persistence of even modest amount residual kidney function (RKF) is associated with improved outcomes, in hemodialysis (HD) patients. The concept of RKF, as currently utilized, is exclusively based upon urine volume and small solute clearance-requiring complete interdialytic urinary collection. This makes accurate and consistent assessment measurement challenging and difficult to implement in clinical practice. More importantly it focuses almost exclusively on glomerular function, rather than a more inclusive consideration of overall kidney function to incorporate assessment of renal tubular mass. The aim of this study was to test the feasibility of obtaining useable 23Na-MRI kidney images, in the setting of dialysis dependance (as compared to normal subjects without CKD) and initially describe the associations between directly imaged medullary sodium content and other components of a more conventional approach to the definition of RKF.

Methods: We included 21 healthy volunteers and 17 HD participants, fasted for eight hours prior to their study visit. Urine samples were collected to measure urinary osmolarity, before MRI scan.

Results: Median (IQR) fasting medulla to cortex ratio was significantly higher 1.56 [1.5 – 1.61] in healthy volunteers compared to HD patients [1.22 [1.13 – 1.3], p=0.0001. Medulla to cortex ratio and medican urinary osmolarity were correlated (r=0.87, p=0.0001) in the whole population. We found a significant association between HD vintage and medulla to cortex ratio whereas we did not find any association with urine volume. Sodium signal intensity distribution within healthy kidney describes two different peaks-relating to well defined cortex and medulla; whereas HD participants displays only a single peak indicative of the markedly lower sodium concentration.

Conclusions: The application of kidney sodium MRI to the study of RKF in patients receiving maintenance HD is practical and provides a previously unavailable ability to interrogate the function of remnant tubular mass.

SA-PO546
Analysis of Microcirculatory Flow Changes After Hemodialysis
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Background: During HD there appears to be a viscosity change in RBCs which leads to a decrease in their deformability changing to a rouleau formation with concurrent increases in viscosity. Increases in both whole blood and plasma viscosity are correlated to increased viscosity of RBC density in the microvasculature post-HD figure 1, along with a calculated increase in viscosity via software analysis (Figure 2). Although the etiology of these findings is unclear, it correlates with the observed increases in cardiovascular events seen among ESRD patients in the immediate days following dialysis.

Methods: Changes to the microcirculation in HD patients have previously been documented by Bemelmans et al by viewing the sublingual mucosa. Microcirculation impairment is an independent predictor of organ dysfunction and death which can be assessed via capillaroscopy examination. We adapted a commercial orthogonal polarization spectral imaging camera to perform capillaroscopy of the conjunctival tissue bed. Unlike the sublingual mucosa, the bulbar conjunctiva demonstrates hemodynamic features not dissimilar to the cerebral cortex.

Results: Early findings demonstrate a profound abnormality in RBC aggregation and RBC density in the microvasculature post-HD figure 1, along with a calculated increase in viscosity via software analysis (Figure 2). Although the etiology of these findings is unclear, it correlates with the observed increases in cardiovascular events seen among ESRD patients in the immediate days following dialysis.

Conclusions: Although the Fåhraeus–Lindqvist effect predicts viscosity decrease with an increase in microcirculatory flow, our study findings demonstrate that in HD, an increase in flow is proportional to an increase in viscosity. Rouleau formation post-HD is abnormal and is postulated to be responsible for the increase in viscosity noted. The increase in viscosity appears unrelated to UF but to HD itself.

SA-PO547
Changes in the Glymphatic System Before and After Dialysis Initiation in Patients with ESRD
Jiyae Yi, Sihyung Park, Yang Wook Kim, Bongsoo Park, Yoo jin Lee, Changmin Heo, Yeongrok Oh, Byeongho Choi. Inje University Haeundae Paik Hospital, Busan, Republic of Korea.

Background: This study evaluated 1) glymphatic system function in patients with end-stage renal disease (ESRD) before dialysis initiation compared to healthy controls, and 2) changes in glymphatic system function after renal replacement therapy including dialysis in patients with ESRD using the diffusion tensor image analysis along the perivascular space (DTI-ALPS) method.

Methods: This prospective study was conducted at a single hospital. We enrolled 14 neurologically asymptomatic patients who initiated hemodialysis or peritoneal dialysis for ESRD, as well as 17 healthy controls. The patients underwent magnetic resonance imaging (MRI) before and 3 months after dialysis initiation, and the DTI-ALPS index was calculated. We compared the DTI-ALPS index before and after dialysis initiation between patients with ESRD and healthy controls.

Results: The DTI-ALPS index differed between patients with ESRD before dialysis initiation and healthy controls (1.342 vs. 1.633, p=0.003) but not between patients with ESRD before and after dialysis initiation (1.342 vs. 1.262, p=0.386). A positive correlation was observed between DTI-ALPS and phosphate levels (r=0.610, p=0.020) in patients with ESRD.

Conclusions: We confirmed glymphatic dysfunction in patients with ESRD but observed no differences before or after dialysis initiation. This may be related to uremic toxins that are not removed by dialysis in patients with ESRD. The results of this study could be used to develop the pathophysiology and treatment of patients with ESRD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO548
Near-Infrared Spectroscopy in Hemodialysis
Arslan Mahmood, Andrew A. Moses, Lenox Hill Hospital, New York, NY.

Background: Near-infrared spectroscopy (NIRS) is a noninvasive monitoring of cerebral oxygenation commonly used in monitoring for ischemia in surgical patients. Sensors are placed to measure oxygenation in the designated area. Infrared waves pass through a regional area to detect deoxygenation prior to widespread ischemia. During Hemodialysis (HD), ESKD patients are known to have abnormalities in cerebral blood flow, but few studies have looked at changes in cerebral oxygenation during HD in these patients. The aim of this study was to evaluate cerebral regional O2 saturation (rSO2) during HD, and to assess any correlation with vital signs such as blood pressure (BP) and heart rate.

Methods: Six inpatients with ESKD undergoing dialysis were enrolled. We used the FDA cleared device, INVOS PM 7100 patient monitor (K211561) and the INVOS Adult rSO2 sensor (K182686) produced by Medtronic. A sensor was secured on each side of the scalp, to measure temporal lobe oxygenation. NIRS monitor was placed at the beginning of HD and was removed 5 minutes after the session ended. Baseline was established during the first five minutes of the treatment. Desaturation was defined as a 20% or greater relative reduction from baseline local blood oxygen level for at least 1 minute.

Results: Patients’ ages ranged from 59-85 years. Baseline rSO2 was adequately obtained in all patients. Desaturation was observed in one out of six patients (Figure). This was a 25% desaturation lasting for 2 minutes and 40 seconds, during which patient was asymptomatic and without change in vital signs. The same patient had a one-time drop in BP to 87/46 but no desaturation was observed during this time. Another patient had a one-time drop in BP to 91/63, without any desaturation observed in this time.

Conclusions: This pilot study was conducted to establish baseline cerebral oxygenation data for ESKD patients undergoing HD. Though a small sample size, this approach has potential to reveal interesting and useful insights to effects of HD on neurological function. We are continuing to gather patients and will use this group to establish norms of NIRS in ESKD patients.

Figure: NIRS data of patient with desaturation marked in red box

SA-PO549
Cerebrovascular Function and Brain Structure in Hemodialysis Patients
Dawn F. Wolfgram,1 Brian Schmit,1,2 Wesley Richerson,2 1Medical College of Wisconsin, Milwaukee, WI; 2Vanderbilt University, Nashville, TN; 3Marquette University College of Engineering, Milwaukee, WI.

Background: Hemodialysis (HD) patients often have decline in cerebral blood flow (CBF) and cerebral oxygen saturation during HD. Cerebrovascular reactivity (CVR) measured at rest may be able to identify individuals susceptible to intradialytic hypoperfusion and ischemic brain injury. We hypothesized that HD patients would have decreased CVR and increased CBF relative to controls and that decreased CVR would be related to structural brain lesions.

Methods: In 10 HD patients and 10 controls, we measured cortical thickness and white matter hyperintensity (WMH) volume from the T1 and T2 FLAIR respectively, CVR from a breath hold during BOLD CVR fMRI, and arterial transit time and CBF from arterial spin labelling. Differences in these measures between the groups were tested by averaging across the tissue and with a pothole analysis. We correlated cortical thickness and WMH volume with cerebrovascular variables to assess the relationship between brain structure and cerebrovascular health in HD patients.

Results: Compared to controls, the HD cohort had decreased cortical thickness, increased WMH volume (p=0.002, p=0.004), and increased white matter CBF (p=0.02). Pothole analysis demonstrated a greater number of increased gray and white matter CBF voxels (p=0.03, p=0.02) and a greater number of decreased gray and white matter CVR voxels (p=0.02, p<0.01). No significant relationships were found between cortical thickness or WMH volume and CVR or CBF.

Conclusions: HD patients have structural injury with decreased cortical thickness and increased WMH. Notably, HD patients had increased CBF and decreased CVR. However, we did not find that decreased CVR correlated with decreased cortical thickness or increased WMH in this pilot study.

Funding: NIDDK Support, Private Foundation Support

SA-PO550
Early Detection of White Matter Changes Through MRI Brain Diffusion Tensor Imaging (DTI) in ESRD Patients on Hemodialysis

Background: Neurological complications like stroke and cognition disorders contribute to morbidity and mortality in CKD patients significantly. It has been postulated that neurological adverse events and renal dysfunction in CKD patients are related at the pathogenesis level. Neurological changes in the brain in CKD patients can be detected by Magnetic resonance studies at a stage earlier than overt clinical symptom manifestation.

Methods: After obtaining approval from the Institutional Ethics Committee, 30 patients with end-stage renal disease on hemodialysis and 10 age-matched control persons without kidney disease underwent routine biochemical studies and an MRI brain on a 3T scanner. Fractional Anisotropy and Mean Diffusivity were calculated for corpus callosum genu and splenium, anterior and posterior corona radiata, pons, and cerebellar hemispheres on both sides. Conventional MRI images were evaluated for changes in small vessel disease. Student’s unpaired T-test was used to determine if the difference in results were statistically significant.

Results: 18 out of 30 hemodialysis patients and three out of 10 control patients had white matter changes of small vessel disease detectable in conventional MRI sequences. Fractional anisotropy was significantly low for corpus callosum genu (p=0.003464, right and left sides respectively) and anterior corona radiata (p=0.04272 and p=0.01653, right and left sides respectively) in hemodialysis patients than control. No significant difference in fractional anisotropy was noted for other locations. Mean diffusivity was higher at corpus callosum genu and anterior corona radiata in hemodialysis patients than in age-matched controls but did not reach statistical significance (p=0.05).

Conclusions: There are white matter changes detectable by DTI imaging in a quantitative manner in anterior corona radiata and corpus callosum genu in hemodialysis patients that is absent in age-matched control persons without renal disease. Further research is needed to use these early quantitative DTI changes to build robust predictive models for prognostication that will lead to comprehensive renal and neurological clinical management in CKD patients.
Intrinsic Prefrential Functional Connectivity According to Cognitive Impairment in Patients with ESRD

Yeongrok Oh, Bongsoo Park, Yang Wook Kim, Sihyung Park, Yoo jin Lee, Changmin Heo, Jiayue Yi, Byeongho Choi. Inje University Haeundae Paik Hospital, Busan, Republic of Korea.

Background: This study aimed to investigate differences in intrinsic prefrential functional connectivity according to the presence of cognitive impairment in patients with end-stage renal disease (ESRD). The NIRS-Lite device was used to acquire NIRS data, and the NIRS-Lite Analysis Tool program was used to process the data and generate a functional connectivity matrix. We obtained functional connectivity measures by applying graph theory using BRAPH program from the connectivity matrix using the BRAPH program. All patients with ESRD underwent a Korean version of the Montreal Cognitive Assessment (MoCA-K) to assess their cognitive function.

Results: Of the 37 patients with ESRD, 23 had cognitive impairment, whereas 14 patients showed no cognitive impairment. Intrinsic prefrential functional connectivity was significantly different between groups. The network measures of the strength, global efficiency, and mean clustering coefficient were lower (4.458 vs. 5.129, p=0.018; 0.397 vs. 0.437, p=0.028; 0.316 vs. 0.421, p=0.003, respectively) in ESRD patients with cognitive impairment than those without cognitive impairment. There were no significant correlations between MoCA-K scores and clinical characteristics.

Conclusion: We found a significant difference in functional coherence and intrinsic prefrential functional connectivity in patients with ESRD. ESRD patients with cognitive impairment have reduced connectivity and segregation in the prefrontal brain network compared with those without cognitive impairment.

Urea Clearance in a Large-Animal Hemodialysis Benchtop Model Using Nanoporous Silicon Nitride Membranes

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Background: Over three-quarters of a million Americans live with the daily complications of end-stage renal disease (ESRD), and 71% of those are on some form of renal replacement therapy. One major concern with current hemodialysis is the non-ambulatory nature of the treatment, with many patients undergoing treatment for four hours, three times a week. Our goal is to make conventional renal replacement therapy more compact, allowing for ambulatory dialysis. To accomplish this, our lab has previously devised and utilized nanoporous silicon nitride (NPN) membranes that demonstrated a 20% urea clearance in a small-animal model (Hill et al., 2020). We modified the NPN membranes for use in a large animal benchtop model by increasing the surface area while maintaining a pore size of 0.35-µm. NPN membranes with a pore size of 35 nm were also developed for testing in the large animal model with the goal of consistent dialysis of uremic toxins without loss of other important macromolecules and blood components (e.g., albumin and white blood cells).

Methods: The large-animal hemodialysis benchtop model consists of a 500 mL circulating analyzer (20 mm urea-spiked 1x phosphate-buffered saline (PBS) or whole heparinized bovine blood) flowing across an NPN membrane counter to 1x PBS, circulating at a rate of 50 mL/min and 120 mL/min respectively. The NPN membranes were contained in a stable 3D-printed housing unit that allows for effective flow-through and the ability to gather transmembrane pressure readings, without damage to the chip. Small samples (~100 µL) were collected from the body of the dialyzer analyze every five minutes for the first thirty minutes, and every fifteen minutes thereafter, over the course of two hours.

Results: The clearance results of the NPN membranes in the dialysis of urea-spiked 1x PBS and blood show a decrease in urea concentration in the analyze over a time of two hours, consistent with that seen in the small-animal model. This data suggests that NPN membranes are effective dialyzers of metabolic waste products, such as urea, in a large-animal model of ESRD.

Conclusion: This study demonstrates the effectiveness of microporous and nanoporous silicon nitride membranes for dialyzing small metabolic waste products in a large-scale animal model.

Funding: NIDDK Support

Impact of Protein Fouling on Molecule Molecule Removal During Initial Dialysis Phase

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Background: Deposition of plasma proteins to the dialyzer membrane during the initial dialysis phase strongly reduces removal capacity of middle molecules such as β2-microglobulin (β2-m). Hydrophilic membrane modification with polyvinylpyrrolidone (PVP) has been shown to reduce protein fouling and to stabilize dialyzer performance.

Methods: Protein fouling to the membrane was simulated during a recirculation experiment with bovine plasma for 30 and 60 min. The clearance of protein fouling was determined in a single-pass setup with bovine plasma at three time points (before protein fouling (0min), after 30min and 60min protein fouling). Clearance values were recalculated based on the membrane surface area.

Results: Across all five investigated dialyzers, mean β2-m clearance reduced by 18.7% after 30min of plasma recirculation (0min: 35.2±9.3 mL/min; 30min: 28.7±7.5 mL/min) after additional 30min of plasma recirculation, β2-m clearance only slightly decreased (60min: 28.4±7.5 mL/min; -1.1% vs. 30min). When comparing the clearance of the different by the dialyzers, the FX CorAL showed low β2-m clearance decrease while having the highest β2-m clearance throughout the experiment (0min: 47.2±3.4 mL/min; 30min: 39.8±9.0 mL/min; 60min: 40.0±1.3 mL/min) as compared to Revaclear (0min: p=0.001; 30min: p=0.001; 60min: p=0.001), Diacap Pro (p=0.001; p=0.001; p=0.001), ELISIO (p=0.001; p=0.001; p=0.001) and Cellenta (p=0.001; p=0.001; p=0.001).

Conclusion: Efficient removal of middle molecules while preserving vital proteins such as albumin is pivotal for patients requiring renal replacement therapy. To prevent loss of dialyzer performance during treatment, novel hydrophilic membranes, such as FX CorAL’s Helixone hydro membrane, has been shown to reduce protein fouling and to stabilize performance during treatment, especially during the initial dialysis phase.
were separated on a LunaNH2 (Phenomenex) HILIC column and detected with a Q Exactive orbitrap mass spectrometer (Thermo Scientific). Statistical analysis was done with a one-way ANOVA test.

**Results:** The concentration of ADMA, homocitrulline, homocysteine, kynurenine, p-cresylsulfate, phenol, and phenylacetylglutamine, and methylguanidine in the spent dialysate decreased by 87.93% (p < 0.001) at a dialysate pulse flow rate of 30 mL/min. After 4 hours of recirculation through the WAK sorbent cartridge

**Conclusions:** The WAK3 effectively adsorbs uremic toxins from dialysate supporting the notion that the device may be effective in treating dialysis patients.

Percentage of toxin removed from dialysate after 4 hours of recirculation through the WAK3 charcoal sorbent

<table>
<thead>
<tr>
<th>TOXIN</th>
<th>% removed</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methyloamine</td>
<td>74.4%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ADMA</td>
<td>95.48%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocitrulline</td>
<td>80.19%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>72.13%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kynurenine</td>
<td>97.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phenol</td>
<td>98.71%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phenylacetylglutamine</td>
<td>93.3%</td>
<td>&lt;0.001</td>
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</tbody>
</table>

**SA-PO557**

**Can Oral Phosphate Binders Be Added to Dialysate to Improve the Efficacy of Hemodialysis?**

**Rouzbeh Tehrani,1 Avrum Gillespie,2 Juliana Alferter.1 Temple University, Philadelphia, PA; 2Lewis Katz School of Medicine at Temple University, Philadelphia, PA.**

**Background:** Can commercially available polymeric phosphate binders, Sevelamer carbonate (SC), be added to the dialysate to improve diffuse clearance and reduce dialysate usage while decreasing blood-dialysate phosphate gradients? Sevelamer carbonate is an orally administered, non-absorbed phosphate-binding anion exchange resin. It is a buffered form of Sevelamer hydrochloride.

**Methods:** This is an in-vitro hemodialysis experiment using 1 liter of freshly collected Li-heparinized porcine blood dialedyzed with an average blood flow rate of 30 mL/min and dialysate flow of 50 mL/min, two peristaltic pumps, Fresenius Optiflux hemodialysis membranes, and CiraPure dialysate concentrate (Rockwell Medical) which was diluted and the pH adjusted using sodium bicarbonate (Solcart B, B.Braun). For the phosphate experiment, 3 tablets of SC were crushed and added to the dialysate, 2700 mg of active SC/L. SC leaching to blood was tested by (i) examining blood specimens after prolonged 5-hour hemodialysis, (ii) using highly concentrated SC-added dialysate (5 to 10 g/L) and increased transmembrane pressure, and measuring the reverse filtrate for SC particles.

**Results:** For the hyperphosphatemia experiment, the start serum phosphorus was 8 mg/dL. After 30 minutes of dialysis, the phosphorus was 5.5 mg/dL. SC was added and the phosphate dropped to 2.5 mg/dL at 100 minutes. SC was then added again and phosphate dropped to 2 mg/dL. No suspended particles were detected passing through the membrane from dialysate to blood.

**Conclusions:** The addition of Sevelamer Carbonate (SC) effectively lowered phosphate using recirculated dialysate and can be incorporated into a novel hemodialysis machine that can recirculate dialysate, reducing water consumption for both in-center and home hemodialysis. While SC effectively reduced phosphate levels, its addition to the dialysate has been found to influence the dialysate pH. Therefore, careful consideration must be given to pH adjustment when utilizing SC. Maintaining appropriate dialysate pH is crucial for ensuring patient safety and optimizing dialysis outcomes.

**SA-PO558**

**Improving the Efficacy and Efficiency of Hemodialysis by Adding Nanoscale Activated Carbon (Nano-Slurry) Sorbent to the Dialysate**

**Rouzbeh Tehrani,1 Avrum Gillespie,2 Juliana Alferter.1 Temple University, Philadelphia, PA; 2Lewis Katz School of Medicine at Temple University, Philadelphia, PA.**

**Background:** Improving the efficacy and efficiency of dialysate for hemodialysis has the potential to improve patient outcomes and reduce waste and energy consumption. Currently, hemodialysis relies mostly on diffusive clearance across a gradient between the patient’s blood and the dialysate. We demonstrate that the addition of nanoparticle sorbents to the dialysate can improve the efficiency of hemodialysis and can allow for the reuse of dialysate.

**Methods:** This is an in-vitro hemodialysis experiment using Li-heparinized porcine blood, two peristaltic pumps, Fresenius Optiflux hemodialysis membranes, and CiraPure dialysate concentrate (Rockwell Medical) which was diluted and the pH was adjusted using medical-grade sodium bicarbonate (Solcart B, B.Braun). One liter of freshly collected porcine blood was dialyzed with an average blood flow rate of 30 mL/min and dialysate flow of 50 mL/min. Nanoscale activated carbon (Nano-Slurry) was tested in this study. The mass of added adsorbents (0.5 to 5 g/L) varied depending on the adsorbent type, targeted blood toxin, and expected removal rate. Absorbent leaching to blood was tested by using highly concentrated Nano-Slurry (10 to 20 g/L) dialysate and increased transmembrane pressure by increasing the dialysate flow rate to 1000 mL/min and measuring the reverse filtrate for nanoparticles by turbidity with a near-infrared turbidity meter.

**Results:** In the single-pass experiment, creatinine was removed in half the time when using Nano-Slurry dialysate. We then did our recirculated dialysate experiment and the Nano-Slurry, creatinine rapidly equilibrated in the control experiment at 30 minutes whereas, the recirculated Nano-Slurry dialysate continued to remove creatinine at the end of the experiment, 100 minutes. BUN rapidly lowered from 17 mg/dL to 7mg/dL, below the calculated equilibrium at 20 minutes. For the absorbent leaching experiment, the reverse filtrate had turbidity that remained unchanged pre- and post-experiment with a measure of 0.03 NTU.

**Conclusions:** Nano-Slurry improved the efficiency in both in-vitro single pass and recirculated hemodialysis models. The addition of nanoscale adsorbents improved the efficiency of dialysis and can be incorporated into a novel hemodialysis machine that can recirculate dialysate, reducing water consumption for both in-center and home hemodialysis.
SA-PO559
Animal Models for Studying Protein-Bound Uremic Toxin Removal
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Background: Protein-bound uremic toxins (PBUTs) are linked with the progression of chronic kidney disease (CKD) and higher morbidity and mortality risks. Conventional dialysis does not effectively remove PBUTs due to their binding to plasma proteins. Therefore, novel approaches to improve PBUT clearance are being developed, but these require validation before clinical trials can be initiated. To gain more insight into suitable CKD animal models we conducted a semi-systematic review to document PBUT concentrations in various models and species.

Methods: The search yielded 1163 records which were included for abstract screening, of which 66 were included for data extraction (Figure 1). All data were extracted by one researcher, after which the data were independently validated by a second researcher. Two specific types of injury were distinguished and analyzed as subgroups for the effect on PBUT levels: nephron loss models (e.g. 5/6th nephrectomy) and tubular damage models (by administration of tubulotoxins, e.g. adriamycin).

Results: PBUT concentrations were reported in studies using rats (n=43), mice (n=16), dogs (n=3), cats (n=4), goats (n=1), and pigs (n=1). Most studies in rodents reported mean uremic concentrations of plasma indoxyl sulfate (IS) close to or in the range of human ESKD, with the highest concentrations in tubular injury models (121.7 µM – 154.1 µM); mean (95% CI), n=15 rat studies). Compared to nephron loss models in rats, a greater rise in plasma IS compared to creatinine was found in tubular injury models (factor 11.2 versus 6.3 for nephron loss models), likely due to the fact that tubular secretory function was relatively more affected than glomerular filtration. The small number of studies and heterogeneity of the data reported precluded detailed analysis of large animal models or other PBUTs.

Conclusions: Tubular injury models in rats appear to be suitable models to mimic human ESKD for in vivo validation of innovative PBUT-lowering strategies.

Funding: Government Support - Non-U.S.

Figure 1. Article selection process.

SA-PO560
A Chronic Intermittent Hemodialysis Pig Model for Functional Evaluation of Dialysis Filters
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Background: Performance evaluation of new dialysis filters is primarily performed in vitro, which can lead to differences in clinical results. Current data on filter performance and safety are available only for actual hemodialysis patients. Herein, we aimed to establish an in vivo dialysis model that could be extrapolated to humans.

Methods: A bilateral nephrectomy porcine model of renal failure was established, in which a double-lumen catheter for human dialysis was subsequently placed in the external jugular vein under general anaesthesia, the tip of which was fixed to the back (Fig 1). Hemodialysis was performed every other day in the same manner as in humans, during which various clinical data were evaluated. The utility of hemodialyzers coated with and without vitamin E (V-RA and ABH)1,2 was subsequently compared using this model.

Results: Hemodialysis treatment was successfully performed in bilaterally nephrectomised pigs under the same dialysis conditions as humans (4 h per session, 3 times a week, for 2 weeks). In accordance with human clinical data, regular dialysis alleviated renal failure in pigs, allowing for sufficient activity. The vitamin E-coated filter showed a significantly greater reduction rate of advanced oxidation protein products (AOPP) during dialysis and a lower quantity of fibrinogen adhesion at the first dialysis on postoperative day 1 than ABH (Fig 2).

Conclusions: Herein, we successfully constructed a pig model of chronic hemodialysis that mimics the pathophysiology and dialysis condition of patients undergoing hemodialysis. This model will be useful for evaluating the performance and safety of dialysis filters before market release.

Funding: Commercial Support - Asahi Kasei Medical Co. Ltd.

Figure 1. The catheter tip was placed at the junction of the anterior vena cava and the right atrium, and the access site was placed dorsally.

SA-PO561
Amino Acid Loss During a Hemodialysis Session Depending on Membrane Materials
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Background: Dialysis-related factors including nutrient loss during a hemodialysis (HD) session may have an important impact on protein energy wasting especially in elderly or malnourished dialysis patients. In this study, we examined dialysate amino acid (AA) loss during a HD session and compared clear space (CS) of AA among three different membranes including acrylonitrile and sodium methallyl sulfonate blends (AN 69) which has significantly smaller amount of albumin loss.

Methods: In 6 maintenance HD patients (6 women), pre-HD plasma basic 20 AA profiles were analyzed in three consecutive HD sessions (blood flow 200ml/min, 4 hours) with different membranes. Simultaneously, dialysate AA losses in each session are measured by continuous effluent collection (2L/hr) from the drainage line. The membranes studied were: cellulose tri-acetate (CTA), polysulfone(PS), and acrylonitrile and AN 69. All membranes had similar surface area of 1.5 square meters. We measured CS using the pre-dialysis plasma AA concentration and AA losses in dialysate, and compared CS among the three membranes.

Results: The total amino acid (TAA) loss for each HD session was 8.2 (5.9-10.0) g for CTA, 8.0 (6.1-9.5) g for PS, and 7.3 (5.0-8.4) g for AN69 (p=0.32). Average of CS for each AA is 2(16-25) L for CTA, 19(16-27) L for PS, 18(15-24) L for AN69 (p=0.36). Total CS for AA is 400(311-474) L for CTA, 362 (302-505) L for PS, 344 (292-451) L for AN69 (p=0.06).

Conclusions: A total of 7 to 8 grams of AA are lost per HD session. No superiority of AN69 for reducing AA loss was not observed in this study.

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

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Background: Bisphenol A (BPA)-based materials are widely employed across various industries, including dialysis. As concerns for BPA’s health risks rise, bisphenol S (BPS)-based materials are increasingly used. However, BPS safety requires further evaluation. To support thorough risk assessments on bisphenols and their exposure for hemodialysis patients, extractables (E) and leachables (L) from 8 commercially available dialyzers were tested.

Methods: For E, dialysate and blood sides of each dialyzer were incubated statically at 37°C with 95% ethanol (EtOH) and collected after 72 hrs. For L, bloodlines, dialysate and blood sides were filled with 17.2% EtOH and recirculated at 300 mL/min and 37°C for 24 hrs. Bloodline controls were run using the recirculation setup. Bisphenols were quantified by liquid chromatography-mass spectrometry using standard addition and stable-isotope labeled standards.

Results: BPA (0.43 - 32.82 µg/device) and BPS (0.02 - 2.51 µg/device) were detected in E from dialyzers and housings made with BPA- and BPS-containing materials (Figure 1). In L, BPA was only detected in one dialyzer made of BPA-containing membrane and housing material. BPS (0.08 - 1.44 µg/device) was detected in L of dialyzers made with BPS-based materials. BPA/BPS were not detected in bloodline controls, cellulose-based membranes, and in Fresenius Medical Care’s FX CorAL 120 dialyzer, a member of the recently FDA-cleared CorAl dialyzer family.

Conclusions: Dialyzers have varied bisphenol amounts based on raw materials and manufacturing process used for housing and membranes. FX CorAL exhibited no detectable bisphenols, as opposed to other dialyzers with synthetic membranes, where varying amounts of bisphenols were detected. To understand the BPS toxicological profile, additional studies should be performed and evaluated as rigorously as BPA.

Funding: Commercial Support - Fresenius Medical Care

SA-PO564

Effect of Dialysis Treatment on Structural Brain Connectivity in Patients with ESRD

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Background: End-stage renal disease (ESRD) patients are known to have reduced structural and functional brain connectivity associated with cognitive function. However, the effect of dialysis treatment on brain connectivity is not understood. This study was designed to evaluate effects of dialysis treatment on structural brain connectivity in patients with ESRD.

Methods: This prospective study was conducted with 20 ESRD patients with pre-dialysis and 35 healthy controls. The patients underwent T2-weighted and three dimensional T1-weighted magnetic resonance imaging (MRI) before and 3 months after dialysis initiation, and cortical thickness was calculated. We applied a graph theoretical analysis for calculating the structural co-variance network based on the cortical thickness. We compared the cortical thickness and structural co-variance network between ESRD patients with pre-dialysis and healthy controls, and between ESRD patients with pre-dialysis and those with post-dialysis.

Results: The mean cortical thickness in both hemispheres was lower in ESRD patients with pre-dialysis than in healthy controls (2.296 vs. 2.354, p = 0.030; 2.282 vs. 2.362, p = 0.004, respectively), and it was higher in ESRD patients with post-dialysis than in those with pre-dialysis (2.333 vs. 2.296, p = 0.001; 2.322 vs. 2.282, p = 0.002, respectively). In analysis of the structural co-variance network, the assortative coefficient was lower in ESRD patients with pre-dialysis than that in healthy controls (-0.062 vs. -0.031, p = 0.029), and it was higher in ESRD patients with post-dialysis than those with pre-dialysis (-0.002 vs. -0.062, p = 0.042).

Conclusions: We found that there were differences in cortical thickness and structural co-variance network before and after dialysis in ESRD patients. This indicates that dialysis treatment affects structural brain connectivity and will contribute to understanding the pathophysiological mechanism of cognitive function alterations resulting from dialysis treatment in ESRD patients.

Funding: Commercial Support - Fresenius Medical Care
determined using the median of all available pre-dialysis eGFR values within a month of the sampling occasion date. Age, sex, dialysis vintage, and target weight were collected. Descriptive analyses and Spearman correlation coefficients were performed.

**Results:** Pre- and post-dialysis levels were obtained from 38 individuals. Values were non-normally distributed (Fig 1). Median UMOD pre-dialysis was 2450 (IQR=1060–5981) pg/mL, and post dialysis was 2870 (IQR=1050–5640) pg/mL, with median difference =16 (IQR=−600–470) pg/mL, P=0.8. UMOD=8000 pg/mL were in the 95th percentile. Pre- and post- dialysis UMOD values were highly correlated (R=0.93, P<0.001 and did not correlate with eGFR, age, sex, dialysis vintage or target weight.

**Conclusions:** Low levels of UMOD are detectable in patients with end stage kidney failure. There is no evidence of removal of UMOD with hemodialysis. Further evaluation of UMOD as a biomarker of potential kidney recovery after acute injury or transplantation or indicator of preserved residual renal function is worth further investigation.

![Uromodulin Levels Before and After Hemodialysis](Image)

**SA-PO566**

**Is the Donnan Equilibrium Still Intact in High-Volume Hemodiafiltration?**

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**Background:** High convective flow in high-volume hemodiafiltration has raised concerns that intradialytic electrolyte balance might be changed compared to standard HDF, requiring adaptations of dialysate electrolyte prescription. The presence of charged proteins in the blood which are too large to penetrate the dialyzer membrane cause an asymmetric small ion distribution governed by the Gibbs-Donnan equilibrium (GDE). Derivations of GDE in most cases ignore the hydrodynamic drag from transmembrane fluid flow. We studied the effect of this flow by numerical simulations in an extended model.

**Methods:** The Nernst-Planck equation was extended by an advective term taking into account the hydrodynamic transmembrane flow as an additional driving force for ion transport. For the simplest case of two oppositely charged monovalent permeable ions a set of differential equations was derived. This allowed for a numerical calculation of permeable ion concentrations on both sides of the membrane depending on the transmembrane flow speed. The deviation of ion concentrations from their equilibrium values was analyzed for different ion species and concentrations for a large range of transmembrane flow rates.

**Results:** Even in a case of a non-zero convective flow, equilibrium concentrations are already reached a few nm from the inner membrane boundary, thus still within the membrane pores (cf. Fig. 1). These concentrations differ slightly from what is expected from classical Gibbs-Donnan equilibrium. However, in a typical HDF treatment, where transmembrane flow speed is less than 10^(-3) ms^-1 this deviation is less than 6 10^(-4) mmol/L.

**Conclusions:** Even in high volume hemodi follows the transmembrane flow has negligible influence on the equilibrium electrolyte concentrations.

**Funding:** Commercial Support - Fresenius Medical Care Deutschland GmbH

**SA-PO567**

**Noninvasive Assessment of Liver Disease and Outcomes in ESKD**

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**Background:** People with ESKD often exhibit risk factors (diabetes mellitus, obesity and hypertension) for non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH). NAFLD and NASH both associate with increased cardiovascular risk and by 2030 NASH will be the leading cause of cirrhosis. Little is known about prevalence and clinical outcomes of NAFLD and NASH in ESKD. We report updated interim results from this study non-invasively evaluating liver disease in ESKD.

**Methods:** This prospective observational study involves 451 prevalent patients with ESKD receiving dialysis for >3 months at 5 UK kidney units. A FibroScan (Echosens) measured hepatic steatosis using controlled attenuation parametry and fibrosis using transient elastography. Survival analyses were performed using Kaplan-Meier estimates and a Cox regression model for multivariate analysis.

**Results:** Median patient age was 62. 61% of patients were male. 93% had hypertension, 48% diabetes and 63% hyperlipidaemia. 33% had a BMI of greater than 30kg/m2. 27% had suspected NAFLD and 12% suspected NASH. There was increased mortality with suspected hepatic fibrosis grades F2-4 (19.1% vs 2.5% in grades F0-1). Kaplan-Meier survival curves are shown in Figure 1. Mortality in participants with suspected hepatic fibrosis grades F3-4 was significantly increased after adjustment for other predictors of survival (Figure 2).

**Conclusions:** There is significant burden of suspected hepatic steatosis and fibrosis in ESKD. Suspected F3-4 fibrosis is an independent risk factor for mortality in this interim analysis. Strategies to improve liver health in advanced kidney disease may be of benefit.

**Funding:** Commercial Support - Associates of Cape Cod, Inc
SA-PO568
The Relationship Between Myocardial Fibrosis and Physical Activity in Individuals Receiving Hemodialysis

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Background: Individuals with end stage kidney disease receiving haemodialysis have high levels of myocardial fibrosis, which is thought to contribute to their excess cardiovascular burden. In addition, these individuals are physically inactive, which directly associates with high levels of cardiovascular and all-cause mortality. However, the relationship between physical activity levels and myocardial fibrosis has not previously been explored.

Methods: This is a post-hoc analysis of baseline data from the CYCLE-HD trial. Participants wore an accelerometer on the upper arm for 7 days; average steps per day were calculated by dividing the total number of steps by days worn. Global, septal and non-septal native T1 times (a surrogate of myocardial fibrosis) were acquired using cardiac MRI. Spearman’s correlation and multiple linear regression analyses (adjusting for age, gender and diabetes) were performed to investigate associations between steps per day and T1 variables.

Results: Data for 102 participants were included. Mean steps per day were 3180±282. Steps per day had a significant negative correlation with global native T1 (-0.308; P = 0.002), non-septal T1 (-0.287; P = 0.004) and septal T1 (-0.275; P = 0.005). This relationship persisted after adjustment (Table 1).

Conclusions: Increased physical activity defined by average daily step count, associates with lower levels of myocardial fibrosis. Overall the levels of physical activity were low (comparable to levels reported in other studies), however these data indicate that even these levels (below recommended guideline levels) may be beneficial. Longitudinal studies are needed to understand the mechanisms behind these findings.

Table 1. Multiple linear regression showing the association between steps per day, Native T1, Non-septal T1 and Septal T1

<table>
<thead>
<tr>
<th>Steps per day and CMR (HR)</th>
<th>P-value</th>
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<td>Native T1</td>
<td>-0.091</td>
<td>&lt;0.01</td>
<td>Non-septal T1</td>
<td>-0.091</td>
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<tr>
<td>Non-septal T1</td>
<td>-0.091</td>
<td>&lt;0.01</td>
<td>Septal T1</td>
<td>-0.091</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

*There was no significant association between myocardial fibrosis and other variables (age, gender and diabetes) in the regression analyses.

SA-PO569
Assessing Muscle Mass and Radiodensity via Chest CT for Prognostic Insights in Hemodialysis Patients

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Background: CKD often leads to PEW, which in turn contributes to the development of sarcopenia. This condition is strongly associated with increased mortality. Consequently, evaluating muscle mass in HD patients is of significant clinical relevance. However, the relationship between muscle mass measured by chest CT and prognosis for HD patients remains unclear.

Methods: Between January 2015 and December 2019, we conducted a retrospective study involving HD patients in a hemodialysis center. Chest CT scans at T12 level were analyzed using segmentation software to assess SMI and SMD.

Results: A total of 303 patients were included, with a mean age of 55.4±16.6 years and a median follow-up period of 4.6 years. During the follow-up period, 78 deaths occurred. Sex-specific cut-offs of SMI and SMD were determined using maximally selected rank statistics: 96 patients(31.6%) with SMI <30 (male) or <24.35 (female) cm²/m² and 99 patients(32.6%) with SMD <38.61 (male) or <31.44 (female) HU were categorized as having lower SMI and lower SMD, respectively. Patients with lower SMI and lower SMD consistently demonstrated an increased risk of any cause deaths, as evidenced by Kaplan-Meier survival curves. After adjusting for confounding factors using multivariate Cox proportional risk models, lower SMI and lower SMD were independently associated with a higher risk of all-cause mortality and non-cardiovascular mortality. This association persisted in subgroup analyses and competitive risk model. Adding SMI and SMD to the established risk model improved the C-index from 0.78 to 0.82 (P <0.001), with similar results observed in NRI and IDI. Decision curve analysis revealed that the prognostic model incorporating both SMI and SMD yielded the highest net benefit for predicting all-cause mortality.

Conclusions: SMI and SMD measurements derived from chest CT-T12 images provide valuable prognostic information, potentially enhancing the criteria for chest CT use in sarcopenia studies among HD patients.

SA-PO570
Association Between Muscle Quality Measured by Computed Tomography and Valvular and Thoracic Aortic Calcification in Maintenance Hemodialysis Patients

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Background: Extra-coronary calcification (ECC) is independently associated with Cardiovascular disease (CVD). Low muscle mass is known to be related to vascular calcification. We evaluated whether muscle quality measured by computed tomography was associated with the risk of ECC in maintenance hemodialysis (MHD) patients.

Methods: The patients who underwent MHD in our Blood Purification Center from January 1, 2020 to December 31, 2022 were enrolled. Chest computed tomography images were collected and an open-source software 3D Slicer (version 5.0.3) was used to assess muscle quality (by skeletal muscle density, SMD, HU) at L1 level. The whole thoracic aorta calcification scores (TACS) and calcification scores of the 3 segments of thoracic aorta, including ascending thoracic aorta (ATACS), aortic arch (AoACS), and descending thoracic aorta (DTACS) were measured by 3D Slicer. 2-dimensional ultrasonic echocardiography was used to assess the number of calcified valves and patients were divided into 3 groups. We used multivariable linear regression analysis and cumulative logit model respectively to explore relationships between SMD and ECC.

Results: The age of 1076 patients was (57.98±14.49) years old, 59.3% of patients were male and the median dialysis age was 52 (17, 96) months. SMD was significantly negatively associated with TACS [model 1 [adjusted for age and sex]; standardized coefficient β, -0.38 [95%CI, -0.51 — -0.24, P<0.001]; model 2 [adjusted for all factors in model 1 plus body mass index, smoking status, history of drug usage and past history]: β, -0.39 [95%CI,-0.51 — -0.25, P<0.001]; model 3 [adjusted for all factors in model 2 plus primary disease, dialysis vintage and laboratory results (albumin, interleukin-6, uric acid, et al)]: β, -0.44 [95%CI, -0.60 — -0.29, P<0.001]). Similarly, SMD was negatively correlated with ATACS, AoACS and DTACS. Additionally, increased SMD reduced the
risk of cardiac valve calcification (model 1: odds ratio [OR], 0.92 [95%CI, 0.89 — 0.95, P<0.001]; model 2: OR, 0.91 [95%CI, 0.88 — 0.95, P<0.001]; model 3: OR, 0.90 [95%CI, 0.86 — 0.95, P<0.001]).

Conclusions: This is the first study evaluating the association between skeletal muscle quality and ECC in MHD patients. We identified significant negative associations between muscle quality and specific markers of ECC.

Funding: Government Support - Non-U.S.

SA-PO571
Intradialytic Plantar Electrical Stimulation Boosts Mobility and Physical Activity in Frail Patients: A Randomized Controlled Trial
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Background: Frailty is notably pervasive in hemodialysis (HD) patients and contributes to diminished physical activity, poor quality of life, and mortality risk. Our study aimed to assess the efficacy of a targeted intradialytic plantar E-stim intervention to enhance mobility in frail diabetic HD patients.

Methods: Participants randomized into intervention group (IG, n=35) and control group (CG, n=33). IG received plantar E-stim treatment and CG had a non-operational device both for 1 hour with their HD sessions for 12-week period. To assess daily physical activity, participants wore a monitoring pendant for two consecutive days both at the onset of the study and following the 12-week intervention.

Results: The IG and CG showed no significant differences in age, sex, BMI, or frailty rates. Remarkable group x time interaction effects were noted in terms of physical activity (total standing transition: p=0.017; total walking transition: p=0.015) and mobility capacity (total steps: p=0.040) among frail patients. The IG demonstrated notable enhancements in standing (+18.1%, Cohen’s d=0.281; Walking: -23.59%, Cohen’s d=0.365). Mobility capacity decline was less in IG (-3.48%, Cohen’s d=0.048), while CG saw a significant reduction (-52.85%, Cohen’s d=0.644).

Conclusions: This study highlights that intradialytic plantar E-stim substantially enhances both physical activity and mobility, particularly among frail HD patients. Given these findings, it is recommended that E-stim be integrated as an adjunctive measure to routine HD treatment.

Funding: Government Support - Non-U.S.

SA-PO573
Sarcopenia with Central Obesity Is Associated with an Increased Risk of All-Cause Mortality in Maintenance Hemodialysis Patients
Oqing Song,1 Sha Fu,2 Junzhe Chen,1 Xiaohong Wang,1 Yuxin Luo,1 Aiqun Liu,1 Ying Tang,1 Naima Mathew,1 Mathew,1 Heba A. Ibrahim,1 Mincy Mathew,5 Heba M. Ateya,6 Yolezd Zitouni,7 Naima S. Rodriguez,2 Jaewon Beom,2 Fadwa S. Al-Ali,1 Hamad Medical Corporation, Doha, Qatar; 2Department of Surgery, Baylor College of Medicine, Houston, TX.

Background: Sarcopenia, a common condition found in maintenance dialysis (MHD) patients, is known to be linked to higher rates of illness and death. Several studies have indicated that central obesity can predict cardiovascular mortality in MHD patients. However, there is a knowledge gap regarding the impact of sarcopenia with central obesity on the survival of MHD patients.

Methods: This retrospective, observational, cohort study enrolled MHD patients on Sept 1-31, 2022. The Asian Working Group for Sarcopenia criteria and the waist hip rate (WHR) were used to diagnose sarcopenia with central obesity. Additionally, demographic, body composition, clinical laboratory and body composition by bioimpedance were collected. The primary outcome is all-cause mortality with MHD patient.

Results: A total of 59 MHD patients were included in this study, specifically, the prevalence of sarcopenia was 44.1% and the prevalence of sarcopenia with central obesity was found to be 49.2%. Over a median follow-up period of 214 days, a total of 5 (8.5%) deaths occurred. Univariate Cox regression analyses revealed several factors associated with an increased risk of mortality, including age (HR: 0.055; p=0.098), 5-time chair stand test (HR: 0.044; p=0.029), and severe sarcopenia with central obesity (HR: 2.651; p=0.001). However, in the multivariate analysis, only severe sarcopenia with central obesity remained independently associated with all-cause mortality (HR: 2.734; p=0.015), indicating that severe sarcopenia with central obesity was linked to an increased risk of all-cause mortality in MHD patients.

Conclusions: It is crucial to consider the presence of central obesity when evaluating the correlation between sarcopenia and adverse outcomes in individuals undergoing dialysis.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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SA-PO574

Sarcopenia Prevalence According to Short Daily and Conventional Hemodialysis Regimens: Preliminary Findings from the SARC-HD Study

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Background: Sarcopenia is a skeletal muscle disorder characterized by the loss of muscle strength, muscle mass, and performance, and is highly prevalent in patients undergoing hemodialysis (HD). Despite the increasing interest and clinical recognition, there is little understanding of how sarcopenia evolves across users of different modalities of HD regimens. Therefore, we investigated the prevalence of sarcopenia according to short daily and conventional hemodialysis regimens.

Methods: This cross-sectional multicenter study included eight dialysis units in Brasilia, Brazil, and enrolled adult patients undergoing HD for ≥3 months. Muscle strength was evaluated by handgrip strength and five-time sit-to-stand test. Call circumference was used to estimate muscle mass, and physical performance through the 4-on-gait speed test. Stages of sarcopenia were defined according to the revised European Working Group on Sarcopenia in Older People. Patients were stratified according to the hemodialysis regimen, short-daily (5 to 6 sessions/week, duration ≥23h) and conventional (3 sessions/week, duration ≤4h).

Results: The study enrolled 258 patients (66% male, 58.3 ± 0.9 years, 45% on conventional HD. The overall prevalence of probable sarcopenia (low muscle strength), sarcopenia, and severe sarcopenia was 26.7%, 26.7%, and 8.5%, respectively. No significant differences were found in the prevalence of sarcopenia, low muscle mass, and low physical performance between patients undergoing short daily and conventional HD (30.3% vs. 22.4%; P > 0.05). The low muscle strength was significantly higher in patients undergoing short daily compared to those receiving conventional HD (19.0% vs. 32.0%; P = 0.024).

Conclusions: Our multicenter study revealed a high prevalence of sarcopenia; however, no significant difference was observed in prevalence between different HD regimens. Our findings on short daily regimens had a higher prevalence of low muscle strength. This highlights a potential association between the HD regimen and the primary manifestation of sarcopenia, precisely muscle strength.

SA-PO575

Body Composition and Coronary Artery Calcification in a Prospective Hemodialysis (HD) Cohort: A Substudy of the NIH THYROID-HD Trial

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Background: Patients with kidney failure on hemodialysis (HD) are at high risk of sarcopenia obesity, highlighting the need for effective nutrition and exercise strategies to improve long-term outcomes. This post-hoc analysis of the PEDAL and CYCLE-HD studies aimed to 1) determine the clinical utility of fat tissue index (FTI) and lean tissue index (LTI) in comparison to body mass index (BMI) and 2) assess the effect of a 6-month intradialytic exercise intervention on FTI and LTI compared to usual care.

Methods: BMI, FTI and LTI were primary secondary endpoints in both the PEDAL and CYCLE-HD trials. BMI was classified as per WHO definitions. FTI and LTI were determined by Bioelectrical Impedance Analysis (BIA) and classified as per the MONDO study, that found an FTI of 4.15km2 and an LTI of 15-20kg/m2 were associated with better survival.

Results: Across both studies, 298 participants had BIA measurement at baseline, with 209 at baseline and 6-months. Mean age was 58±15 years, 65% male, median HD vintage 1.3 years (IQR 0.5-3.4) and mean BMI of 28.3±6.3kg/m2. BMI correlated with FTI (r=0.79; p<0.0001). Of those with healthy BMI (n=198), 17% were over-nourished by BMI (FTI>15kg/m2) and 74% under-nourished (FTI<15kg/m2). Conversely, among those with an FTI of 4.15km2, 14% were categorised as overweight or obese by BMI. There was no significant correlation between BMI and LTI, 24% had BMI <30kg/m2 and LTI<15kg/m2 (sarcopenic obesity); only 16% had both FTI>4.15km2 and an LTI of 15-20kg/m2. With intradialytic exercise, there was no significant difference between the groups in change over 6 months for LTI (0.33, CI -1.08-0.41; p=0.4) or FTI (0.16, CI -0.69-1.00; p=0.7), regardless of compliance.

Conclusions: This study highlighted issues of body composition misclassification using conventional BMI cut-offs in HD patients. Only a minority of patients had both LTI and FTI within the range associated with best survival. The majority of patients had hidden sarcopenia with nearly 75% with normal BMI being sarcopenic. 6-months of intradialytic exercise did not improve body composition, suggesting alternative interventions are required to target fat and lean tissue mass and enhance patients’ survival.

SA-PO576

Body Composition and Its Response to Intradialytic Exercise in Patients Undergoing Maintenance Hemodialysis

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Background: The association between muscle strength and outcome in chronic kidney disease is well recognized and sarcopenia is a major risk factor for mortality. The primary manifestation of sarcopenia, precisely muscle strength. This highlights a potential association between the HD regimen and the primary manifestation of sarcopenia, precisely muscle strength.

Results: The study enrolled 258 patients (66% male, 58.3 ± 0.9 years, 45% on conventional HD. The overall prevalence of probable sarcopenia (low muscle strength), sarcopenia, and severe sarcopenia was 26.7%, 26.7%, and 8.5%, respectively. No significant differences were found in the prevalence of sarcopenia, low muscle mass, and low physical performance between patients undergoing short daily and conventional HD (30.3% vs. 22.4%; P > 0.05). The low muscle strength was significantly higher in patients undergoing short daily compared to those receiving conventional HD (19.0% vs. 32.0%; P = 0.024).

Conclusions: Our multicenter study revealed a high prevalence of sarcopenia; however, no significant difference was observed in prevalence between different HD regimens. Our findings on short daily regimens had a higher prevalence of low muscle strength. This highlights a potential association between the HD regimen and the primary manifestation of sarcopenia, precisely muscle strength.

Changes in Modified Creatinine Index Following Bone Fractures in Patients Undergoing Maintenance Hemodialysis

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Background: Previous research has shown associations between lower skeletal muscle mass and a subsequent increased risk of bone fractures in hemodialysis patients. However, limited data exist on whether fractures lead to a loss of muscle mass in this population.

Methods: We analyzed a historical cohort study of 2,292 patients undergoing maintenance hemodialysis in Japan. We compared longitudinal changes in modified creatinine index (mCI) as a surrogate marker of muscle mass in a subcohort of patients who experienced fractures during the 7-year study period and those who did not, matched by propensity score at 1:3. Follow-up started immediately prior to the occurrence of fracture in the fracture group and at study enrollment in the non-fracture group.

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Results: During a median follow-up of 5.4 years (IQR, 2.5-7.0 years), 113 patients experienced clinical fracture. Among the 164 retained patients, 98 patients had data on mCI over time. We measured the mean CV for hs-cTnI values was 19.6% (2%-67%) with significant difference between URI and patients had values higher than 50 ng/L (6 males, 1 female). The highest mean value was 23.8 ng/L – 60% higher than URI. More male patients had hs-cTnI levels in the highest quartile on chronic HD without signs of ACS with mean value of 30.1 ng/L out of all the patients. In total, 3 to 5 values per patient depending on the dialysis regiment. Upper reference limit was used to reveal the association between the serum syndecan-1 concentration in pre-HD and hypotension. Age, sex, and BNP were included in the model as covariates to adjust for confounders. Results: In total, 92 patients were enrolled. The median HD period was 40 months. The most common primary illness was diabetic nephropathy. In pre-HD, the median serum syndecan-1 concentration was 67.7 ng/mL. In post-HD, the median serum syndecan-1 concentration was 98.3 ng/mL. According to the general standardized estimating equations (GEE) model adjusted for age, sex, BNP, and amount of water removed per hour, no association was found between serum syndecan-1 concentration in pre-HD and appearance of intradialytic hypotension (odds ratio (OR): 1.001, P<0.741). However, a GEE model using the same adjustment factors showed that the greater the amount of change in serum syndecan-1 concentration before and after HD, the more complications appeared (OR: 1.005, P<0.013). The study revealed that the quantitative assessment of the endothelial glycoalyx injury by measuring the concentration of serum syndecan-1 during HD is associated with intradialytic hypotension. Results: A total of 170 (52.3%) patients died during the observation period. When adjusting for age, sex, diastolic blood pressure, diabetes mellitus and cardiovascular disease, the patients with higher log GNR/IL-6 had a significantly lower mortality risk (Hazard ratio [HR]: 0.58, 95% CI: 0.41-0.82; P=0.002). Higher log GNR/CRP (HR: 0.74, 95% CI: 0.62-0.91, P=0.006) and higher log GNR/PTX3 (HR: 0.46, 95% CI: 0.22-0.93, P=0.03) are also related to lower mortality risk.

Conclusions: The ratio of GNR to plasma inflammatory proteins levels, especially the GNR/IL-6 ratio, may be a useful biomarker for assessing mortality risk in hemodialysis patients. Nutritional risk screening is expected to improve the mortality prediction power of inflammatory biomarkers.

SA-PO580

Endothelial Glycoalyx Injury due to Hemodialysis Induces Intradialytic Hypotension

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Background: Hemodialysis (HD) plays a pivotal role in replacing renal function for patients with end-stage renal failure. When the patients undergo hemodialysis, HD complications, such as intradialytic hypotension and arrhythmia, are inevitable. The endothelial glycoalyx injury, which exists on the inner surface of vascular endothelial cells and maintains vascular homeostasis, has been suggested to be impaired by hemodialysis. However, it is unclear whether the endothelial glycoalyx injury is associated with HD complications.

Methods: We enrolled the patients who underwent outpatient hemodialysis at Gifu Seirya Hospital between April 2022 and July 2022 (346 hemodialysis sessions). Patients aged <20 years. This single-center retrospective study evaluated the association between syndecan-1, an endothelial glycoalyx dysfunction marker, and complications of hemodialysis. Complication events, as the primary outcome, were defined as intradialytic hypotension, arrhythmia, and subjective symptoms such as chest pain, nausea, general malaise, and leg cramps during HD. Patients undergoing outpatient maintenance HD at Gifu Seirya Hospital underwent blood tests at the beginning of each month. The GEE model revealed the association between the serum syndecan-1 concentration in pre-HD and hypotension. Age, sex, and BNP were included in the model as covariates to adjust for confounders.

Results: In total, 92 patients were enrolled. The median HD period was 40 months. The most common primary illness was diabetic nephropathy. In pre-HD, the median serum syndecan-1 concentration was 67.7 ng/mL. In post-HD, the median serum syndecan-1 concentration was 98.3 ng/mL. According to the general standardized estimating equations (GEE) model adjusted for age, sex, BNP, and amount of water removed per hour, no association was found between serum syndecan-1 concentration in pre-HD and appearance of intradialytic hypotension (odds ratio (OR): 1.001, P<0.741). However, a GEE model using the same adjustment factors showed that the greater the amount of change in serum syndecan-1 concentration before and after HD, the more complications appeared (OR: 1.005, P<0.013). The study revealed that the quantitative assessment of the endothelial glycoalyx injury by measuring the concentration of serum syndecan-1 during HD is associated with intradialytic hypotension.

SA-PO581

Variability of Troponin I Levels in Patients on Chronic Haemodialysis over One Week

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Background: Patients undergoing chronic haemodialysis (HD) have remarkably higher risk for major adverse cardiovascular events. Haemodynamic and volume changes between dialysis sessions lead to constant cardiac burden and strain which could increase cardiac troponin levels without signs and symptoms of an acute coronary syndrome (ACS). This makes it more difficult to diagnose acute disorders. Primary goal was to evaluate the basal troponin levels of HD patients on their first weekly treatment (the highest volume overload) and observe value oscillations during the week.

Methods: Data of 67 patients (24 female, 43 male) undergoing chronic HD programme at Dubrava University Hospital were collected after acquiring informed consent. Troponin levels were measured multiple times during the period of one week, using Beckman Coulter High-Sensitive Troponin I (hs-tTnI) assay - before every HD session, after the first session that week and the day after the first session, what resulted with 3 to 5 values per patient depending on the dialysis regiment. Upper reference limit (URI) for hs-tTnI is <14.9 ng/L for female patients and <19.8 ng/L for male patients. The results: Before the first session, mean hs-tTnI value was 5.9 ng/L (95% CI: 2.5 - 21.2, Lower 95% CI: 2.5 - 21.2, n=60; 1.77 ng/L, P>0.05) and the lowest before the last session in the week (25.8 ng/L). A 7.7% peak rise in mean value was recorded after one dialysis session. The coefficient of variation (CV) was measured for each patient and the range for hs-tTnI levels was 19.6% - 67% with significant difference between female (13.5%) and male (23%) patients.

Conclusions: Our results show that hs-tTnI levels were elevated in 54% of patients on chronic HD without signs of ACS with mean value of 30.1 ng/L out of all the patients. In total, 3 to 5 values per patient depending on the dialysis regiment. Upper reference limit was used to reveal the association between the serum syndecan-1 concentration in pre-HD and hypotension. Age, sex, and BNP were included in the model as covariates to adjust for confounders.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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SA-PO582
Comparative Analysis of Cardiovascular Performance in Hemodialysis and Heart Failure Patients
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Background: Patients on hemodialysis (HD) exhibit significant impairment in cardiovascular functional capacity that may be comparable to those with non-CKD associated heart failure. The problem is that to-date, no studies have directly compared cardiovascular functional differences between patients on HD compared with non HD patients with heart failure with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). We hypothesized that patients on HD exhibit unique exercise ventilatory response patterns compared to those with HFrEF and HFpEF.

Methods: We conducted a cross-sectional analysis of patients on thrice-weekly HD versus HFpEF (EF ≥40%) and HFrEF (EF <40%) patients who underwent cardiopulmonary exercise test (CPET) at Indiana University. A total of 90 patients (age=55 [13] years; n=30 per group) were included in this analysis.

Results: There were no group differences in age, sex, or diabetes (all p>0.05). The HD group had a higher prevalence of hypertension (p<0.001), lower hemoglobin (Hgb; p<0.001), and lower beta blocker (BB) use (p<0.001) compared to both HFrEF and HFpEF, and a higher proportion of smokers compared to the HFrEF group (p=0.017). After adjusting for these covariates, peak oxygen uptake (VO2Peak) was lower in the HD (12.9 [12.0-14.1] mL/kg/min) and HFpEF (13.0 [12.2-14.3] mL/kg/min) groups compared to HFrEF (16.3 [15.5-17.6] mL/kg/min; p=0.028). Percent of heart rate reserve (% HRR) was lower in the HD group (37.8 [31.6-39.8]; p<0.01) compared to both HFrEF (57.0 [20.9-39.1]) and HFpEF (61.0 [54.8-63.0]). Additionally, VE/VCO2 slope was lowest in the HD group compared to HFrEF and HFpEF (p<0.001). Hg, smoking, VE/VCO2 slope, and %HRR were significantly associated with VO2Peak in the HD group; this difference with sex, race, VE/VCO2 slope, and %HRR for HFpEF, and sex, BB use, and %HRR for HFpEF.

Conclusions: Patients on HD exhibit similar declines in VO2Peak as those with HFpEF without significant CKD undergoing evaluation for heart transplant, exemplifying the dramatic effects of CKD on cardiovascular health. Chronotropic incompetence and impaired skeletal muscle reserve may be predominant drivers of impaired VO2Peak in HD patients, while impaired lung capacity and cardiac output may be predominant drivers in patients with HFrEF and HFpEF.

SA-PO584
Cardiac Autonomic Innervation Is Decreased in Postmortem Tissue from Individuals with ESKD Compared With Those Without
Qandeel H. Soomro, Valeria Mezzano, Navneet Narula, David M. Charytan. New York University Grossman School of Medicine, New York, NY.

Background: Cardiac innervation changes can lead to an imbalance in neural activation and arrhythmias. Although described in other disease states, changes in cardiac innervation have not been studied in ESKD.

Methods: Age and DM matched cases with ESKD and controls without ESKD (10/group) who underwent autopsy at NYU-affiliated hospitals (2012-2020) were identified. Demographic and CV history was collected from autopsy and medical records. Case and controls were selected based on availability of LV anterior wall sections without extensive fibrosis in the area of interest. We performed H&E staining, and immunohistochemistry for S100 (all nerves), Tyrosine hydroxylase (TH, sympathetic nerves) and trichrome staining for fibrosis. Staining and fibrin were quantified within regions of interest in the epi-, mid- and endocardial ¼ as density per mm² (primary outcome) or fibrin %.

Results: Mean age: ESKD 66.7 vs. controls 65.6 y; sex: 50% female in both groups and DM was (80% in both groups), whereas 60% were Black in the ESKD group vs. 40% in the control group. All ESKD patients had ischemic heart disease vs. with 30% of controls. Most common cause of death: myocardial infarction (50% in ESKD, 30% controls) followed by pump failure. Overall nerve density was lower in ESKD compared to controls: S100 density in the mid (63.97/mm² vs. 106.7/mm², P=0.04) and endocardial (62.6/mm² vs. 203.2/mm², P=0.003) thirds. Sympathetic nerve density was lower in dual-stained sections, particularly in the endocardial region (65.9/mm² vs. 180.0/mm², P=0.002). Fibrosis was higher in those with ESKD in all regions (p<0.009 vs. 0.005, mid=0.024 vs. 0.006, endo=0.033 vs. 0.006, P<0.05 for all). Fibrotic area was not correlated with nerve density (overall and for sympathetic nerves) in regions of interest (P>0.05 for all).

Conclusions: Reduced overall nerve density and sympathetic innervation observed in ESKD. Further studies are needed to evaluate cardiac innervation patterns in ESKD and its link to arrhythmia.

Funding: Private Foundation Support

Figure: Top panel: S100 positive and dual-positive nerve density: the sub-epicardial region (a), mid (b), and sub-endocardial regions (c, f).
SA-PO585

Automatic Detection of Intradialytic Paroxysmal Atrial Fibrillation and Flutter in Single-Lead ECG

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Background: Intradialytic paroxysmal atrial fibrillation and flutter (AF/AF) can result in hemodynamic instability and suboptimal dialysis dose. To achieve appropriate prevention and management of intradialytic paroxysmal AF/AF, the first step is precise detection during hemodialysis session. Herein, we developed a Transformer-based model to automatically segment AF/AF in single-lead electrocardiography (ECG) by self-supervised learning and masked signal modelling.

Methods: To develop a model, we used 11 open source databases containing 5,684-hour ECG signals from 2,017 patients. To validate a model, intradialytic ECG signals were retrieved from 4-hour 30 hemodialysis sessions at Seoul National University Hospital. AF/AF was defined as a ≥10-second duration, and the Swin Transformer model with wide window-size was adopted as a main architecture. The model performance was evaluated with F1 score.

Results: The model achieved F1 scores of 0.9612 and 0.9731 in segmenting AF/AF and other rhythms, respectively. Throughout cross-database, F1 scores ranged between 0.8889 and 0.9968 depending on the prevalence of AF/AF. Ablation analysis identified that the performance was attributable to pretraining with random signals and unlabeled database. The present model was superior to previous models in detecting AF/AF particularly when training and testing databases were matched. When applying to intradialytic ECGs, the model showed favorable performance in segmenting AF/AF areas.

Conclusions: The model with self-supervised learning and masked signal modelling maintains robust performance in various databases, which will help automatic detection of intradialytic paroxysmal AF/AF.

SA-PO586

Clearance of Cardiac Troponins Depends on Hemodialysis Mode: A Randomized Cross-Over Trial

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Background: Diagnosis of acute myocardial infarction (AMI) is difficult in hemodialysis (HD) patients as they less likely present typical features, thus, diagnosis relies on biomarkers. There is inconclusive data on cardiac Troponin (cTn) kinetics during HD without considering membrane characteristics.

Methods: We included prevalent, clinically stable HD patients and measured cTnI (cTnI and cTnII) concentrations before, during and after HD with different modalities (low-flux HD, high-flux HD, hemodialfiltration [HDF] and medium cut-off (MCO)-HD). Treatment characteristics were standardized and similar between groups. The primary aim was to compare relative changes of cTnI from baseline to after 1 hour of HD (ΔcTnI) for different dialysis modalities with secondary outcomes including absolute and relative changes of cTnI during and after HD, using linear mixed models adjusted for subjects, sequence, period and treatment.

Results: Of 20 patients, one patient was excluded because of NSTE-AMI, thus, 19 were included in final analysis. Of those 47.4% were female (mean age 65.5a±13.4 years, median dialysis vintage 19 months [min. 3, max. 165]). Different ΔcTnI were observed for MCO (least square mean [LSM] -21.9 ± 2.7% vs. low-flux [-22 ± 2.7%, p<0.001] and MCO vs. high-flux (LSM -6.8 ± 2.7%, p=0.001) with no difference for MCO vs. HDF (LSM -21.2 ± 2.7%, p=0.81). Similar results were observed post HD. For absolute changes, LSM for MCO were -21.2 ± 3.2 pg/mL, -6.4 ± 3.2 pg/mL for high-flux, -20.2 ± 3.2 pg/mL for HDF treatment and +2.3 ± 3.2 pg/mL for low-flux HD after one hour. There was no clear trend in cTnI kinetics.

Conclusions: Standard diagnostic AMI algorithms cannot be applied during HD. A Δ of ≥20% of cTnI, recommended by the SONG-HD MI group, occurs without evidence of ACS when MCO-HD or HDF are applied.

SA-PO587

Serum Endocan as a Risk Factor for Aortic Stiffness in Patients on Maintenance Hemodialysis

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Background: Endocan is secreted by the activated endothelium and plays a central role in inflammation and endothelial dysfunction, angiogenesis and vascular smooth muscle cell proliferation, it is associated with cardiovascular disease. This cross-sectional study aimed to assess the relationship between serum endocan levels and carotid–femoral pulse wave velocity (cfPWV) in patients on maintenance hemodialysis (HD).

Methods: Blood samples were collected from 122 HD patients. Serum endocan concentrations were measured with an enzyme-linked immunosorbent assay kit. Aortic stiffness was defined as a cfPWV of more than 10 m/s, while cfPWV values ≤10 m/s defined the control group, according to the ESH-ESC 2018 guideline.

Results: Of the 122 HD patients, aortic stiffness was diagnosed in 53 (43.4%) and higher percentages of diabetes (p < 0.001), hypertension (p = 0.030), were of older age (p = 0.007) and had higher systolic blood pressure (p = 0.011) and endocan levels (p < 0.001) in those with aortic stiffness than those without. After adjusting for factors significantly associated with aortic stiffness by multivariate logistic regression analysis, serum endocan (odds ratio [OR]: 1.566, 95% confidence interval [CI]: 1.224–2.002, p = 0.001), age (OR: 1.040, 95% CI: 1.001–1.080, p = 0.045), and diabetes (OR: 4.067, 95% CI: 1.532–10.798, p = 0.005) were independently associated with aortic stiffness in patients with chronic HD. Multivariable forward stepwise linear regression analysis also confirmed that the logarithmically transformed endocan level (β = 0.405, adjusted R² change = 0.152, p < 0.001) was an independent predictor of cfPWV values. The area under the receiver operating characteristic (ROC) curve predicting aortic stiffness by serum endocan level was 0.713 (95% CI: 0.620–0.806, p < 0.001).

Conclusions: Serum endocan level positively correlates with cfPWV and is also an independent predictor of aortic stiffness in maintenance HD patients.

SA-PO588

The Association Between Adipokines and Cardiovascular (CV) Risk Factors in Hemodialysis Patients

Sarwary Khan,1 Peter N. Van Buren. 1The University of Texas Southwestern Medical Center, Dallas, TX.

Background: Non-traditional risk factors in cardiovascular (CV) disease among hemodialysis (HD) patients include mineral bone disease and extracellular volume overload. Adiponectin is an adipokine that has an inverse relationship with CV disease in the general population, but studies in HD patients show conflicting results regarding its association with CV morbidity and mortality. We explored associations between adiponectin and leptin with various CV risk factors in a subset of an HD cohort.

Methods: We conducted a cross-sectional study of hypertensive HD patients. We measured adiponectin and leptin with ELISA from frozen plasma obtained in a midweek treatment. BP was measured per HD protocol. And we obtained pre and post HD measurements of ECV with bioimpedance spectroscopy. We conducted Pearson correlation and multiple linear regression analysis to determine associations between adipokines and other clinical variables.

Results: There were 24 participants who had adiponectin levels (mean 12238 [504] ng/mL) with 58% men, 58% Black, and 50% with diabetes. There were no differences in adiponectin based on sex, race or diabetes. Adiponectin correlated negatively with fat free mass (r=−0.51, p=0.02) and dry weight (r=−0.44, p=0.03). Leptin correlated positively with

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO589

Association of Bioimpedance Parameters with Changes in Blood Pressure During Hemodialysis: A Secondary Analysis of the Frequent Hemodialysis Network (FHN) Daily Trial

Enass Saved,1,2 Yousef M. Farag,1 Katherine S. Ravi,1,2 Glenn Cerrit,4 Finnian R. McCausland,1,2 Brigham and Women’s Hospital, Boston, MA;1 Harvard Medical School, Boston, MA;1 Bayer US, New Jersey, NJ; Stanford School of Medicine, Stanford, CA.

Background: Intradialytic hypertensive (IDHyper) affects 5-15% of patients and is associated with cardiovascular and all-cause mortality. Hypervolemia is thought to be a major etiological factor, yet the association of objective measures of volume with IDHyper is not well described.

Methods: In post hoc analyses of the FHN Daily Trial (n=234), using data from baseline, 1, 4, and 12 months (n=800), random effects regression was used to assess the association of bioimpedance measures of volume and general health (vector length and phase angle) with post-HD SBP (continuous) and any increase in SBP (categorical) from pre- to post-HD. Models were adjusted for randomized group, age, sex, race, BMI, vascular access, HD vintage, hypertension, heart failure, diabetes, residual urea clearance, pre-HD SBP, hemoglobin, phosphorus, and eKt/V.

Results: Mean age was 50 ± 14 years; 39% were female; 43% were Black. Shorter vector length (per 50 Ωm) was associated with higher post-HD SBP (3.1 mmHg; 95% CI 2.0, 4.2). Fig. 1 and higher odds of IDHyper (OR 1.64; 95% CI 1.13, 2.39). The lowest tertile of vector length (vs. highest) was associated with higher post-HD SBP (6.3 mmHg; 95% CI 3.9, 9.3) and a trend toward higher odds of IDHyper (OR 2.09; 95% CI 0.81, 5.35). Narrower phase angle (per 1 degree) was associated with higher post-HD SBP (1.0 mmHg; 95% CI 0.3, 1.6), and higher odds of IDHyper (OR 1.33; 95% CI 1.03, 1.72). The lowest tertile of phase angle (vs. highest) was associated with higher post-HD SBP (5.5 mmHg; 95% CI 3.2, 8.4) and higher odds of IDHyper (OR 2.74; 95% CI 1.11, 6.76).

Conclusions: Bioimpedance measures of volume status are independently associated with higher post-HD SBP and risk of IDHyper. Incorporation of bioimpedance measurement at individual HD sessions may help identify a subgroup of patients at risk of IDHyper.

Funding: NIDDK Support

Table 1: Linear regression (univariate and multivariate) analyses using plasma adiponectin as the outcome

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Univariate</th>
<th>Model 1</th>
<th>Model 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin (mg/L)</td>
<td>0.14</td>
<td>0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Average Sys BP</td>
<td>0.14</td>
<td>0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Sync (HPL Type I)</td>
<td>0.13</td>
<td>0.12</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI</td>
<td>0.15</td>
<td>0.15</td>
<td>0.17</td>
</tr>
</tbody>
</table>

Mean vector length and mean post-HD SBP

SA-PO590

Use of Novel and Conventional Cardiac Biomarkers to Assess Cardiovascular Risk in Hemodialysis Patients

Zachary J. Neronha,1 Andy Chau, Frank J. O Brien. Washington University in St Louis School of Medicine, St Louis, MO.

Background: Hemodialysis patients experience greatly increased morbidity and mortality. Although the underlying etiology is not completely understood, volume overload likely plays an important role given their elevated risk of cardiovascular disease and especially heart failure. Biomarkers are commonly used to clinically assess volume status in cardiology patients, but cardiac biomarker use in dialysis patients is complicated by an incomplete understanding of biomarker clearance during dialysis and the complex interplay of renal and cardiac causes of volume overload. Here, we investigate a panel of conventional and novel cardiac biomarkers in a group of hemodialysis patients categorized by their baseline ejection fraction.

Methods: We performed a descriptive, prospective cohort study utilizing a group of hemodialysis patients at the Chromalloy American Kidney Center, an outpatient hemodialysis center in St. Louis, MO serving approximately 150 ESRD patients. Study enrollment was randomized, and consisted of 35 patients separated into 3 groups with ejection fractions <40%, 40-50%, and >50% based on a recent echocardiogram. The mean age was 62 and 94% were African American. Pre-dialysis blood was drawn to measure NTproBNP, high-sensitivity troponin T (hsTnT), galectin-3, growth differentiation factor-15 (GDF-15), and soluble ST2 (sST2).

Results: Randomization produced a distribution of patients across the cohorts that was relatively equivalent in age, ethnicity and gender and differed with respect to EF. Preliminary results suggest that one cohort experienced increased novel cardiac biomarker expression. Patients with a lower ejection fraction had biomarker expression more suggestive of volume overload than those with preserved ejection fraction. Those with an EF of ≥50% also had a high level of cardiac biomarker expression. More study is needed to evaluate how cardiac biomarker data varies with volume optimization, and any predictive value it may have for major adverse cardiovascular events. We therefore plan to follow this patient cohort for an additional year to assess any changes in biomarker expression, future adverse events, and the impact of volume optimization on biomarker expression.

Funding: NIDDK Support

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NTproBNP</td>
<td>0.13</td>
<td>0.016 - 0.404</td>
<td>0.88</td>
</tr>
<tr>
<td>hsTnT (IU/mL)</td>
<td>0.32</td>
<td>0.078 - 0.005</td>
<td>0.026</td>
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</table>

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

Underline represents presenting author.
SA-PO592

The CompAct-HD Trial Reports an Acute Complement Activity-Associated Inflammatory Response Within 15 Minutes of Starting Hemodialysis

Andy Herbert,1 Duha Ilyas,2 Elizabeth A. Blackburn,1 Leonard Ehab,2 Jennifer Mackie,3 Sandip Mitra,4 Invizius Ltd, Motherwell, United Kingdom; 5Manchester Foundation Trust, Manchester, United Kingdom.

Background: It is well established that kidney patients experience aberrant complement pathway activation. A heightened inflammatory state is thought to contribute to excess cardiac deaths and cardiovascular events in those undergoing hemodialysis (HD). The aim of the CompAct-HD trial is to characterize complement activation and biomarker response to blood-membrane-circuit interaction during HD.

Methods: Six timed intradialytic blood samples were collected in 300 HD patients during a standard treatment with ultrapure water and high flux membranes. Complement activity potential was determined from timepoint 1 and inflammatory biomarkers from timepoints 2 to 6. Highly multiplexed assays enabled us to determine 60 biomarkers of complement activation and inflammation from a single blood sample.

Results: The 6 blood samples for each patient revealed changes in inflammatory biomarkers within 15 minutes (T3, sCD40L, panel A) of starting dialysis. There was a wide range in the magnitude of this response between individuals. Most biomarker levels increased, peaking during the first hour of dialysis and then fell; not always to the level at the start of dialysis. Interrogating the data for sCD40L, to remove patients with Alternative Pathway activity in the first and second quartile showed that patients with complement activity above the median experienced a larger median inflammatory response at all time points (panel B).

Conclusions: Patients with an elevated complement activation potential experienced an exaggerated acute intradialytic inflammatory response within 15 mins of HD treatment, which did not always resolve to baseline by the end of the dialysis session.

Funding: Commercial Support - Invizius Ltd

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SA-PO593

Immune Response of Heterologous vs. Homologous Prime-Boost Regimens with Adenoviral Vectored and mRNA COVID-19 Vaccines in Immunocompromised Patients

Chang Chu, Bernhard K. Krämer, Berthold Hocher. Universitätshospital Mannheim, Mannheim, Germany.

Background: Due to rare but major adverse reactions to the AstraZeneca adenoviral ChAdOx1-nCoV-19 vaccine (ChAd), German health authorities recommended adults under 60 who received one dose of ChAd, to receive a second dose of the BioNTech mRNA BNT162b2 vaccine (BNT) as a booster. Studies in the general population suggest an enhanced efficacy of the heterologous (ChAd-BNT) compared to the homologous (BNT-BNT) vaccination regimen. However, an analysis of the efficacy in patient populations with a high risk of severe COVID-19 due to acquired immunodeficiency is still missing.

Methods: We therefore compared both vaccination regimens in healthy controls, patients on dialysis and patients with rheumatic diseases concerning the humoral and cellular immune response.

Results: The humoral and cellular immune response differed substantially in healthy controls compared to patients with acquired immunodeficiency. Overall, the most significant differences between the two immunization regimens were found in neutralizing antibodies. These were higher after a heterologous immunization. Healthy controls responded well to both vaccination regimens. However, the formation of neutralizing antibodies was more pronounced after a heterologous immunization. Dialysis patients, on the other hand, only developed an adequate humoral and particularly cellular immune response after a heterologous immunization. Rheumatic patients also - to a weaker extent - compared to dialysis patients - benefited from a heterologous immunization.

Conclusions: In conclusion, the heterologous COVID-19 vaccination regimens (ChAd-BNT) seem to have an advantage over the homologous vaccination regimens, especially in immunocompromised patients such as patients with end-stage kidney disease treated with hemodialysis.

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SA-PO594

Clinical and Biological Profile and Factors Associated with High Blood Lead Levels in Chronic Hemodialysis Patients in a Western French Guiana Hospital Center

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Background: Lead is toxic to the body. Its chronic intoxication combines various clinical and biological disorders that can be life-threatening. In French Guiana, lead poisoning is particularly worrying, as the incidence rate is nearly sixty times higher than in metropolitan France. In chronic hemodialysis patients, lead levels are often higher and can lead to several adverse consequences. Hence, the interest of this study, which is to describe the clinical and biological characteristics of chronic hemodialysis patients with high blood lead levels and to identify the associated factors to draw attention to its screening and the prevention of its complications.

Methods: Descriptive and analytical cross-sectional study that included 65 patients on chronic conventional hemodialysis: with an annual biological assessment in December 2022, including a serum lead assay. The outcome was the notion of hyper lead level, defined by a lead level > 85 µg/l. We described the clinical, biological, and dialytic parameters of patients with hyper lead levels and in logistic regression, we identified the factors that are correlated according to a significance threshold P<0.05.

Results: In total, 54% of patients had hyper lead levels, of which 2/3 were female. They were older, with an average age of 62. No patients had occupational exposure to lead. 94% were hypertensive and half were diabetic. 1/4 had anaemia and all had resistance to erythropoietin. Their ferritin levels were slightly lower, with an average of 721 µg/L. The mean albumin was 30 g/l, pre-albumin was 28 g/l, the mean parathyroid hormone was elevated at 1355 ng/ml, NT-pro BNP at 9144 ng/ml. The mean CRP was 10.8 mg/L. They had collapsed residual diuresis and natriuresis with averages of 150 ml and 12 mmol/24 hours, respectively. There was a significant positive correlation between elevated BLL and young age and negative correlation with female sex, low serum albumin, prealbumin, protein and ferritin levels, and collapsed residual diuresis.

Conclusions: High blood lead levels are common in the Guayanese chronic hemodialysis population in which it is correlated with female sex, malnutrition, iron deficiency and residual poor renal function and probably with resistance to erythropoietin treatment. It is necessary to screen in at-risk populations to prevent complications associated with it.
SA-PO595
Validity and Adequacy of Animal Models in Haemodialysis Research: A Systematic Review

Background: With the worldwide dialysis population growing rapidly, there is an urgent need for haemodialysis (HD) innovations. However, before novel HD technologies can be implemented, extensive preclinical testing is required. Currently, there is no consensus on the most suitable animal model (species, type and validation of kidney injury etc.) for HD innovation research, nor are there gold standards for reporting efficiency outcomes.

Methods: This review, registered in PROSPERO (CRD42022307144), involved a systematic search in PubMed and Embase for relevant studies up to February 4th 2022. After removing duplicates, 5723 abstracts were screened for eligibility by three independent reviewers. Inclusion was based on publication of a HD intervention in any animal model with adequate kidney failure. Data from individual reports were subsequently extracted using predefined parameter sheets.

Results: Of the 5723 abstracts screened, 195 records were included as full text and 41 full text articles were included for data-extraction. Data extraction has been completed for all articles, but only qualitative analysis has been conducted thus far. Studies most frequently used dogs (54%), followed by rats (27%), pigs (8%), goats (6%), sheep, and cats (both 2%). Dog studies were primarily conducted before 2010, with a shift towards other large animals observed thereafter. Relevant descriptives such as strain, sex, weight, and age were not systematically reported, with only 4 (9%) records reporting all four parameters and 23 (49%) not reporting two or more. Regarding kidney injury, 42 (89%) studies used an acute kidney injury model, with kidney injury induced via surgery in 43 (91%) studies. One study validated the presence of kidney injury by measuring eGFR, and both or all parameters. Finally, 30 reports (64%) performed only a single dialysis session per animal.

Conclusions: Use of dogs in HD research has significantly declined over the past decades, potentially due to a shift in public ethical perception. A notable concern is the wide variation in reporting quality over time, highlighting the necessity for clear guidelines to drive innovative HD research.

Funding: Government Support - Non-U.S.

SA-PO596
Hyperammonemia in Multiple Myeloma (MM): Rare but Serious Complication
Erik Mai, Salim Vilayet, Zipporah Krishnasami. Medical University of South Carolina, Charleston, SC.

Introduction: MM is characterized by abnormal plasma cell proliferation and clinical manifestations such as hypercalcemia, renal insufficiency, anemia, and bone lesions. Encephalopathy associated with MM can stem from hypercalcemia, hyperviscosity, or uremia. In rare cases, certain myeloma cell lines can cause hyperammonemia which can result in cerebral edema, high intracranial pressure, and high mortality rates. We present a case of hyperammonemic encephalopathy complicating relapsed refractory MM (RRMM) following an autologous stem cell transplant.

Case Description: A 62-year-old African American woman with RRMM following an autologous stem cell transplant presented with bone pain, increasing lethargy and confusion. Laboratory studies showed anemia, thrombocytopenia, low Kappa-Lambda ratio and normal calcium levels. Despite a normal liver function test, she had elevated ammonia levels, peaking at 157.3 umol/L. Her blood gas indicated chronic primary respiratory alkalosis (pH 7.51, PCO2, 23mmHg, HCO3-, 180mmol/L) due to ammonia-stimulated ventilation. A head CT was negative for acute pathology. Findings were consistent with MM-induced hyperammonemic encephalopathy. Lactulose and rifaximin were started, but her ammonia level remained elevated. To aid in ammonia clearance, she underwent continuous renal replacement therapy (CRRT) at a dose higher than standard (~35mL/kg/hr), while receiving aggressive chemotherapy (DCEP). After four days, there was an improvement in her ammonia level and mentation, and CRRT was discontinued. However, the patient was readmitted for hyperammonemic encephalopathy and ultimately transitioned to hospice care due to treatment failure.

Discussion: Hyperammonemic encephalopathy should be considered in MM patients with decreased consciousness. The exact mechanism is unclear but may be related to the production of ammonia by myeloma cell lines or to myeloma-related hormonal factors which can affect amino acid metabolism leading to hyperammonemia. While rare, this manifestation may indicate an advanced disease state and an unfavorable prognosis. Management lacks consensus, but chemotherapy is crucial. Lactulose and rifaximin may reduce ammonia levels; however, renal replacement therapy is more effective in ammonia clearance and may prevent complications from prolonged hyperammonemia, including cerebral edema.

SA-PO597
A Case of Hepatic Encephalopathy During Hemodialysis

Introduction: Hepatic encephalopathy (HE) is a serious neurological complication of portal hypertension (PH). A variety of dialysis-related factors can increase the risk of HE.

Case Description: A 50-year-old male with a history of nodular regenerative hyperplasia complicated by PH and recurrent ascites despite transjugular intraportal stent (TIPS) and kidney failure on hemodialysis (HD), hospitalized 2 times in 2 months for recurrent episodes of altered mental status (AMS) during HD sessions. The etiology of the AMS was suspected to be due to HE after an acute episode of confusion was witnessed during an inpatient HD treatment. Subsequent evaluation during this witnessed episode suggested worsening alkalosis during the course of his treatment (Table 1). Therefore, in subsequent HD treatments, his prescription was modified to lower blood flow rates and use of a lower bicarbonate (HCO3-) bath (25 instead of 35). During the following 3 inpatient sessions, there were no more episodes of AMS. He subsequently underwent a TIPS revision which led to a complete resolution of his recurrent episodes of AMS.

Discussion: Ammonia exists in the blood as NH3 and NH4+, but only NH3 can cross the blood brain barrier (BBB). Respiratory and metabolic alkalosis favors the production of NH3, and its CSF concentration can increase 2-3 fold. As a result, we suspect that in patients with PH who have undergone TIPS, HD can augment their risk of HE. Moreover, intradialytic hypotension (IDH) can lead to increased portosystemic shunting and increased ammonia levels. In this individual, the recurrent episodes of AMS occurring during HD sessions can plausibly be explained by a presumed increase in NH3 levels crossing the BBB and precipitating HE. The use of a lower HCO3- bath (25), and prevention of IDH, successfully temporized the patient while we awaited revision of his TIPS procedure.

SA-PO598
Hydroxocobalamin-Triggered Blood Leak Detection During Hemodialysis in a Liver Transplant Patient
Mauricio Ostrosky-Frid, Charles T. Owens, Laila S. Lakhani. The University of Texas Southwestern Medical Center, Dallas, TX.

Introduction: High-dose intravenous hydroxocobalamin, known as Cyanokit, is routinely administered for vasopleshic shock, a life-threatening complication from cardiac surgery when conventional vasopressors are insufficient to maintain an appropriate mean arterial blood pressure goal. In liver transplant patients, hydroxocobalamin use has become more common for vasoplegia and to decrease time on pressor dependence post-transplant. After liver transplant, some patients with acute kidney injury require continuous renal replacement therapy (CRRT) followed by transition to intermittent hemodialysis (IHD). Hydroxocobalamin is mostly excreted in the urine and has a half-life of 26-31 hours. It also has a deep red color, causing discoloration of body fluids, including urine and dialysis effluent. IHD machines have a light sensor to detect small blood leaks into the effluent as a safety feature to prevent unwitnessed hemolysis or bleeding into the filter. Interestingly, hydroxocobalamin is detected as a blood leak, which halts the hemodialysis procedure. Hydroxocobalamin does not affect CRRT, so patients remain on CRRT for approximately 5 days and then transition to IHD.

Case Description: A 67-year-old male with decompensated NASH cirrhosis and acute kidney injury from hepatorenal syndrome requiring dialysis underwent a liver transplant. He received hydroxocobalamin and was transferred to the ICU where he was started on CRRT briefly, and, given no pressor requirement, IHD was initiated. However, the IHD machine detected hydroxocobalamin as a small blood leak and stopped the procedure. CRRT was restarted after another 72 hours and no complications were noted.

Discussion: Hydroxocobalamin-triggered blood leak detection is common and can increase time on CRRT. Fresenius IHD machine has a photometric sensor consisting of a green and red light transmitter and a photodetector. An alarm is triggered when green light is absorbed by blood and hydroxocobalamin is capable of triggering this alarm. Alternatives to allow for earlier transition to hemodialysis are other IHD machines that have different sensors that do not detect hydroxocobalamin, empirical adjustment of dialysate and blood flow to decrease detection of hydroxocobalamin, and treating intraoperative vasopleshic syndrome with methylene blue instead of hydroxocobalamin, which does not impair IHD.
SA-PO599

Purpuric Rash After Starting Hemodialysis: Not the Immediate Suspect
Etty Kruzel Davila,1,2 Ashraf Badran,1 Teuta Zeitun.1,2 1Galilee Medical Center, Nahariya, Israel; 2Bar-Ilan University The Azrieli Faculty of Medicine, Ramat Gan, Israel.

Introduction: Hemodialysis patients are at risk to develop vitamin C deficiency. Several factors can contribute to vitamin C deficiency, including potassium restricted diet, hemodialysis clearance of water soluble vitamins and increased oxidative stress leading to vitamin C utilization. However, clinical manifestation of scurvy is rare or overlooked. Herein, we report a case of scurvy in a hemodialysis patient.

Case Description: A 74-year-old patient with end stage kidney disease due to diabetic nephropathy has been treated with hemodialysis since 2020. During 2022, she was hospitalized several times due to pulmonary edema. A purpuric rash with perifollicular erythema was noted on her lower legs (Figure A). She also complained of gingival bleeding. Laboratory exam demonstrated undetectable vitamin C level (less than 4 mg/L), hypoalbuminemia and elevated CRP. Based on her dermatologic findings and labs results, a diagnosis of scurvy was made. After 2 months of daily vitamin C supplement, her symptoms and rash resolved, without episodes of pulmonary edema. Echocardiography demonstrated improved LV function (EF 35% improved to 45%), suggesting a therapeutic role for vitamin C repletion.

Discussion: Recommendation of Clinical Practice Guidelines for Nutrition in CKD about regular vitamin C supplementation is opinion based. The absence of rigorous recommendation stems from lack of double blind randomized controlled clinical trials that explored the potential beneficial effect of vitamin C supplementation and possible deleterious effect of calcium oxalate supersaturation, accumulation and deposition. This case is a reminder that scurvy can occur in hemodialysis patients and may contribute to cardiovascular complications. A high clinical awareness is warranted in order to diagnose this treatable devastating disease.

SA-PO600

Recurrent Severe Hypersensitivity Reactions Following New Start of Hemodialysis
Colton Jensen, Chidimma Enyinna, Brendan Ferraro, Alison F. Fitzgerald. University of Vermont, Burlington, VT.

Introduction: Hypersensitivity reactions are a known complication of dialysis. Most cases are due to ethylene oxide, membrane filters, or medications. We present a case of a patient with recurrent hypersensitivity reactions on dialysis despite numerous changes to his dialysis configuration.

Case Description: A 78 yo male with chronic kidney disease and hypertension presented to our hospital with anuric AKI requiring hemodialysis (HD). A few minutes prior to the end of his first HD session, he developed hypotension for which treatment was stopped. 90 minutes into his second session, he developed hypotension, loss of consciousness (LOC), and ventricular tachycardia, all of which resolved after treatment was stopped. He had no significant electrolyte abnormalities, no ischemic changes on EKG, and his hemoglobin was stable. No other patients who underwent HD that day had a similar reaction. During his next 4 sessions, he developed LOC and hypotension requiring norepinephrine despite switching dialysis machines and reverse osmosis machines, as well as using a hypoallergenic dialyzer (Cellenta-19), priming the circuit with 2 liters of saline, and pre-treatment with diphenhydramine, cimetidine, and prednisone.
His symptoms occurred progressively sooner with subsequent HD sessions and resolved each time with discontinuation of treatment. An IgE level was elevatated but an ethylene oxide IgE level, C3/C4, and trypase were normal. An ethylene oxide IgE level obtained 1 month later was normal. He tolerated treatment with a NxStage machine with gamma sterilized tubing but did not tolerate a subsequent attempt using an Optiflux dialyzer and Novaline bloodlines. He did tolerate further treatments with a Revacure dialyzer and Novaline bloodlines. The patient became progressively debilitated with difficult road to recovery. He elected to forgo further HD treatments and opted for comfort-oriented care.

Discussion: This patient developed a constellation of symptoms most consistent with the setting of DOI. Multiple components of his dialysis apparatus, he was found to be non-tolerant of ethylene oxide treated components and tolerant of the gamma irradiated ones. This case demonstrates the potential severity of dialysis reactions and the importance of considering every step and component in evaluating the cause.

SA-PO601
A Unique Case of Dialysis Hypersensitivity Reaction in a Critically Ill Patient on Continuous Renal Replacement Therapy
Nicole Wyatt, Anna M. Burgner. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Allergic reactions are well-established life-threatening complications of dialysis, however these reactions pose a diagnostic challenge in critically ill patients on continuous renal replacement therapy (CRRT) who may have other severe illnesses confounding the picture. We present a case of a dialysis-related anaphylactie type reaction to a CRRT system sterilized with ethylene oxide (EtO).

Case Presentation: A 48-year-old male with hypertension and undifferentiated inflammatory arthritis presented with shortness of breath and dark tarry stools. The patient’s initial work up was significant for anemia with hemoglobin 4.1 g/dL and concern for pneumonia. The hospital course was complicated by acute hypoxic respiratory failure requiring mechanical ventilation, septic shock requiring vasopressor support, and ARDS. He was transferred to ATN and a creatinine of 4.01 mg/dL from prior baseline 0.94 mg/dL. Nephrology was engaged for initiation of CRRT due to worsening pulmonary edema in the setting of oliguria >72 hours. The patient experienced repeated episodes of severe hypotension upon starting CRRT which required escalation of vasopressor doses. These episodes persisted despite the use of heparin and albumin and saline. He also experienced repeated episodes of circuit cloting despite anticoagulation with heparin and citrate. There was high suspicion for a dialysis-related reaction to the EtO sterilized CRRT system and the patient was transitioned to intermittent hemodialysis with a steam sterilized system which was tolerated without any complications. He underwent another session without incident and ultimately experienced kidney recovery.

Discussion: This case highlights the importance of having high clinical suspicion for dialysis related reactions, particularly in the ICU setting when the diagnosis may be more challenging. We believe the patient’s repeated severe hypotension when starting CRRT was likely due to an IgE mediated hypersensitivity to the EtO sterilized CRRT system. EtO, a chemical known to cause type A dialysis reactions, is no longer used to sterilize most dialyzers however it is important to recognize several CRRT systems as EtO sterilized. EtO, a chemical known to cause type A dialysis reactions, is no longer used to sterilize dialyzers however it is important to recognize several CRRT systems as EtO sterilized. Due to this, it is imperative to increase provider education and awareness of dialysis reactions particularly in the complex ICU setting.

SA-PO602
Dialysis in Diabetic Ketoacidosis (DKA)? Profound Acidemia in the Setting of Diabetic Ketoacidosis Triggered by Inferior ST-Elevation Myocardial Infarction (STEMI)
Alex Barnes, Ali Mehdi, Laura Ferreira Provenzano. Cleveland Clinic, Cleveland, OH.

Introduction: Diabetic ketoacidosis (DKA) is a life-threatening condition that may cause severe acidemia impairing cardiac contractility and vascular tone. The role of bicarbonate therapy remains controversial. We present a case of severe DKA triggered by an myocardial infarction that required continuous venovenous hemodialysis (CVVHD) for severe acidemia.

Case Description: A 32 year old female with poorly controlled Type 1 Diabetes mellitus presented to our ED on 10/17 to 12/82 with shortness of breath, and confusion after heavy alcohol use and skipping insulin. She was hemodynamically stable but obtunded with dry mucus membranes and Kussmaul respirations. VBG showed a pH<6.8, pCO2 16mmHg, bicarbonate<2mM/L, potassium 9.9mM/L, and lactate 125mmg/dL. Serum glucose was 125mg/mL, BUN >45mM/L, and creatinine 2.24mg/dL (baseline 0.7mg/dL). ECG revealed ST elevations in inferior leads. The patient’s pH normalized and a left heart catheterization was done revealing an 80% thrombotic lesion in the RCA which was stented. Dialysis was continued for 8 hours on day 2. On hospital day 16 the hemoglobin dropped to a nadir of 5.9 g/dL that did not respond appropriately to blood transfusions. Plasma free hemoglobin was elevated with undetectable haptoglobin. Direct antibody testing was negative. Liver enzymes, fibrinogen, and platelets were stable. There was concern for intradialytic hemolysis based on amber tinge in the effluent dialysate bag and otherwise unrevealing workup. CRRT pressures were reviewed and within normal ranges and no kinks were identified in the circuit. Plasma free hemoglobin was measured pre and post filter which identified a 20% decrease after filtration. CVVHD was not associated with further improvement in serum hemoglobin and normalization in plasma free hemoglobin. No additional evidence of hemolysis was identified. The CRRT circuit was reused with a new filter from a different lot on hospital day 18 with no further hemolysis observed.

Case Conclusion: Hemolysis is a serious condition that may be associated with worse morbidity and mortality in the setting of severe illness. CRRT access sites as well as the patient’s presentation was significant for negative outcomes in the dialysis. Once an implicated component has been identified, the circuit should be reset with monitoring for improvement of hemolysis. CRRT use is increasing in ICUs, so clinicians should be aware that filter induced mechanical hemolysis is a rare but plausible cause of hemolysis that can be easily corrected.
Columbus, OH was successfully treated by IV methylene blue. She was admitted for her 3rd cycle of CRT due to tubular toxicity from Ifosfamide. Her creatinine partially recovered and remained normal. She also had recurrent AKI, severe metabolic acidosis and hypokalemia that was attributed to her encephalopathy after an acute kidney injury (AKI).

Patients. We discuss a case of a 63-year-old female who developed ifosfamide-induced neurotoxicity with the worrisome complications of ifosfamide therapy occurring in about 10-40% of the patients. Ifosfamide-induced neurotoxicity is a disabling, often devastating iron poisoning that may lead to serious and life-threatening complications. It is caused by the generation of reactive oxygen species and free radicals, which can cause oxidative stress and damage to cells. The mainstay of treatment is supportive care, which includes hydration, diuresis, and the use of chelating agents. The patient was started on CVVHD given the concern of poor renal response to methylene blue. She was started on CVVHD given the concern of poor renal response to methylene blue. Both nephrostomy tubes were patent and kidney ultrasound showed no hydronephrosis.

Introduction: An 18 Year old man with unremarkable past medical history was admitted to the hospital with intentional overdose of ibuprofen and iron. He was initiated on chelation agent, deferoxamine, and referred to our center for transplant evaluation. His initial renal function was significant for an iron level of 330 ug/dl. Peak iron levels of > 3000 ug/dl were seen 3 hours after presentation and trended to < 90 ug/dl. 48 hours after presentation. Baseline serum creatinine of 0.5-0.8 mg/dl, and at the time of his presentation was 0.78 mg/dl and so toxicology recommended initiation of CRT to ensure deferoxamine and chelating iron/oxygen free radicals stored in the kidneys. 5 days after ingestion, the patient successfully underwent hepatitis C virus positive orthotopic liver transplant. He was eventually liberated from renal replacement therapy 7 days after initiation.

Discussion: This case highlights the important supportive role of CRT in the management of iron overdose. Iron poisoning can lead to significant hemodynamic instability, including hypotension and fluid shifts and it can also lead to direct toxic effects. Iron poisoning can also lead to electrolyte derangements such as hyponatremia, hyperkalemia, or metabolic acidosis. In both instances, CRT helps maintain fluid balance by allowing for precise control of fluid removal, replacement, and electrolyte adjustments. Additionally, chelating agents are mostly excreted in the urine unchanged. In cases where iron chelation therapy is utilized, especially if there is any renal impairment, CRT can assist in removing the chelating agent from the bloodstream and preventing its accumulation and potential adverse effects. In cases where iron overload is present, the use of CRT is essential if patients are receiving chelation therapy or have any degree of renal insufficiency.

Ivosfamide-Induced Neurotoxicity Treated with CRT

A 64-year-old female who was being treated with antibiotics through a right arm PICC for leg stump infection was transferred to ICU due to acute kidney injury and septic shock. Norepinephrine and vasopressin were infused as vasopressors through the PICC. A right internal jugular Trialysis catheter was inserted to infuse the norepinephrine and vasopressin. The vasopressors were infused via a peripheral intravenous line due to the proximity of the tip of the PICC to the Trialysis catheter arterial end hole. CRT was reattempted after switching vasopressors infusion from the PICC to the distal port of the Trialysis catheter. Patients’ hemodynamics stayed stable affirming the suspicion of vasopressor removal by CRT.

Discussion: Inadvertent removal of vasopressors should be considered as a potential cause of hemodynamic instability during CRT initiation. Risk can be mitigated by infusing the vasopressors away from the arterial end hole of dialysis catheter either distally or proximally, which can be achieved by repositioning the tip of catheter.

Dialysis Disequilibrium Syndrome in a Patient with a Relatively Low Blood Urea Nitrogen (BUN)

A 39-year-old patient with a history of lung transplant 5 years ago for idiopathic pulmonary fibrosis, stage 5 chronic kidney disease secondary to CNI toxicity, was admitted with severe nausea/vomiting. On physical examination his BUN was 20, normal vital signs, and no pericardial rub or asterixis were noted. Laboratory results: sodium 135, potassium 4.1, creatinine 8.9, blood urea nitrogen (BUN) 65, bicarbonate 18, blood venous gas 7.26/41. Hemodialysis (HD) was initiated (duration 2 hours, blood flow rate: 200 mL/min, dialysate flow rate: 400 mL/min, dialysate sodium: 138 mEq/l, dialysate bicarbonate: 25 mEq/l, fluid removal: 0.5L, urea reduction rate: 90%). Norepinephrine and vasopressin were infused as vasopressors after his first HD, the patient complained of nausea/vomiting, and moderate to severe headaches. DDX was suspected and 100 mL of 3% hypertonic saline was administered with rapid resolution of the symptomatology, a subsequent head CT scan did not show cerebral edema.

Discussion: DDS is an uncommon but serious complication after HD initiation primarily caused by cerebral edema. The pathogenesis is not clearly defined. The generation of osmotic gradients due to the rapid reduction of extracellular urea and other osmolytes could create a transient osmotic gradient between plasma and brain cells. Rapid correction of metabolic acidosis during HD could lead to intracellular cerebral acidosis. Risk factors include first HD, extremes of age, markedly elevated BUN (>175 mg/dl), and conditions associated with increased permeability of the blood-brain barrier (BBB). Hypertonic saline or mannitol to reduce the osmotic gradient is recommended as first-line therapy. Interventive measures involving delaying the HD session, withdrawing sodium modeling, or the prophylactic use of hypertonic saline or mannitol. The development of DDS in this patient was unexpected, considering his low BUN and the HD prescription that was used. Potential explanations include the generation of organic osmolytes in uremic patients and the increased urea, that increase the permeability of the BBB and act as osmotically active substances generating an osmotic gradient. The prompt treatment led to full neurologic recovery.
left kidney were eventually procured and successfully transplanted. Family played an immense role in deceased-donor procurement and helped with every manner.

**Discussion:** Nearly half of discarded kidneys from 2010-2020 were from donors with AKI. Management of organ donor with AKI is often curtailed due to hemodynamic and electrolyte instability. Dialysis can correct the effects of AKI, but is rarely started after brain death. Extracorporeal kidney-replacement therapy following brain death has not been extensively explored, CKR has been studied to some extent. Brain dead patients with AKI treated CKRT have a favorable outcomes in organ donation. At our center, a significant reduction trend was observed in S. Iron of 23%. The monthly admission rate, units of PRBC transfused, S. Iron and Ferritin.

<table>
<thead>
<tr>
<th>Variables</th>
<th>2021</th>
<th>2022</th>
<th>2023</th>
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<tbody>
<tr>
<td>Monthly admissions</td>
<td>1.6 (±0.3)</td>
<td>2.5 (±0.7)</td>
<td>3.4 (±0.7)</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean transfusions</td>
<td>3.6 (±0.5)</td>
<td>1.8 (±0.7)</td>
<td>1.2 (±0.4)</td>
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<tr>
<td>Mean (SE)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Donor</td>
<td>18.9 (2.0)</td>
<td>18.3 (1.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Mean (SE)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>S. Iron</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SE)</td>
<td>455 (75)</td>
<td>5055 (170)</td>
<td>390 (75)</td>
</tr>
<tr>
<td>Mean (SE)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>48.0 (2.5)</td>
<td>32.2 (2.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean (SE)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

SA-P0610

The Role of Duloxetine for Management of Persistent Hypotension in ESKD

Rasha Mohamed Abdul Rahman,1 Salmon Al Jerdi,2 Awais Nauman,3 Essa Abubelaiga1

1Hamad Medical Corporation, Doha, Qatar; 2Weill Cornell Medicine - Qatar, Doha, Qatar.

**Introduction:** Uremic neuropathy is a known complication of end stage kidney disease (ESKD) that has significant morbidity and mortality. It can present as distal sensory, motor neuropathy, or autonomic dysfunction that worsen over several months. ESKD patients can develop intra-diarytic hypotension or persistent hypotension due to sympathetic and parasympathetic dysregulation characterized by preserved cardiac index, abnormality of reflex tachycardia, anhidrosis and reduction of tachycardia threshold. Duloxetine, a norepinephrine and serotonin reuptake inhibitor, has been used for the treatment of neuropathic pain and anxiety in ESKD patients with no specific cause. Therefore, thought to be associated with uremic neuropathy causing sympathetic and parasympathetic dysregulation. Despite intensifying hemodialysis, use of midodrine, hydrocortisone, and fludrocortisone, patient had no improvement in hypotension. Due to the severe hypotension the patient developed bilateral ischemic retinopathy and vision loss, multiple small bowel ulceration, and peripheral neuropathy. Patient was started on duloxetine 40mg daily trial for peripheral neuropathy. Within one week of therapy, patient noted improvement in neuropathic pain and in addition, blood pressure increase to 50/26. With Blood pressure improvement, patient developed diffuse and constant pulsing headaches required oral analgesic. Upon discontinuing duloxetine, headaches resolved and blood pressure returned to her baseline (41/19).

**Discussion:** Duloxetine has been commonly used for treatment of depression and anxiety in addition to peripheral neuropathy. One of the known side effects of duloxetine is hypertension, which is thought to be due to increased in norepinephrine levels, therefore, aggravating alpha-receptor, arterial vasoconstriction and increase systemic vascular resistance. Hence, duloxetine has a potential role in management of uremic neuropathy and an alternative treatment of persistent hypotension in ESKD.

SA-P0611

One-Year Effect of Deferoxamine in Sickle Cell Disease with ESRD

Jason R. Ledoux, Jafar Alsaid. Ochsner Medical Center, New Orleans, LA.

**Introduction:** Sickle cell disease patient may develop Iron overload due to multiple transfusions. Iron chelation is recommended for treatment. Deferoxamine is eliminated through the kidneys and bowels. In ESRD the elimination is only by bowels. It can be removed by hemodialysis as reported. We are reporting the changes in serum Iron, Ferritin, hospital admission rates and transfusions frequency in an ESRD patient with sickle cell disease after using Deferoxamine for a year.

**Case Description:** 29 years old patient with Sickle cell disease. ESRD for 3 years, started with PD and transitioned to HD 3X weekly for the past year. He had recurrent admission for painful and hemolytic crises with frequent blood transfusions. Iron levels increased up to 235 mg/dL (45-160) and Ferritin reached 7973 ng/ml (20-300). Hb levels were 8.2 g/dL (11.0-15.0) with a hematocrit of 27.1%, hemoglobin of 49% and MCV of 79fl. He was started on Deferoxamine 200mg IV after each dialysis in June 2022 until May 2023.

**Discussion:** Deferoxamine is proven to be used with heavy metal intoxication. It is cleared through the kidneys and bowels. In patients with impaired renal function elimination of Deferoxamine will be reduced. Hemodialysis is reported to improve the clearance. Limited data is available on using the drug with Iron overload among dialysis patients. With no specific cause. Therefore, thought to be associated with uremic neuropathy causing sympathetic and parasympathetic dysregulation. Despite intensifying hemodialysis, use of midodrine, hydrocortisone, and fludrocortisone, patient had no improvement in hypotension. Due to the severe hypotension the patient developed bilateral ischemic retinopathy and vision loss, multiple small bowel ulceration, and peripheral neuropathy. Patient was started on duloxetine 40mg daily trial for peripheral neuropathy. Within one week of therapy, patient noted improvement in neuropathic pain and in addition, blood pressure increase to 50/26. With Blood pressure improvement, patient developed diffuse and constant pulsing headaches required oral analgesic. Upon discontinuing duloxetine, headaches resolved and blood pressure returned to her baseline (41/19).

**Discussion:** Duloxetine has been commonly used for treatment of depression and anxiety in addition to peripheral neuropathy. One of the known side effects of duloxetine is hypertension, which is thought to be due to increased in norepinephrine levels, therefore, aggravating alpha-receptor, arterial vasoconstriction and increase systemic vascular resistance. Hence, duloxetine has a potential role in management of uremic neuropathy and an alternative treatment of persistent hypotension in ESKD.
Discussion: The patient was discharged the next day without a PE CT scan, EDW adjustment for his dialysis and lower pain medication. The use of POCUS helped to identify a right heart strain pattern with an eccentricity index >1 in diastole only. The POCUS findings before and after HD negated the need for additional studies which in this patient carried significant risk secondary to his severe contrast allergy.

Results: A total of 1723 reviews have been completed on 668 patients. Our analysis revealed that 1065 medications were being appropriately dosed and 146 medications required interventions. Of those that required intervention, 125 medications were rescheduled to be given after dialysis and 21 medications required dose adjustment (chart 1). Common medications identified are demonstrated in chart 2.

Conclusions: Approximately 12% of medications reviewed required an intervention for dose/timing adjustment and 10% were defaulted to be given prior to dialysis. A pharmacist, via electronic review, was able to reduce these potential errors and next steps may include utilizing Electronic Medical Records solutions to automate error reduction.

![Chart 1](image1.png)

![Chart 2](image2.png)

SA-PO614
The Uncertainty of Bleeding Risk Monitoring for ESKD Patient on Continuous Anticoagulation Infusion

Introduction: Patients with end-stage kidney disease (ESKD) are at increased risk of bleeding due to: chronic anemia, uremic platelet dysfunction, vascular calcification, and dialysis-related complications. Additionally, the risk of venous thromboembolism is also heightened, making anticoagulation management challenging. This case report presents the unfortunate outcome of an ESKD patient who experienced acute intracranial bleeding after initiation of heparin infusion for ischemic digits, leading to death.

Case Description: Patient is a 38-year-old female with ESKD secondary to diabetes mellitus (DM) on peritoneal dialysis (PD) and a history of scleroderma. She presented with progressive digit pain and discoloration. During hospital stay, she developed worsening respiratory status due to ESBL pneumonia, requiring intubation. She was started on epoprostenol given concern for Raynaud’s crisis, as well as heparin infusion for severe atherosclerotic vascular disease with stenosis. Unfortunately, hospital course was further complicated by a non-operative intraperitoneal bleed with cerebral edema and herniation, leading to eventual extubation and transition to comfort care.

Discussion: Bleeding events in ESKD patients, ranging from bruises and bleeding at venipuncture sites to intracranial hemorrhage, significantly contribute to mortality and morbidity. Furthermore, blood transfusions can lead to alloimmunization and limit future transplantation options. In this case, several factors contributed to the adverse events. Team factors, including limited communication between the medical teams involved, may have hindered comprehensive management given patient’s ongoing anticoagulation need. Patient factors, such as multiple comorbidities (ESKD, cardiovascular disease on aspirin) and the initiation of epoprostenol (a potent platelet aggregation inhibitor), further increased bleeding risk. Lastly, hospital policies, such as specific protocol tailored to ESKD patient that minimizes bolusing and allow for slower infusion rates could have potentially prevented these adverse events and improve patient outcomes.
Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age in years</td>
<td>Average age: 58</td>
</tr>
<tr>
<td>Race</td>
<td>Black</td>
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<tr>
<td>Cause of ESKD</td>
<td>29 DM 6-HTN 3GN 10 Other</td>
</tr>
<tr>
<td>Duration of treatment (yr)</td>
<td>Average: 5.7 yr</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>Modality of dialysis (MM)</td>
<td>41 HD 37 PD</td>
</tr>
<tr>
<td>No. of patients involved in care</td>
<td>Average: 3</td>
</tr>
<tr>
<td>No. of prescribed medications</td>
<td>Average: 9</td>
</tr>
<tr>
<td>Mean MDR following (N = 30)</td>
<td>20±5 ml/d</td>
</tr>
</tbody>
</table>

Image 1

SA-PO617

Efficiency of a Fully Integrated Hemodialysis (HD) Machine in the Acute Care Setting

Nazli Atefi,1,2 Nasha Elavia,1,2 Zain Haq,1,2 Jagman S. Chahal,1,2 Abutaleb A. Ejjaz,1,2 Ami M. Patel,1,2 VA Medical Center Baltimore, Baltimore, MD; 1University of Maryland Medical System, Baltimore, MD.

Background: TabloTM, which is a fully-integrated, adaptive hemodialysis (HD) machine with an internal water purification system without requiring traditional water treatment resources, has a 300 mL/min restriction in the maximum attainable dialysate flow rate (DFR). We investigated the efficiency of TabloTM in the acute hospital setting.

Methods: We conducted a prospective, single-center analysis. All Veterans with ESKD, who completed ≥ 3hrs of hemodialysis with available blood urea nitrogen pre- and post-treatment, from February 2023 to May 2023 were included. Urea reduction ratio (URR) and calculated Kt/V were compared for selected variables.

Results: 38 Veterans with total of 69 HD sessions met the inclusion criteria for analysis. Participants were 94.2% males, mean age 67.2±10.2 years, dialyzed for 211.3±91 mins, blood flow rate (BFR) 334.1±13.1mL/min, with Optiflux F160 (43.5%) and F180 (56.5%) dialyzers, average ultrafiltration 1.9±0.6 L, arteriovenous fistula (26%), arteriovenous graft (5.7%) and central venous catheter (68.3%). Kt/V and URR for 211.3±9.1 mins, blood flow rate (BFR) 354.1±13.1mL/min, with Optiflux F160 (43.5%) and post-treatment, from February 2023 to May 2023 were included. Urea reduction ratio (URR) and calculated Kt/V were compared for selected variables.

Conclusions: The restriction of DFR to 300 mL/min with TabloTM system compromises adequacy of dialysis in acute care setting. This may be mitigated by prolonging session times, albeit at the expense of higher resource utilization. Future studies are necessary to compare adequacy of TabloTM and conventional dialysis machines using higher typical DFR in a larger cohort.

Figure 1 Multivariable analysis of dialysis adequacy with Tablo™

SA-PO619

Blood Flow Rate Accuracy with Dality Hemodialysis System

Clayton Poppe, Nicholas Hyun, Blaine Murakami. Dality, Irvine, CA.

Background: As laid out by Williams, Jensen, Gillum and Nabut, blood flow accuracy in hemodialysis machines often does not match the manufacturers’ stated accuracy at high blood flowrates. Flowrates might be lower by as much as 80-100 ml/min at a setpoint of 500 ml/min. This compares to the stated accuracy of +/-10% by most hemodialysis machine manufacturers. This difference in blood flowrate can lead to a reduction in Kt/V of 8.4%, depending on the dialysate flowrate. The Dality Hemodialysis System corrects for the factors responsible for reducing the expected flowrate leading to more accurate control of the blood flowrate and thus a higher Kt/V that better matches the theoretical value for dose delivered. [1] Williams HF, Jensen K, Gillum D, Nabut J. Blood pump speed vs. actual “compensated” blood flow rate. Nephrol Nurs J. 2007 Sep-Oct;34(5):491-9, 525. PMID: 18041451.

Methods: The challenge in controlling blood flow is that parameters that are appropriate for high blood flows may not work for low flowrates. An algorithm that predicts the flowrate from independent variables is used to control the blood flow using a Proportional-Integral-Differential (PID) control methodology. The factors feeding into this algorithm are independently correlated with changes in blood flow. These include: - Pump head speed - Inlet and Outlet Pressures - Tubing Aging - Temperature

Results: The graph on the left-hand side of Figure 1 shows the accuracy of blood flow control at 100 ml/min while the graph on the right-hand side shows the accuracy of blood flow control at 500 ml/min. The green line represents the measured flow from a reference flowmeter while the orange line represents the algorithmically calculated flow from the device. Actual flowrates are well within the stated accuracy of +/-10% for both low and high flowrates.

Conclusions: Understanding the variables that lead to changes in blood flow and using them to control blood flow in real time can lead to better blood flow accuracy. This in turn can lead to higher average Kt/V for higher treatments with high blood flowrates.

Figure 1: Blood FlowRates of 100 ml/min (right) and 500 ml/min (left)

SA-PO618

Increasing Incidence and Prevalence of Patients on Kidney Replacement Therapy over the Last 40 Years in Uruguay

Leonel Lizardo,1,2 Maria Laura Cerutti, Alejandro Ferreiro,1,2 Maria A. Gonzalez-Recinos,1,2 Autoris: (1) Nephrology Division, Montevideo, Uruguay; (2) Uruguay Renal Dialysis Registry, Montevideo, Uruguay.

Background: From 1980 onwards chronic dialysis (CD) and kidney transplantation (KT) are accessible for the entire population. In Uruguay, from 1981 to 2020, we have studied the growth of the incidence and prevalence of patients on CKD, KT and KT recipients.

Methods: The aim of this study is to describe the trends in the incidence (I), the prevalence (P) and the survival of patients on KT over the last 40 years.

Results: The P increased from 41 to 1227 pmp (Fig 1). The P on CD increased from 38 to 1981 to 820 pmp in 2020. The P of patients on KT increased from 3 on 1981 to 407 pmp in 2020. The growth of the I and P of CD and KT was higher in the first 2 decades (1981-2000) (278% vs 48%, 533% vs 113%, 1592% vs 23% and 3066% vs 291%) (Fig 2). The growth of the P rate of KT was 10 times higher than the CD P rate. The age on admission to CD increased from 44±13.5 in 1981 to 62±17.1 years in 2020, while those over 65 years increased from 3.0 to 52.4%. The crude M on CD increased from 14.8 ± 17.1 years in 2020, while M has remained stable in recent years.

Conclusions: The I and P of patients with CKD on KT in Uruguay have increased between 1981 and 2020 with a higher percentage growth in the P rate of KT. Despite the increasing admission patients older than 65 years, M has remained stable in recent years.

Comparison between mortality rate among chronic dialysis patients and the uruguayan general population

<table>
<thead>
<tr>
<th>Age</th>
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<tbody>
<tr>
<td>0-15</td>
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<tr>
<td>15-54</td>
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<tr>
<td>55-84</td>
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<tr>
<td>85+</td>
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</table>

CD: chronic dialysis patients; GP: general population

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

Underline represents presenting author.
Implementing a Protocol for Incremental Hemodialysis in Incident Patients with ESKD: A Quality Improvement Project
Ali Tahá,1 Alexander Messina,1 Alexander Tom,1 Reman I. Altar,1 Nancy Fiteau,1 Daniel Blum,2 Emile Triinh,1 Catherine L. Weber.3 McGill University Health Centre, Montreal, QC, Canada; 2Hopital General Juif, Montreal, QC, Canada.

Background: Incremental hemodialysis (HD) is the process whereby the frequency of HD is adapted to the patient’s residual kidney function, initially starting at twice a week with an increase based on clinical indications. Incremental HD potentially facilitates the transition to HD, reduces patient and caregiver burden, improves quality of life and reduces costs. We sought to increase the number of patients commenced on incremental HD at a tertiary care academic center and to develop a safe process to monitor these patients.

Methods: We performed a prospective cohort quality improvement study. Starting November 1 2022, we aimed to start 75% of eligible incident chronic HD patients on incremental HD within 1 year. Eligible patients were defined as medically stable with no acute, active medical issues, and no indication for more frequent HD. The primary outcome measure was percentage of incident ESKD patients started on incremental HD. The balancing measure was the number of patients requiring transition to three-times per week HD. The incremental HD process was developed with input from all stakeholders.

Results: Between November 1 2022 and March 31 2023, among 35 incident chronic HD patients, 14 were eligible for incremental HD, of which 9 started incremental HD. As of May 2023, 6 patients remain on two-times per week HD and 3 patients required an increase to three-times per week HD. The process developed included a) a patient information sheet about incremental HD b) nursing education, c) a nurse led protocol whereby the patient performs a 24 hour urine collection for volume and the nurse completes a safety checklist every 6 weeks, and d) an alert system for the MD to review the patient’s HD prescription if they have uremic symptoms, is volume overloaded or hypotensive.

Conclusions: We successfully initiated 64% of eligible incident HD patients on incremental HD, of which two-thirds remained on twice-weekly HD. Our next steps will include feedback from patients and healthcare staff through quantitative and qualitative surveys with the goal of optimizing our protocol and expanding it to all dialysis units at our center.

SA-PO621
Zikora U. Nnadike,1 Anjali Shah,1 Carol A. Gray,2 Loren C. Cobb,3 Christopher M. O’Donnell,1 Jose E. Navarrete,1 Jason Cobb.2 Emory University School of Medicine, Atlanta, GA; 2Emory Healthcare, Atlanta, GA; 3 Meharry Medical College, Nashville, TN.

Background: An overlooked population is the number of insurable involuntarily discharged hemodialysis (HD) patients receiving maintenance HD. Presented is a case series examining involuntarily discharged HD patients receiving maintenance HD in inpatient settings in an urban US population.

Methods: Retrospective chart review of potential involuntarily discharged HD patients from Emory – 2023 observed at Emory Hospitals and Grady Memorial Hospital. Studied were insurable end stage kidney disease (ESKD) patients who started HD as inpatient and were seen for inpatient dialysis >60 days and patients involuntarily discharged from a HD center.

Results: Among the 25 ESKD patients – all Black race and 68% male. 13 discharged for noncompliance, 8 discharged for disruptive behavior, 3 for insurance reasons, and 1 undetermined. HD vascular access – permacath (n=13), arteriovenous graft (n=4), and arteriovenous fistula (n=8). Observed hospitalizations for HD ranged from 3 to 298. The 3 patients discharged for insurance reasons included 2 patients initiated HD as an inpatient and declared ESKD and received HD as an inpatient >60 days. Suspected noncompliance prevented them from being accepted despite being insurance eligible. 16 patients received a second chance outpatient HD center, and 1 was discharged from the second chance HD unit.

Conclusions: This case series brings attention to a vulnerable nephrology population. Most of the patients were discharged for subjective reasons like noncompliance and the impact of biases are hard to determine, but the patients being 100% Black is remarkable. The high level of success with second chance HD center placement demonstrates a need for interventions. More data is needed to examine geographic variances, economic impact, and the psychological toll emergency-only outpatient HD is having on these patients.

SA-PO622
Characteristics and Outcomes of High-Acuity Patients Referred for Outpatient Dialysis
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Background: Dialysis-requiring hospitalized patients with co-morbid high-acuity needs are challenging to place in outpatient dialysis centers, leading to extended hospital stays. In 2018, we established a program for physician evaluation of high-acuity patients to develop protocols for admittance to outpatient dialysis centers. The program provides care coordination with the discharging hospital, necessary dialysis-related medical equipment, and training of center staff to manage need for bed or bariatric bed, left ventricular assist device (LVAD), tracheostomy, behavioral issues requiring supervision, infection with communicable organisms, or other high-acuity co-morbid conditions. Little is known about the safety or efficacy of outpatient dialysis for high acuity patients.

Methods: We describe the characteristics and outcomes of patients referred to the program from January 2018 through April 2023.

Results: The program received 468 referrals, of which 149 (31.8%) initiated dialysis at outpatient dialysis centers of a mid-size non-profit dialysis provider. 304 patients were excluded due to reasons including inadequate staffing or space, clinical instability, and overcomplex management needs. The most common indications for admission were the need for a special gurney or bed (99 patients), tracheostomy (22), and LVAD (6). The mean (SD) age was 62.7 (14.0) years, 41% were female, and 59% had diabetes. 21% of patients had a central venous catheter at the time of referral into the program. During 152 patient-years of follow-up, re-hospitalization rate at 1 month was 37%, with an admission rate of 2.7 per patient-year and 21 hospital days per patient-year. Despite this, 94% of the patients’ survival time was spent out of the hospital. Survival rates at 3, 6, and 12 months were 76%, 71%, and 59% respectively.

Conclusions: A program that utilizes nephrologist evaluation, care coordination, additional equipment, staffing, and training can facilitate hospital discharges and address the care needs of high-acuity patients undergoing dialysis in the outpatient setting. Despite high comorbidity, these patients can benefit from being out of the hospital the majority of their time post admission to the dialysis center.

SA-PO623
Nephrologist Involvement in the Multi-Organ Failure Patient with Artificial Liver Support Systems: Experience of the Single-Center Extracorporeal Therapy Program in Mexico
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Background: The role of the nephrologist in intensive care is critical and includes the implementation of extracorporeal therapies, such as combined artificial hepatic-renal support, which provides time for rapid inclusion in an emergency liver transplantation program and recovery from acute failure. The most used methods are the molecular adsorbent recirculating system (MARS) and single-pass albumin dialysis (SPAD).

Methods: Objective: To expose the experience in the multiorgan support of critically ill patients with extracorporeal liver and kidney support therapies at the Centro Medico Nacional 20 de Noviembre. Retrospective study of patients with acute liver failure from 2016 to 2023 who underwent MARS or SPAD therapy.

Results: Of 21 patients, 43% were women and 57% men, with an average age of 38 years. The etiology of the liver disease was autoimmune in 47%, hepatitis A infection in 19%, cryptogenic in 14%. Ten of these patients had a previous liver transplant, 47% with recurrence of the disease or chronic resection; the indication for liver support was 66% for acute chronic liver failure and 34% for acute liver failure, with SOFA score 9.8±8, MELD...
score 25±15. Five patients received MARS and 16 SPAD, with a total of 63 sessions (average of 3 sessions per patient), with a bilirubin clearance rate of 29.2% (3-47%). Acute kidney injury was present in 62%, of these 54% required CRRT. We found an average survival of 6 months (1 to 56 months) and mortality of 80%.

**Conclusions:** The use of MARS or SPAD is a therapeutic bridge that allows clinical improvement of the patient or liver (re)transplantation in acute liver failure. Despite the high mortality, there is substantial room for improvement that favors comprehensive care processes in the critically ill patient. Survival of these patients varies according to the severity and availability of donated organs.

SA-PO624

**Rural Alaskan Experience Insourcing Innovative Dialysis Technology**

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**Background:** Patients requiring dialysis in rural areas often face obstacles for treatment such as distance to care, financial limitations, and mistrust of the medical community. Studies have revealed moving geographic location of medical services closer, has a positive impact on health, economic and psychosocial states. Alaska has a paucity of acute dialysis services outside of the major cities like Anchorage and Fairbanks, leading to significant cost and complexity to the delivery of care to patients in these areas. Mat Su Regional hospital is a 125-bed hospital located an hour from Anchorage and operationalized a dialysis service line to improve access to care for rural patients in Palmer, AK using an innovative dialysis system, Tablo®. This describes the first year of Intermittent Hemodialysis (IHD) and Sustained-Low Efficiency Dialysis (SLED) treatments.

**Methods:** A retrospective chart review through the hospitals Electronic Health Records (EHR) was performed on all IHD and SLED treatments since implementation in February 2022.

**Results:** Since implementation of dialysis services in February 2022, there were 340 combined IHD and SLED treatments in the hospital. Only 1 patient was transferred for care compared to 70 patients the year prior. Training for ICU nursing staff consisted of Tablo hub training modules, 2-hour hands on training and 2-12 hour treatments with preceptor on the device. In the ICU there were 23 unique patients with 65 total SLED treatments. CLABSI rate was 0% and mortality rate was 43% (Fig 1) with 70% of those patients being male. Most treatments where longer than 10 hrs. (98%) and 49% used automated saline flushes as method for anticoagulation and 9% of treatments ended due to clotting (Fig 2). There was a 4.3% COVID rate.

**Conclusion:** Implementation of a new dialysis service line using Tablo decreased hospital transfers and displacement of patients in rural Alaska. Mortality rates were slightly better than national averages as were clotting events. Training of staff was relatively easy which allowed hospital wide adoption. More research is needed to increase dialysis services into rural areas for better patient outcomes.

SA-PO625

**Building a Framework for Enhancing Dialysis Services in Conflict-Affected Regions: A Multi-Level Action Plan**

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**Background:** The provision of dialysis to patients with ESKD in areas affected by conflict poses various challenges. Reports have shown a high incidence of hepatitis B&C among patients on hemodialysis (IHD) & poor HD operations in Northwest (NW) Syria, an area enduring armed conflict. A framework is necessary to address the hindrances to HD in such environments.

**Methods:** The Health Cluster Hub in Turkey is collaborating with Johns Hopkins University to spearhead a quality improvement initiative for HD in NW Syria. Objectives are to address difficulties of HD in this region and enhance care delivered by NGOs administering HD. The project comprises 3 phases: baseline assement, setting up basic standards & action plan, and putting a support supervision system, alongside creating a framework to attain these targets.

**Results:** The 1st phase involved a survey of HD centers and 2 workshops utilizing the fishbone technique & theory of change models to map the necessary changes. Through this phase, an action plan (Fig 1) was developed and involved various stakeholders with different objectives. The 2nd phase focused on building quality curricula, which were subsequently taught through courses, creating a record system, & establishing minimal standards for HD centers. Furthermore, a framework was created to address dialysis services in NW Syria and other conflict settings (Fig 2).

**Conclusions:** As it is the responsibility of the nephrology community and humanitarian agencies to ensure quality care for patients with ESKD, we propose a comprehensive framework to enhance HD care in unstable areas. This framework involves engaging all stakeholders in care delivery, establishing minimum standards, and mitigating risks to patients.

**Funding:** Government Support - Non-U.S.
SA-PO627

It Takes Time: Developing a Standardized Strategy to Improve Timely Modality Education and Home Dialysis Choice Rates in Patients with Advanced Kidney Disease in Toronto, Canada

Background: Patients with progressive chronic kidney disease (CKD) should receive timely education that allows them to choose a treatment path that aligns with their care goals and lifestyle. Home-based dialysis modalities have been associated with increased quality of life and reduced health care costs. Modality education has been shown to increase rates of home dialysis as the initial dialysis strategy. Delays in timely education may reduce home dialysis choice rates. Barriers to timely modality education include lack of a standardized referral process, physician practice variation and patient preparedness to engage in discussion. The aim of this study was to assess whether the implementation of a standardized referral process could increase the rates of timely modality education and home dialysis choice.

Methods: This was a quality improvement study performed at a single center in Toronto, Canada between 2019-2023. Patients with a 2-year Kidney Failure Risk Equation (KFRE) of ≥ 40% were recommended for modality education as outlined by the provincial regulatory body. Rates of modality education and home dialysis choice were recorded on a quarterly basis both before and after implementation of a standardized referral process.

Results: 1451 encounters were identified between 2019-2023. Prior to initiation of a standardized referral process, 647/1134 (57.1%) of eligible patients received modality education and 218/647 (33.7%) of educated patients chose home dialysis as their preferred modality. After initiation of a standardized referral process, 177/317 (55.8%) of eligible patients received modality education and 54/177 (30.5%) of patients choose home dialysis as their preferred modality.

Conclusions: There was no significant change in modality education or home dialysis choice rates after initiation of a standardized strategy. Timing of education should not be restricted to arbitrary cut-off values but requires ongoing mentorship and support of patients at an early stage of disease course.

SA-PO628

Shared Decision-Making Intervention Regarding Dialysis Modality in Patients with Stage 5 CKD
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Background: Patients with kidney failure must make complicated decisions about the dialysis modalities used either at home or in-hospital. Different options have varying levels of impact on patients’ physical and psychological conditions and their social life. The purpose of this study was to evaluate the implementation of an intervention designed to achieve shared decision making (SDM) in patients’ options for dialysis.

Methods: SDM was performed after consent was written for stage 5 chronic kidney disease patients before dialysis, and 435 cases were performed in 408 patients from December 16, 2019 to June 30, 2021. Among these, 101 patients were compared by SDM measurement scale, patient satisfaction, disease recognition scale survey, and dialysis method.

Results: The average age of participants was 56 years, with a gender composition of 55 males (54.5%) and 46 females (45.5%). Following SDM, the final dialysis methods decided upon by patients and clinicians were peritoneal dialysis (67 patients, 66.3%), hemodialysis (22 patients, 21.8%), and kidney transplantation (1 patient, 1.0%).

Conclusions: Among participating patients, SDM was effective when used to decide on dialysis treatment, and patients were satisfied with the dialysis method decision process. On the disease awareness scale, those who participated in this project had relatively high positive and low negative perceptions, so it can be concluded that SDM was relatively effective. The implementation of SDM was helpful in selecting patients’ best dialysis methods, and SDM scale results were higher in the peritoneal dialysis group than in the hemodialysis group.
SA-PO630
Incidence of Fungal Peritonitis and Exit Site Infections Among Peritoneal Dialysis Patients in a Mid-Sized Dialysis Provider
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Background: Fungal infections are a relatively rare complication of peritoneal dialysis (PD). These infections include fungal peritonitis, an especially serious complication, and fungal growth at the catheter exit site. Surprisingly little is known about the epidemiology of fungal infections among PD patients in the United States. We estimated the incidence of fungal peritonitis and exit site infection (ESI) in a multi-center cohort of PD patients.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. We identified patients who initiated PD between January 1, 2011, and March 31, 2023, and retained those that initiated PD during the first year after diagnosis of end stage kidney disease. Patients were followed until diagnosis of first fungal infection (either peritonitis or ESI), death, conversion to hemodialysis, kidney transplantation, recovery of function, or April 30, 2023. We estimated the cumulative incidence of each of fungal peritonitis and ESI, and used Cox regression to estimate associations of age, sex, diabetes, and time-varying modality subtype (continuous ambulatory, automated) with the risk of fungal infection.

Results: The cohort included 5743 patients. Overall, 115 patients experienced a fungal infection: 94 patients experienced peritonitis at a mean of 27.9 months after PD initiation, 2 patients experienced an ESI at a mean of 32.0 months after PD initiation, and 2 patients experienced both complications. The cumulative incidence of fungal peritonitis was 0.9% at 2 years after PD initiation and 1.7% at 4 years. No associations with fungal peritonitis were statistically significant, although age of 18-44 years, relative to 45-64 years, and continuous ambulatory PD were associated with lower hazard. At 3 months after fungal peritonitis, the cumulative incidence of conversion to hemodialysis was 80.4%. The cumulative incidence of fungal ESI was 0.4% at 2 years after PD initiation and 0.7% at 4 years. At 3 months after fungal ESI, the cumulative incidence of conversion to hemodialysis was 18.6%.

Conclusions: Fungal infection is a rare event in PD patients, with little overlap between fungal peritonitis and ESI. Fungal infection tends to occur late in the course of PD. Fungal peritonitis is highly likely to be followed by PD discontinuation in the short run.

SA-PO631
Risk Factors for Peritoneal Dialysis Failure: Retrospective Cohort Study
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Background: Patients who start intermittent peritoneal dialysis (IPD) as a bridge therapy to continuous ambulatory peritoneal dialysis (CAPD) may present failure of the IPD technique before starting due to multiple factors. The principal factors identified with loss of technical were peritonitis, tunnelitis, and definitive failure. The aim of this study was to estimate the incidence of technique failure in IPD patients with the IPD program at the General Hospital of Mexico.

Methods: Retrospective cohort study that included 199 patients with IPD, was reviewed the patient records of peritoneal dialysis, during the period between January 2008 and May 2023. The incidence was estimated, and risk factors for technique failure.

Results: A total of 199 patient records were included; 58% (115) were men, with a mean age of 45.4±14.9 SD years, 65% (127) had diabetes type 2, and 94% had systemic hypertension. In the 62% (123) patients, the initiation of renal function replacement therapy was urgent. It was identified that in 70% (139) of patients, the first catheter was placed percutaneously and 30% (60) was surgical. The catheter type was pig tail in the 90% (185) of the cases, the loss of technique was identified in 24% (48) of patients, including as causes of etiologies events of dysfunction that required catheter replacement and events of peritonitis, the analysis of the first event of peritonitis increased the risk of failure.

Conclusions: The principal factor associated with losing the technique was peritonitis, even when the patient did not use dialysis outside of the hospital. Peritonitis is a frequent and serious complication of peritoneal dialysis (PD), representing the most common cause of conversion to hemodialysis in the long term. It is necessary to integrate strategies for the care and management of the ambulatory catheter during IPD.

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

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Peritoneal Dialysis-Related Mycobacterium abscessus Infections: A Case Series
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Background: Catheter-associated infections are an important cause of morbidity and catheter loss in people using peritoneal dialysis (PD). Mycobacterium abscessus is a rapidly growing non-tuberculous mycobacterium (NTM) that has innate antimicrobial resistance. M. abscessus is an uncommon etiology of PD catheter associated infections, with only a handful of cases reported and only 2 cases reported in USA. Thus, there is a lack of evidence-based guidance on management of M. abscessus PD catheter infections. During routine clinical care, we encountered several patients with PD related infections due to M. abscessus. We sought to determine risk factors for M. abscessus PD catheter associated infections and describe treatment outcomes.

Methods: This is a retrospective study in which medical records from one 700-bed tertiary care hospital and one regional dialysis center were reviewed. Information was abstracted to a study-case specific case report form. Epidemiological, clinical characteristics, M. Abscessus complex subtypes, management, and fate of PD were explored. This study was approved by relevant IRBs.

Results: We identified 7 patients diagnosed with M. abscessus PD catheter infection. Among these 7 patients, 4 (57%) presented with symptoms suggestive of peritonitis and 3 (43%) with exit site infections (ESI) / tunnel infections. 7% were males (4/7) with median age of 42 years (range 42-88). Original kidney disease was diabetic nephropathy in 57% (4/7) and mean time on PD before developing NTM infection was 20.5 months. Subspecies were identified in 6 (85%) and revealed 4 (57%) with abscessus and 2 (28%) with massiliense. 5 patients (72%) were managed with upfront PD catheter removal and antibiotics with good outcomes. PD catheter salvage was attempted in two patients (28%) initially presenting with ESI. One of these patients progressed over a year to peritonitis and tunnel abscess due to M. abscessus despite continued antibiotics. The other was shifted to hemodialysis (with PD catheter removal) after persistent M. abscessus ESI in the context of antibiotic intolerances.

Conclusions: M. abscessus is an important cause of PD catheter-associated infections. Management of peritonitis and tunnel infections requires catheter removal and prolonged antimicrobial therapy. Catheter removal should be considered in people with ESI.

Peritonitis-Free Survival in Peritoneal Dialysis According to Staphylococcus spp. Nasal Carriage
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Background: Mexico ranks second with the highest prevalence of peritoneal dialysis (PD) in Latin America. Yucatan in Mexico has the highest prevalence of obesity, diabetes, and kidney stones, the main risk factors for progression to kidney failure (KF). The Agustin O’Haran General Hospital receives patients with chronic kidney disease without affiliation to any health service in which PD is the first line treatment for KF. In our center, PD associated peritonitis continues to be a major cause of hospitalization, PD failure, transition to hemodialysis, and even death. Previous reports suggested that nasal carriage of Staphylococcus spp (SS) conferred an increased risk of PD related peritonitis, however this notion has been challenged by new evidence.

Methods: We conducted a prospective study from March 1st 2019 to March 31st 2023. We included all incident PD patients who underwent nasal swabbing prior to PD catheter placement. Patients were followed for at least 30 days after PD catheter placement. Patients were followed up for at least 30 days after the PD catheter placement. We included all PD patients who underwent nasal swabbing prior to PD catheter placement. Patients were followed for at least 30 days after PD catheter placement with a mean follow up of 138.9 days. Data were censored for patients who had mechanical complications, did not develop peritonitis or were lost to follow up. 46 cases of peritonitis occurred during the follow up. The etiology of PD related peritonitis included 17 SS, 14 non SS, 8 polymicrobial and 7 TN peritonitis cases. Peritonitis free survival in nasal carriers of SS was 76.2% compared to 69.3% in patients with CN. There was no significant difference in peritonitis free survival between the two groups.

Conclusions: Nasal carriage of SS does not appear to have an impact on peritonitis free survival. The benefit of performing a nasal culture prior to PD catheter placement remains to be elucidated.

Peritonitis Impact on Technique Failure and Time to First Peritonitis Event in Peritoneal Dialysis: A Retrospective Multicenter Cohort Study in the National Health System of the Dominican Republic
Sergio D. Hernandez-Ordonez,1* Erwin I. Campos,1,2 Elianny S. Polanco,1 Zuñiga Lara,1 Mercedes Aquie,1 Jose C. Divino-Filho,1 Janny Guzman Chavez,1 Miguel A. Cuevas Budhant,1 Alfonso Ramos,1 Mackrotech,1,3 Macrotech,4 Santo Domingo, Dominican Republic; 2Pontificia Universidad Catolica Madre y Maestra - Campus Santo Tomas de Aquino, Santo Domingo, Dominican Republic; 3Karolinska Institutet Enheten for medicinska njursjukdomar, Huddinge, Sweden; 4Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico; 5Universidad Nacional Autonoma de Mexico Departamento de Educacion Medica, Tlalnepantla, Mexico.

Background: Peritonitis is a concern in peritoneal dialysis (PD) as it is a common complication that impacts outcomes and technical survival. It is a frequent cause of technique failure. The aim of this study is to estimate the impact of peritonitis on technique failure and determine the time to the presentation of the first peritonitis event.

Methods: A retrospective, multicenter, and descriptive cohort study was conducted on patients enrolled in the home PD program of the National Health System of the Dominican Republic. Peritonitis was diagnosed based on the ISPD guidelines. The analysis included incident PD patients enrolled between January 1st, 2016, and December 31st, 2022. Demographic data were collected and presented as mean ± SD for quantitative variables, while qualitative variables were reported as absolute and relative frequencies. A Binary logistic regression was performed for the possible association between variables of interest using Odds Ratio, with a confidence interval of 95% and p value < 0.05. To assess survival, only peritonitis events were considered using Kaplan-Meier curves and the Log-Rank test.

Results: We studied 4,476 incident patients with a median follow-up of 693 days, with a range of 30 to 2,465 days. The mean age was 57 ± 15 years, and 58% of the patients were males. Among the patients, 393 (8.7%) experienced a peritonitis event, with 53 (1.1%) having two events, and 10 (0.22%) patients experiencing three or more events. Out of the 11 cases of a single peritonitis event, 79% were cured, 12% transitioned to hemodialysis (HD), and 7.9% died. The median time to the first peritonitis events was 474 days (CI 431-517). The factors associated with the development of peritonitis were patients older than 65 years (OR: 1.94; 95% CI: 1.49-2.52; p<.001) and having been on therapy for more than a two-year period (OR: 2.86; 95% CI: 2.10-3.88).

Conclusions: in this analysis, factors such as older age and a longer duration of therapy were associated with an increased risk of developing peritonitis. The time at the first event is higher than reported in other studies. These highlight the importance of implementing preventive strategies and close monitoring in PD.

Funding: Commercial Support - Macrotech

Peritonitis Impact on Technique Failure and Time to First Peritonitis Event in Peritoneal Dialysis: A Retrospective Multicenter Cohort Study in the National Health System of the Dominican Republic
Sergio D. Hernandez-Ordonez,1* Erwin I. Campos,1,2 Elianny S. Polanco,1 Zuñiga Lara,1 Mercedes Aquie,1 Jose C. Divino-Filho,1 Janny Guzman Chavez,1 Miguel A. Cuevas Budhant,1 Alfonso Ramos,1 Mackrotech,1,3 Macrotech,4 Santo Domingo, Dominican Republic; 2Pontificia Universidad Catolica Madre y Maestra - Campus Santo Tomas de Aquino, Santo Domingo, Dominican Republic; 3Karolinska Institutet Enheten for medicinska njursjukdomar, Huddinge, Sweden; 4Instituto Mexicano del Seguro Social, Ciudad de Mexico, Mexico; 5Universidad Nacional Autonoma de Mexico Departamento de Educacion Medica, Tlalnepantla, Mexico.

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Funding: Commercial Support - Macrotech
Urine Dipstick: A Point-of-Care Tool for the Diagnosis of Peritoneal Dialysis-Associated Peritonitis

Juan P. Gomez Villarreal, Ricardo A. Garza Treviño, Rita B. Aguilar, Mara C. Olivo Gutierrez, Giovanna Y. Arteaga Muller, Lilia M. Rizo Topete, Elisa M. Guerrero Gonzalez. Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico.

Background: PD-associated peritonitis is a complication that impacts the morbidity and mortality of patients. The ISPD recommends diagnosing peritonitis when at least two of the following criteria are met: clinical features such as abdominal pain or cloudy dialysis effluent, dialysis effluent WBC > 100×10⁶/L with > 50% PMN, or positive dialysis effluent culture. The Spanish Society of Nephrology suggests using a urine dipstick for early diagnosis based on a new strip designed to test PD fluid.

Methods: A prospective study was conducted at the Hospital Universitario Dr. José Eleuterio González, evaluating consultations for PD-associated peritonitis from the emergency department to the nephrology department during August 2022 through February 2023. After a 2-hour exchange, samples were taken and the strip testing (Siemens multistix10 SG) were to the laboratory for cytochemical analysis, culture. The strip results were read while waiting for a 2-minute and were interpreted by a nephrologist.

Results: 30 patients were screened, confirming the diagnosis of PD-associated peritonitis based on the strip and cytochemical results. The demographic data shown in Table 1. The strip tested showed a sensitivity of 75% and specificity of 100% when using a cutoff of 3 crosses. However, these values changed when using a cutoff of 2 crosses, resulting in a sensitivity of 95% and specificity of 100%.

Conclusions: Urine dipsticks are feasible, and cheap tools that can be useful for the diagnosis of PD-associated peritonitis with great sensitivity and specificity saving time for the initiation of the antibiotic. It also helps conserve resources and enables patients to continue treatment outside the clinic using a simple method.

Peritoneal Dialysis and Technique Survival in Diabetic Patients

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Background: Management of end stage renal disease (ESRD) in diabetic patients is an ongoing challenge. Despite potential adverse metabolic effects, peritoneal dialysis (PD) is considered safe and suitable in diabetic ESRD treatment. Previous descriptions of poor technique survival have been contradicted by recent studies, in line with improved dialysis technique and reduced technique-associated complications. We evaluated technique survival in diabetic patients on PD.

Methods: Clinical records of incident PD patients from 2000-2022 were examined. Kaplan-Meier method and log-rank test were used to compare technique survival rate between diabetic and non-diabetic patients. Adjusted HR were calculated using Cox regression.

Results: A total 235 incident PD patients were included, 23% diabetic. Mean age of PD onset 54 ± 15 years. Patients with diabetes mellitus (DM) were older (61±14 vs 41±15 years), mostly male (74 vs 24%), with higher cardiovascular (CV) burden (p=0.05). Assisted PD modality was more prevalent in this group (29 vs 5%, p=0.05). Median technique survival in DM and non-DM patients was 31 (CI 95% 22-39) and 52 months (CI 95% 42-62), respectively (p<0.002). Main reasons for PD suspension included technical failure (39%) and PD-associated infectious complications (35%). No significant difference in Infectious complications was observed between the two groups (35% vs. 44%, p=0.513). Modality suspension due to autonomy loss was higher in DM group (12% vs. 3%, p=0.05). In the univariate model, rate of technique failure was higher in the DM group (HR=1.9, CI 95% 1.2-2.8, P=0.003). This association was not verified in the multivariate model. Due to protocol changes in PD prescription after the availability of biocompatible solutions, separate time period analysis before and after 2008 revealed HR 4.7 (CI 0.5% 0.73-29.0 P=0.007) and HR of 1.3 (CI 95% 0.3-2.2, p=0.415), respectively.

Conclusions: Decreased technique survival in DM patients was not verified when considering separate time period analysis, with better outcomes in recent years. This reflects technical improvements, biocompatible solutions and prescription tailoring. CV management remains key, and strategies to mitigate the menace of autonomy loss are essential in this subgroup, including helper signaling and increased support for assisted PD.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO639
Success Rates and Safety of Two Non-Guided Percutaneous Catheter Placement Techniques for Peritoneal Dialysis in Urgent-Start Dialysis: A Single-Center Experience Retrospective Cohort Study
Rafael Moreno-Novala, Froylan David Martínez-Sanchez, Mauricio A. Salinas-Ramírez, Joana B. Juarez, Erika K. Tenorio-Aguirre. Hospital General Dr. Manuel Geu González, Mexico City, Mexico.

Background: The optimal technique for catheter placement in uremic patients remains debated. In our center we have been using our non-guided percutaneous modified Seldinger technique. With the availability of the peritoneal dialysis catheter kit in our center, we modified our non-guided Seldinger technique for patients with urgent start dialysis requirement.

Methods: This was a single-center retrospective cohort study of patients hospitalized with urgent-start dialysis requirement of a single center in Mexico City. We aimed to summarize the success rates and safety of our two percutaneous non-guided insertion methods.

Results: A total of 117 patients with urgent-start dialysis requirement were included. Two percutaneous catheter insertion techniques were used, the non-guided percutaneous modified Seldinger technique 62.9% and the non-guided percutaneous modified Seldinger technique with peritoneal dialysis catheter kit technique 48.1%. The mean age of the patients was 54.92 ± 14.49 years, 40.5% were women, the mean body mass index (BMI) was 25.79 ± 4.77 kg/m², BUN 95 ± 57 and the median in-hospital stay was 19.28 (10-20) days. Overall, 73.3% had diabetes, 76.7% hypertension, and the time from admission to catheter insertion was 7 (3-10) days. The analysis showed that the patients who underwent placement with peritoneal dialysis catheter kit had fewer replacement requirement (p=0.028), and there was no difference in migration, peritonitis, and catheter leak between both groups.

Conclusions: The use of the peritoneal dialysis catheter kit in urgent start dialysis requirement provided less catheter replacement.

SA-PO640
Evaluation of Impact of Residual Renal Function on Clinical Outcome, Quality of Life, and Prognosis in Patients on Continuous Ambulatory Peritoneal Dialysis (CAPD)
Sweety Kakoti, Mitul Bora, Tomnony Das, Dhruvajyoti Choudhary. Apollo Hospitals Guwahati, Guwahati, India.

Background: Residual renal function (RRF) in patients with ESRD receiving dialysis is defined as the ability of the native kidneys to eliminate water and uremic toxins. It provides small solute clearance, has role in maintaining fluid balance, phosphorus control, and removal of middle molecular uremic toxins, and contributes significantly to the overall health. It is a powerful predictor of mortality.

Methods: A Prospective Observational Study conducted in Apollo Hospitals, Guwahati for 1 year. Study Population included all patients who were initiated on CAPD during this study period after excluding those fulfilling exclusion criteria. Their RRF was calculated as the average of urea clearance (Kru) and creatinine clearance (Crcl) in 24 hrs doing nocturnal HHD. Demographics and results from the survey are presented in table 1. A total of 77 patients (age of 50.7 years, 15.6% female, and 23.4% with diabetes) were included. All patients self-punctured their AVF, and the median frequency of dialysis was five sessions per week. During a median follow-up of 116 months, we observed 11 deaths and 19 instances of TF. Unadjusted 5- and 10-year adverse event-free survival was 83.5 and 67.2%, respectively. Both age (aHR 1.09) and diabetes (aHR 4.17) were significantly associated with TF. Cardiovascular disease was the most frequent cause of death, and VA trouble was the primary cause of TF. VA-related TF occurred after 100 months of HHD initiation.

Conclusions: Although the long-term prognosis of HHD patients was favorable, access-related TFs occurred more frequently in patients with long-term HHD. Thus, careful management of VA is important to improve treatment survival.

SA-PO641
Predictors of Long-Term Patient and Technique Survival in Home Hemodialysis Patients

Background: Home Hemodialysis (HHD) enhances patient quality of life and survival, yet it also increases the risk of access-related complications due to the frequency of treatments. The influence of these complications on long-term treatment survival, particularly in patients with arteriovenous fistulas (AVF), remains unclear. Therefore, our study aims to follow AVF patients over a prolonged period to evaluate long-term treatment survival and identify its predictors in HHD patients.

Methods: We conducted an observational study involving all incident HHD patients at our facility from 2001 to 2020. The cumulative incidence of all-cause mortality and procedure failure (TF) as a composite outcome was calculated at 5- and 10-year intervals. Cox proportional hazards models were used to identify patient characteristics or comorbidities that predicted TF and death.

Results: A total of 77 patients (age of 50.7 years, 15.6% female, and 23.4% with diabetes) were included. All patients self-punctured their AVF, and the median frequency of dialysis was five sessions per week. During a median follow-up of 116 months, we observed 11 deaths and 19 instances of TF. Unadjusted 5- and 10-year adverse event-free survival was 83.5 and 67.2%, respectively. Both age (aHR 1.09) and diabetes (aHR 4.17) were significantly associated with TF. Cardiovascular disease was the most frequent cause of death, and VA trouble was the primary cause of TF. VA-related TF occurred after 100 months of HHD initiation.

Conclusions: Although the long-term prognosis of HHD patients was favorable, access-related TFs occurred more frequently in patients with long-term HHD. Thus, careful management of VA is important to improve treatment survival.

SA-PO642
Reframing the Role of Buttonhole Cannulation (BHC) in the Home Hemodialysis (HHD) and Self-Care Settings: Outcomes of BHC as a Primary Technique in a Large Single-Center HHD Program
Waleed Zafar, Maria Bermudez. Geisinger Medical Center, Danville, PA.

Background: HHD remains underutilized in the U.S. Fear of needle insertion is one of the main patient barriers for widespread adoption of HHD. BHC, once considered the preferred method for self-cannulation given patient- and fistula-friendliness, has fallen out of favor due to concerns about infectious complications. The quality of evidence concerning potential risks of BHC is low. We describe experience from a single center HHD program regarding utilization of BHC technique.

Methods: Patients currently enrolled in the HHD program were surveyed regarding the use of BHC. Since the program predominantly utilizes BHC, we also evaluated the incidence of bacteremia in all patients enrolled in the HHD program between 2008 and 2022. Results: Between 2008 and 2022 a total of 76 patients were ever enrolled in the HHD program at a single center of whom 18 (23.7%) were currently active, 13 were successfully transplanted, 19 transitioned to in-center hemodialysis and 23 died. No episodes of bacteremia were documented in the HHD program over this period. 14 of the 18 currently active patients who had arteriovenous fistulas were surveyed and 13 of them used BHC technique. All but 2 patients did short daily HHD with remaining two doing nocturnal HHD. Demographics and results from the survey are presented in table 1.

Conclusions: Our 14-year single center experience with BHC has helped develop key elements for the successful implementation of this technique: a single cannulator per fistula, multidisciplinary patient-centered selection, longitudinal education, strict infection control, and reliable nursing support. These have shown to be important in patient and care partner empowerment as well as low incidence of infectious and noninfectious complications.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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SA-PO643
A Nephrologist-Driven Percutaneous Peritoneal Dialysis Catheter Insertion Service Increases the Prevalence of Peritoneal Dialysis: A Single-Centre Experience in Singapore

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Background: The incidence and prevalence of end-stage kidney disease (ESKD) requiring dialysis is increasing all over the world, including Singapore. Despite the well-documented benefits of peritoneal dialysis (PD) in offering better quality of life and preservation of residual renal function, only around 15% of prevalent ESKD patients are on PD in Singapore. The aim of the study is to report the success of a percutaneous PD catheter insertion service in increasing the prevalence of PD in a large academic renal centre.

Methods: The number of prevalent PD patients was stagnant in our centre, over last 5 years, despite the consistent growth in the number of ESKD patients requiring dialysis during this period. From early 2022, the interventional nephrologists started a percutaneous PD catheter insertion service. Based on pre-determined criteria, the patients were selected for appropriate method of PD catheter insertion by the nephrologists, as illustrated in figure 1.

Results: Since 2022, 75.9% of the PD catheters were inserted percutaneously by interventional nephrologists, with appropriate selection of patients, is safe and reliable. This service provides timely access creation and increases the penetration of PD.

Conclusions: Percutaneous PD catheter insertion by nephrologists, with appropriate selection of patients, is safe and reliable. This service provides timely access creation and increases the penetration of PD.

SA-PO644
Longevity of Percutaneously Placed Peritoneal Dialysis (PD) Catheters: Single-Center Study

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Background: Percutaneously placed PD catheters have shown similar short-term (1 year) outcomes as compared to surgically placed catheters and have been used increasingly. Data on the longevity of these catheters are sparse.

Methods: We conducted a retrospective chart review study of 114 catheters in 91 patients who initiated PD between 2014 and 2020 at University Health System home dialysis center. The last follow-up was December 2022. PD catheters were placed percutaneously (n=81) either by interventional radiologists or nephrologists, or by laparoscopic surgery (n=33) when there were concerns of hernia or adhesions due to prior extensive abdominal surgery or refractory peritonitis. Demographic and clinical data were analyzed using descriptive statistics.

Results: In the percutaneous group, mean age was 46.4 ± 13 years, 66% were male, mean BMI was 29.6 kg/m² and diabetes was the cause of kidney failure in 69% of patients. The surgical cohort had similar demographics except mean BMI was 31.2 ± 7.6 kg/m². Median longevity of an individual catheter determined from PD start to cessation was 90.4 (30.6, 158.8) weeks for the percutaneous and 68.7 (29, 123) weeks for the surgical group. Reasons for catheter removal are shown in figure 1. The percutaneous group had 0.26 episodes of peritonitis per patient-year, while the surgical group had 0.40 episodes per patient-year. The most common mechanical complications were slow drain and leakage, and these were similar between the two groups. Non-randomization precludes comparison analysis between the groups.

Conclusions: This single-center experience demonstrates that percutaneously placed PD catheters are a viable alternative for long-term PD therapy. Further studies from large centers or databases are needed to confirm our findings which have implications for the direction of PD programs to allocate resources appropriately.
**SA-PO646**

**Surgical Outcomes Associated with Simple vs. Complex Peritoneal Dialysis Catheter Placement**

**Ankur Shah,1,2 Susie L. Hu,1,2 Christina A. Raker,1,2 Brown University Warren Alpert Medical School, Providence, RI; 2Rhode Island Hospital, Providence, RI.**

**Background:** Patients receiving peritoneal dialysis are dependent upon stable, reliable access to their peritoneal cavity via a surgical or percutaneously placed catheter. Advanced laparoscopic catheter placement has been demonstrated to have better catheter related outcomes compared to simple placement. In this study, we report baseline characteristics and 30 day surgical outcomes of simple versus complex laparoscopic PD catheter placement in a national US based cohort.

**Methods:** We conducted a retrospective analysis using the NSQIP database from January 1, 2013, to December 31, 2018. Patients who underwent peritoneal dialysis catheter placement were identified using relevant Current Procedural Terminology (CPT) codes. Simple catheter insertion was defined as the absence of additional procedures while complex was defined as catheter extension or omentopexy. Data on patient characteristics, surgical approach (simple or complex), and postoperative outcomes were extracted. The primary outcomes of interest included death, length of stay, and surgical site infection.

**Results:** A total of 9,593 patients who underwent laparoscopic peritoneal dialysis catheter placement were included in the analysis. Of these 89.95% received simple catheter placement, while 10.05% underwent advanced techniques. Patients who underwent complex catheter placement had no difference in mortality (adjusted odds ratio (aOR) 0.54, 95% CI 0.34 – 0.73, p = 0.06), or prolonged length of stay (>7 days) (OR 0.95, 95% CI 0.91 – 1.00, p = 0.63) compared to patients receiving simple catheter placement.

**Conclusions:** This study demonstrates that advanced peritoneal dialysis catheter placement techniques are associated with similar surgical outcomes compared to simple techniques. It is already known that patients receiving advanced catheter placement have lower rates of catheter tip migration, flow obstruction, and better long term catheter survival. These findings suggest that the adoption of advanced techniques may lead to improved long-term catheter related outcomes without sacrificing short term surgical outcomes.

**Funding:** Clinical Revenue Support

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**SA-PO647**

**Evaluating the Impact of the Advancing American Kidney Health Executive Order on Global Search Interest: An Interrupted Time Series Analysis**

**Ankur Shah,1,2 Roger Chou,1 Susie L. Hu,1,2 Christina A. Raker,1,2 Brown University Warren Alpert Medical School, Providence, RI; 2Rhode Island Hospital, Providence, RI.**

**Background:** AAKH aimed to improve kidney health outcomes by transforming the kidney care landscape. Understanding the general impact of such policy interventions is crucial for public health surveillance and policy planning.

**Methods:** We conducted a retrospective analysis using Google Trends data from two time periods: January 1, 2013, to December 31, 2018, and January 1, 2019, to December 31, 2021. Search interest data were extracted using relevant keywords related to kidney health and care. An interrupted time series analysis was performed to assess the impact of the AAKH executive order on global search interest trends. Segmentation was conducted at the time of policy implementation (July 2019) to compare pre- and post-intervention periods.

**Results:** Overall, interest in home dialysis, home hemodialysis, and peritoneal dialysis were steadily increasing in both the USA and globally. In the USA and globally, relative interest in peritoneal dialysis outweighed home hemodialysis. Home hemodialysis had the greatest variability in RSV with 2014 and 2015 had zero RSVs, leading to the observed dip in the lowest curve.

**Conclusions:** AAKH has not increased awareness of home dialysis beyond the nephrology community. More steps must be taken to raise awareness and understanding of home dialysis.

**Funding:** Clinical Revenue Support

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**SA-PO645**

**Medical Peritoneal Dialysis Catheter Insertion Can Increase Peritoneal Dialysis (PD) Patient Population: A Single-Centre Study**

**James Talbot-Ponsonby, Yasar Z. Khan, Daniel Jones, Seema Shrivastava, Edward Stern. St George’s University Hospitals NHS Foundation Trust, London, United Kingdom.**

**Background:** Peritoneal dialysis (PD) can offer improvement in quality of life and treatment costs compared to hemodialysis. Access to PD is often limited by catheter insertion facilities. PD catheters can be inserted surgically (laparoscopic or open, both typically under general anaesthesia) or medically (percutaneous, under local anaesthesia).

We examined the benefits of introducing a medical PD catheter service in a tertiary renal unit in addition to a surgical service which was already available.

**Methods:** Safety data (incidence of peritonitis within 90 days and of catheter malpositioning) were reviewed in the electronic health record from July 2017-June 2019 (surgical insertions alone) and July 2019-June 2021 (medical and surgical insertions). PD prevalence was tracked over 6 years.

**Results:** From June 2017-July 2019 there were 44 surgical catheter insertions compared to 63 (33 medical, 30 surgical) from July 2019-June 2021: a 43% increase in incident PD patients. There was no significant difference in early peritonitis (14% in surgical vs 15% in medical, p=0.77) or malposition (7% in surgical vs 9% in medical, p=0.70). Prevalent PD patients fell by 15% from 2016-2019 but grew by 79% in the 3 years after introduction of medical catheter insertions.

**Conclusions:** Introducing percutaneous PD catheter insertion by nephrologists was associated with an increase in PD patients with no increase in complications. Contraindications to medical insertion include significant obesity or previous major abdominal surgery. A hybrid medical/surgical service allowed most patients to be offered PD while avoiding general anaesthesia and minimising operating theatre usage. A limitation in this study is the groups arent matched for complication risk: technically challenging patients will tend to be offered surgical insertion. Nevertheless, we demonstrated that introduction of medical PD catheter insertion can grow the PD population without an increase in complications.

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Comparison of USA vs. Global changes in trends pre- and post-AAKH by segmented linear regression.

### Key:
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USA trends in relative search volume, 2012-2021

SA-PO649

Creatinine Clearance Predicts Longitudinal Phosphate Levels Irrespective of Achieved Urea Kt/V: A Peritoneal Dialysis-MONDO Analysis

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Background: Serum phosphate (PO4) is associated with worse outcomes among kidney failure patients, and its dialysis clearance is not well predicted by small solute kinetics. Guidelines in peritoneal dialysis (PD) recommend using urea Kt/V over creatinine clearance (CrCl) to monitor dialysis adequacy. We hypothesize that this recommendation may lead to suboptimal PO4 control. We designed this study to evaluate if CrCl predicts longitudinal PO4 irrespective of achieved Kt/V.

Methods: We performed a longitudinal analysis of multiple cohorts of incident PD patients – Fresenius Medical Care Latin America (FMC-LATAM), Renal Research Institute (RRI), Mount Sinai Hospital, Hospital Civil Guadalajara, and the BRAZPD cohort. The exposures were first available Kt/V and CrCl after 90 days of PD initiation. The outcome was longitudinal PO4. Results were pooled using a random-effects metaanalysis. The primary estimate was the linear coefficient from linear mixed regression models with random effects. Models were then compared by log-likelihood ratios (LLR) to assess the information added by CrCl on models with Kt/V.

Results: 16.796 patients were included – RRI (n=653), Sinai (n=131), BRAZPD (n=171), LATAM (n=15631), and Guadalajara (n=210). Mean ages ranged from 45 (Guadalajara) to 58 years (Sinai). In most datasets, Kt/V and CrCl were associated with longitudinal PO4 despite adjusting for sex, age, and PO4 binder use. The pooled estimates, despite being heterogeneous, confirmed the results (Figure). For all datasets, including CrCl on models adjusted with Kt/V improved information (LLR tests p< 0.05 for all datasets).

Conclusions: Among incident PD patients, CrCl predicts longitudinal PO4 irrespective of achieved urea Kt/V. Our results suggest that CrCl may be an important measurement in clinical practice to monitor PO4 clearance in PD patients.

SA-PO650

Effect of Roxadustat vs. Erythropoietin on Nutritional Status in Peritoneal Dialysis Patients: A Retrospective Study

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Background: Roxadustat have been used to treat renal anemia in patients undergoing dialysis. The effect of roxadustat on nutritional status in peritoneal dialysis (PD) patients remains uncertain. We aimed to explore the effect of roxadustat on nutritional status, and explore the possible modifiers for the association in PD patients.

Methods: The current study included 136 PD patients with renal anemia. The primary efficacy endpoints included changes from baseline in nutrition-related parameters. Linear regression analysis was performed to analyze the correlation between use of roxadustat with Subjective Global Assessment (SGA) and Malnutrition-Inflammation Score (MIS). Logistics regression analysis was used to evaluate the risk factors for the indicators of MIS.

Results: After a median treatment observation of 20.0 (25%-75%=16.0–21.0) months, the changes from baseline in serum albumin, prealbumin, total cholesterol, high-density lipoprotein cholesterol, blood urea nitrogen and creatinine levels were not significantly different between two groups. Besides, the use of roxadustat was inversely associated with MIS (β=-0.263; 95% CI: -2.430, -0.096), and was positively associated with SGA (β= 0.440; 95% CI: 0.045, 0.834). Additionally, compared to patients in rHuEPO group, those with the use of roxadustat were associated with more dietary intake (OR, 0.405; 95% CI: 0.190-0.865) and fewer gastrointestinal symptoms (OR, 0.365; 95% CI: 0.164-0.809).

The inverse association between the use of roxadustat with MIS was stronger in patients without RRF (P for interaction=0.019).

Conclusions: In short, this study found that the use of roxadustat was inversely associated with MIS and positively associated with SGA in PD patients.

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SA-PO651

Profiles of Iron and Anemia Indices and Associations in Mental Health Among Incident Peritoneal Dialysis Patients in Brazil and the United States

**Vladimir Rigolod,1,2 Peter G. Pecoits,3,5 John W. Larkin,2 Yue Jiao,2 Len A. Usvyat,1 Franklin W. Maddux,2 Peter Kotanko,1,3 Roberto Pecoits-Filho,1 Thyago P. Moraes,3 Murilo H. Guedes,1,3 Pontificia Universidade Catolica do Parana, Curitiba, Brazil; 4Fresenius Medical Care, Waltham, MA; 5Renal Research Institute, New York, NY; 6Fresenius Medical Care, Cremona, Italy; 7Icahn School of Medicine at Mount Sinai, New York, NY; 8EPICENTER - Center for Epidemiology and Clinical Research, Curitiba, Brazil.

**Background:** Management of iron stores and anemia are important to maintaining quality of life in dialysis, yet the associations in mental health are unknown in Peritoneal Dialysis (PD). We aimed to identify and describe the trends in KDQOL mental component summary (MCS) scores and cohort-characteristics in patients starting PD in Brazil (BR) and the United States (US), with a focus on iron and anemia indices and related medication use.

**Methods:** Patients included data on adults who started PD between Dec 2004-Jan 2011, that had ≥1 TSAT, hemoglobin (Hgb), ferritin, and KDQOL result within the first 180 days of PD. We described the BR and US cohort characteristics based on the following MCS categories: ≤35, >35-40, >40-50, >50. Higher MCS scores show better mental health. This preliminary analysis is descriptive, and it does not include multivariable adjustments.

**Results:** In both cohorts (BR=2022 vs US=1657), age (mean age in BR=57.3 vs US=55.6) and albumin levels were consistent (both ≥3.7 g/dL). The US cohort had fewer males (BR=45% vs US=54%) and more patients with a white race (BR=62% vs US=72%). TSAT levels and erythropoietin stimulating agent use were higher in the US vs BR (Figure). Lower MCS scores were associated with higher ferritin & TSAT levels in BR, though not observed in the US. Higher MCS scores were positively associated with IV iron use in the US, but not observed in BR. Younger patients showed the lowest MCS scores in the US, while the inverse was found in BR.

**Conclusions:** In this preliminary descriptive analysis, we found some unique profiles in iron and anemia markers associated with mental health outcomes. Although some of these findings may be related to practice patterns, iron and anemia management may potentially influence the mental health of patients at PD initiation. Further investigations are needed to understand this relationship and its implications for patient care and outcomes.

**Funding:** Commercial Support - Pontificia Universidade Catolica do Parana, Fresenius Medical Care, BaxterHealthcare

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**SA-PO652**

**Higher Iron Deficiency Rates Among Incident Peritoneal Dialysis Patients Without Anemia in Brazil and United States**

**Vladimir Rigolod,1,2 Brianna Hartley,1,3 Peter G. Pecoits,3 Yue Jiao,2 John W. Larkin,2 Luca Neri,2 Len A. Usvyat,1 Franklin W. Maddux,2 Jeroen Kooman,1 Peter Kotanko,1,3 Roberto Pecoits-Filho,1 Thyago P. Moraes,1,3 Murilo H. Guedes,1,3 Pontificia Universidade Catolica do Parana, Curitiba, Brazil; 4Fresenius Medical Care, Waltham, MA; 5Nova Southeastern University, Clearwater, FL; 6Maastricht University Medical Center, Maastricht, Netherlands; 7Renal Research Institute, New York, NY; 8Fresenius Medical Care, Cremona, Italy; 9Icahn School of Medicine at Mount Sinai, New York, NY; 10EPICENTER - Center for Epidemiology and Clinical Research, Curitiba, Brazil.

**Background:** The profiles of iron deficiency (ID) are undefined in the peritoneal dialysis (PD) population. This study examines the prevalence of and patient characteristics associated with ID states and the coexistence of anemia in incident PD patients in the United States (US) and Brazil (BR).

**Methods:** We used data from adults starting PD at 122 clinics in BR and >2500 clinics in the US. We included patients who had at least 1 hemoglobin (Hgb), ferritin, and transferrin saturation (TSAT) measurement within 180 days of PD start. ID was defined as TSAT <20%. ID states were categorized as: a. functional ID, no anemia (TSAT <20%, ferritin >200 ng/mL, Hgb ≥10 g/dL), b. functional ID with anemia (TSAT <20%, ferritin >200 ng/mL, Hgb <10 g/dL), c. absolute ID, no anemia (TSAT <20%, ferritin >200 ng/mL, Hgb <10 g/dL), and d. absolute ID with anemia (TSAT <20%, ferritin >200 ng/mL, Hgb <10 g/dL).

**Results:** Patients starting PD in BR (n=1,365) and the US (n=12,303) had mean age of 59.8 (BR) & 55.2 (US) years, 46.4% (BR) & 55% (US) were male, 61% (BR) & 70% (US) were of a white race. ID was present in >10% of incident PD patients, with a slightly higher prevalence in BR (~4 percentage points). Rates of ID states were relatively consistent in BR and US for functional and absolute ID in patients without anemia, and these represent ≥80% of all ID cases (Figure 1). However, functional and absolute ID rates among patients with uncontrolled anemia were ≥3 fold higher in BR vs US.

**Conclusions:** Prevalence of ID at PD start is >10.6% and ID primarily exists in patients without anemia in both BR and US. Current recommendations suggest ID screening in patients with low Hgb, considerations that may be having implications on patient care. For instance, patients with functional ID had mean ferritin >400 ng/mL, yet levels were ≥150 ng/mL higher in those with vs without anemia. Ongoing research is underway to understand the trajectories and outcomes associated with ID in PD.

**Funding:** Commercial Support - Pontificia Universidade Catolica do Parana, Fresenius Medical Care, BaxterHealthcare

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**SA-PO653**

**Constipation and Clinical Outcomes in Peritoneal Dialysis: Results from Thailand PDOPPS**

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**Background:** Patient-reported outcome measures (PROM) has gained international recognition as important predictors of clinical outcomes in peritoneal dialysis (PD). We sought to understand the associations between patient-reported constipation and clinical outcomes.

**Methods:** Constipation was determined in patients across 22 facilities in Thailand Peritoneal Dialysis Outcomes and Practices Study (PDOPPS) during 2014-2017. Constipation was diagnosed using both objective assessment tools (Bristol Stool Form Scale [BSFS]) and self-reported questionnaire, constipation severity score (CSS). BSFS is a 7-level scale visual inspection of feces (from 1 to 7, from hard to softer) based on its texture and morphology. Whilst the CSS measures duration (1 item) and severity (7 items: frequency of bowel movement, difficulty, pain, completelessness, attempt duration, defecation assistance, frequency of attempt failure) of constipation and is a self-filled questionnaire, with participants being asked to respond on a 5-point Likert scale coded.

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Cox proportional hazards model regression was used to estimate associations between comorbidity and clinical outcomes, including mortality, hemodialysis (HD) transfer and peritonitis.

**Results:** 634 of 975 randomly selected PD patients from 22 facilities reported their constipation by using BSFS and CSS. In this questionnaire, the patients rated their constipation as well as a change in constipation over time. Constipation was common in the PD population, particularly in patients with older age, marriage, diabetes, lower educational level, and worse nutritional status (including lower time-average serum albumin and phosphate concentrations). Interestingly, self-reported constipation at baseline was significantly associated with shorter time to first and higher rates of peritonitis (hazard ratio [HR] 1.74, 95%CI 1.29-2.34) and death (HR 2.43, 95%CI 1.82-3.24) but not HD transfer (HR 1.25, 95%CI 0.7-2.21) after adjusting for age, gender, PD vintage, comorbidities, shared frailty by study sites, and serum albumin.

**Conclusions:** Patient-reported constipation was independently associated with higher risks of peritonitis and all-cause mortality, but not HD transfer. This warrants further investigation to identify effective interventions.

**SA-PO654**

**Role of Remote Monitoring in Automated Peritoneal Dialysis: Impact in SONG-PD (Standardized Outcomes in Nephrology-Peritoneal Dialysis) and Results from RPM-APD Multicenter Study**

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**Background:** The use of remote monitoring (RPM) in automated peritoneal dialysis (APD) has shown lower hospitalization rates in those patients who used this technique in addition to another series of clinical advantages such as greater technique survival. The present study evaluated the association between RPM use and SONG-PD outcomes.

**Methods:** A prospective observational multicenter cohort study included 232 patients in 16 Hospitals. A RPM program was used in 176 of the patients and 56 were treated with APD without RPM. The primary outcomes were standardized outcomes in Nephrology (SONG)-PD clinical outcomes and quality of life (EQ-5D-L). Data was recorded at least during 6 months. Propensity score matching (PSM) 1:1 was used to evaluate the association of RPM exposure with outcomes.

**Results:** There were no differences between baseline and demographic characteristics. Before PSM, APD with RPM (n=176) vs without RPM (n=56) was associated with less mortality (n=1 vs n=4)(HR 195%CI: 0.08 (0.01-0.69) (p=0.020) and with better technique survival (n=10 vs n=11) (HR 195%CI: 0.25 (0.11-0.59) p=0.001). After PSM, APD with RPM continued to associated with better technique survival (figures 1 and 2)

**Conclusions:** The use of an RPM program in APD patients may be associated with better technique survival. RPM could be a tool for improvement of APD therapy.

**Funding:** Commercial Support - Baxter Health Company

**Table 1. Clinical Outcomes Associated with RPM in Matched Sample**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>APD RPM N=56</th>
<th>APD without RPM N=56</th>
<th>OR (95%CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonitis</td>
<td>12 (21.4)</td>
<td>18 (32.1)</td>
<td>0.50 (0.37-0.72)</td>
<td>0.021</td>
</tr>
<tr>
<td>Infections per patient-year</td>
<td>1 (0.5)</td>
<td>2 (0.3)</td>
<td>3.11 (0.69-15.26)</td>
<td>0.792</td>
</tr>
<tr>
<td>Cardiorenal disease</td>
<td>1 (0.5)</td>
<td>2 (0.3)</td>
<td>3.92 (0.84-12.2)</td>
<td>0.061</td>
</tr>
<tr>
<td>Mortality</td>
<td>1 (1.8)</td>
<td>4 (7.1)</td>
<td>0.24 (0.03-2.26)</td>
<td>0.204</td>
</tr>
<tr>
<td>Technique survival</td>
<td>3 (5.6)</td>
<td>11 (19.3)</td>
<td>0.23 (0.09-0.63)</td>
<td>0.024</td>
</tr>
</tbody>
</table>

**SA-PO655**

**Association Between Age, Frailty, and Change in Health-Related Quality of Life After Dialysis Initiation?**

Maude Pichette,1 Louis-Philippe Laurant,1 Remi Goupil,1 Naouel Elftouh,1 Annie-Claire Nadeau-Frédette,2 1Hôpital Maisonneuve-Rosemont Centre de Recherche, Montreal, QC, Canada; 2Hôpital du Sacré-Cœur de Montréal Centre de Recherche, Montreal, QC, Canada.

**Background:** Despite its key importance, changes in health-related quality of life (HRQOL) after dialysis start are still poorly understood. This study aimed to assess the association between age, frailty and changes in HRQOL during the transition to home dialysis and in-center hemodialysis (ICHID).

**Methods:** HRQOL was measured using the KDQOL-SF questionnaire. Frailty was evaluated at study baseline using the Clinical Frailty Scale. Changes in physical component summary (PCS), mental component summary (MCS), and kidney-specific domains (burden, symptoms/problems and effects of kidney disease) were assessed in linear regressions comparing scores 6-months before and 6-months after dialysis start, with adjustment for age, frailty, dialysis modality and gender.

**Results:** Among a cohort of 121 CKD patients, 59 patients initiated dialysis (68 ±13 years, 61% ICHD and 39% home dialysis). HRQOL trajectories, stratified by age and frailty are illustrated in Figure 1. After adjustment, there were no statistically significant predictors associated with score changes at six months. There was however a nearly significant interaction between age and frailty (p=0.052) for MCS whereby frailty was associated with a trend towards decreased MCS for patients <65 years (B -18.1, 95% CI -37.4; 1.2, p=0.06), without a significant change in older patients. We also observed a trend towards improved score in the Problems/Symptoms in patients >65 years (vs <65 years) after dialysis start (B 10.7, -0.3; 21.7, p=0.055).

**Conclusions:** This small prospective study showed that age and frailty may be associated with HRQOL after dialysis start, although we did not identify statistically significant associations. It demonstrates the importance of individualizing the choice of kidney replacement therapy, avoiding generalizing the expected evolution of patients on the basis of isolated characteristics such as age or frailty.
International Comparison of Home Dialysis Uptake: A Multi-Registry Analysis from the INTEGRATED Research Group

Naoual Elftouh,1,2 Isabelle Ethier,1,2 David W. Johnson,3,4 Eric D. Weinhandl,1 Karthik K. Tennakone,2,5 Thierry Llobbedez,2,6 Clémence Béchade,1,7 Naoual Elftouh,1,2 Mark Lambie,1,8 Annie-Claire Nadeau-Fredette,1,9 INTEGRATED Research Group,1 Centre Hospitalier Universitaire de Caen, Caen, France; 2Cancers et préventions, Caen, France; 3Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada; 4Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada; 5Princess Alexandra Hospital, Wooloongabba, QLD, Australia; 6The University of Queensland, Saint Lucia, QLD, Australia; 7University of Minnesota Twin Cities, Minneapolis, MN; 8Dalhousie University Faculty of Medicine, Halifax, NS, Canada; 9Keele University Faculty of Medicine & Health Sciences, Keele, United Kingdom; 10Royal Stoke University Hospital, Stoke-on-Trent, United Kingdom; 11Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada; 12Hôpital Maisonneuve-Rosemont Centre de Recherche, Montreal, QC, Canada.

Background: There is a wide variability in home dialysis use from a high of 50% of patients receiving home dialysis in New Zealand to less than 10% in France. We aimed to compare patterns and predictors of home dialysis uptake across different registries.

Methods: This multi-national registry study of home dialysis included data from Australia, New Zealand, Canada, France and USA. Analyses were performed independently in each registry using identical statistical approaches. Multivariable adjusted clustered Cox models were used to evaluate predictors of home dialysis initiation within the first year of kidney replacement therapy (KRT), excluding pre-emptive transplantation.

Results: The proportion of patients starting KRT on home dialysis was 29% in ANZDATA, 22% in CORR, 9.2% in REIN and 8.8% in USRDS. Patterns of transfer from in-center hemodialysis to home dialysis varied widely across countries, with a marked increase in the proportion of transfer to home dialysis 3 months after KRT start in CORR, ANZDATA and USRDS. After adjustment for patient-related characteristics, patients were most likely to initiate home dialysis within the first month of KRT in all registries. There was a diverging association between sex and home dialysis uptake: females had a lower use of home dialysis in Canada and Australia/New Zealand, and higher use in France and USA.

Conclusions: This study showed marked international differences in the pattern of home dialysis uptake within the first year of KRT. Further work should aim to identify how practice patterns, and governance strategies can mitigate these differences to improve access to home dialysis.

Funding: Private Foundation Support

Is the Cost of the New Home Dialysis Techniques Still Advantageous Compared to In-Centre Hemodialysis?

Dario Roccatello, Roberta Fenoglio, Savino Sciascia. University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases, Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, University of Turin, Turin, Italy.

Background: Three main factors should be considered in the economic evaluation of home dialysis: the progressive reduction in the cost of consumables for in-centre hemodialysis (IC-HD), the widespread use of incremental Peritoneal Dialysis, and the renewed interest in Home Hemodialysis (H-HD). Registries data on incidence and prevalence of dialysis modalities are heterogeneous, showing widespread underemployment of home dialysis. Based on results in clinical and quality of life benefits, underemployment could be no more justified.

Methods: We compared the direct and indirect costs of PD (53 patients), H-HD (21 patients) and IC-HD (180 patients) by measuring the dialysis activity performed from January 1, 2019 to December 31, 2019 at the San Giovanni Bosco Hub Hospital, Turin (Italy). A cost analysis of the different dialysis techniques (DP and HD, home and hospital) was also carried out.

Results: To obtain comparable weekly costs, the following strategy was applied: a) calculating the average weekly frequency of dialysis sessions based on the dialysis modality, b) normalizing the cost of individual sessions per patient per week, c) calculating the monthly and yearly costs. PD proved to be the least expensive (€ 23,314.79 per patient per year), while H-HD has a lower average cost than IC-HD (€ 35,535.00 vs € 40,708.98).

Conclusions: Our data analysis confirms the low cost of Continuous Ambulatory PD and PD. Compared to all other hemodialysis modalities and even Automated Peritoneal Dialysis, Home Bicarbonate Hemodialysis has the lowest costs and the weekly cost of Frequent Home Hemodialysis was found to be comparable to that of In-Centre Bicarbonate Hemodialysis.

Funding: Other U.S. Government Support

Factors Affecting Survival Rate in Diabetic Patients Who Underwent Immediate-Start Peritoneal Dialysis

Hyunjin Cho, Jee Young Lee, Jung Hwan Park, Young-II Jo. Division of Nephrology, Dept of Internal Medicine, Konkuk University Medical Center, Seoul, Republic of Korea. Konkuk University Medical Center, Gwangju-gu, Seoul, Republic of Korea.

Background: Peritoneal dialysis (PD) patients with diabetes mellitus (DM) are known to have poorer survival compared to PD patients without DM. However, there are few studies on risk factors associated with patient survival in diabetic end-stage renal
disease (ESRD) patients underwent PD. The aim of this study was to identify factors independently associated with patient survival in diabetic ESRD patients who received immediate-start peritoneal dialysis (ISPD) without a break-in-period.

**Methods:** In this retrospective cohort study, 178 consecutive patients who started PD at Konkuk University Hospital from August 2005 to March 2023 were enrolled, and 144 patients with ISPD were finally analyzed. These patients were divided into the DM and the non-DM group. The primary outcomes were factors independently associated with patient survival in the DM group, estimated using a Cox proportional hazards regression model. Kaplan-Meier method was used to calculate patient survival rates.

**Results:** Among 144 patients, 93 (64.3%) had diabetes. The 1-, 5-, and 10-year patient survival rates of the DM and non-DM group were 97.6%, 86.9%, 35.1% and 98.4%, 92.1%, 65.6%, retrospectively. Compared to the non-DM group, the DM group had significantly higher age and body mass index (BMI), and significantly lower hemoglobin and serum albumin levels. However, only CVD was independently associated with patient survival in the DM group in univariate analysis, and this association was confirmed in multivariate analysis (Table 1).

**Conclusions:** Our study showed that CVD was the only factor independently associated with patient survival in ISPD patients with diabetes. Other factors such as age, BMI, hemoglobin, and serum albumin level did not appear to affect patient survival in diabetic ESRD patients who underwent ISPD without a break-in-period.

### Table 1. Multivariable Cox regression analysis for 10-year patient survival in the diabetic group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00 (0.96-1.04)</td>
<td>0.933</td>
</tr>
<tr>
<td>BMI (kg/m²)▶</td>
<td>1.25 (1.13-1.38)</td>
<td>0.781</td>
</tr>
<tr>
<td>CVD</td>
<td>3.72 (1.03-12.64)</td>
<td>0.044</td>
</tr>
<tr>
<td>LK: acid</td>
<td>1.15 (0.92-1.41)</td>
<td>0.208</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.21 (0.89-5.53)</td>
<td>0.123</td>
</tr>
</tbody>
</table>

Table 1. Multivariable Cox regression analysis for 10-year patient survival in the diabetic group

SA-PO660

Healthcare Resource Utilization (HCRU) in Prevalent Dialysis Patients Undergoing Peritoneal Dialysis in the United States

Julie Rouette,¹ James B. Wetmore,²,³ Sally Wetten,⁴ Haifeng Guo,⁵ Gema Requena,⁶ Saying Li,⁷ George Mu,⁸ Liuyan Ma,⁶ Jolyon Fairburn-Beech,⁴ David T. Gilbertson,⁷ Anna Richards,⁸ Jianrong Liu,⁴ GSK, Montreal, QC, Canada; ⁷ Chronic Disease Research Group, Hennepin Healthcare Research Institute, Minneapolis, MN; ⁸ Division of Nephrology, Hennepin Healthcare, Minneapolis, MN; ⁹ GSK, Brentford, United Kingdom; ⁶ GSK, Collegeville, PA.

**Background:** CKD is associated with increased HCRU. The US prevalence of patients (pts) undergoing peritoneal dialysis (PD) has more than doubled since 2000. We characterized the HCRU rate in prevalent PD pts in the US.

**Methods:** This observational cohort study used 2017–2019 United States Renal Data System data. Adults (≥ 18 years [yrs]) undergoing PD on Jan 1, 2018 (index) and with 6 months of Medicare fee-for-service coverage prior to index (incl.) were included. Follow-up was from index until death, loss of Medicare coverage, kidney transplantation, or Dec 31, 2019. All-cause HCRU was measured as the total number of services provided/total follow-up time (rate per patient-year [PY]).

**Results:** 20,647 PD pts were included (median age, 62.2 yrs; median dialysis duration, 2.7 yrs; Table 1). Diabetes was the most prevalent comorbidity (55.4%) and cause of ESKD (39.9%). Median follow-up was 2 yrs. During follow-up, rate of hospitalization was 1.52 PY; of intensive care unit use 0.37; of skilled nursing facility (SNF) use 0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of patients (>100) had generally lower HCRU; pts outside of large metro areas had a lower HCRU rate (0.29; and of emergency department (ED) encounters 1.09 (Table 2).

**Conclusions:** In the US, PD pts had a 5.2 hospitalizations and 1.09 ED encounters per PY. Pts treated in units with >100 pts had generally lower HCRU rates.

**Funding:** Commercial Support - Funded by GSK (Study 213716)

SA-PO661

Effect of ESRD Prospective Payment System on Utilization of Peritoneal Dialysis in Patients with Kidney Allograft Failure


**Background:** The Center for Medicare and Medicaid Services introduced ESRD Prospective Payment System (PPS) in 2011 to increase the utilization of home dialysis modalities, including peritoneal dialysis (PD). Several studies have shown a significant increase in PD utilization after PPS implementation. However, its impact on patients with kidney allograft failure remains unknown.

**Methods:** We conducted an interrupted time series analysis using data from the United States Renal Data System that include all adult patients with allograft failure who started dialysis between 2005 and 2019. We compared the PD utilization in the pre-PPS period (2005-2010) to the fully implemented post-PPS period (2014-2019) for early (within 90 days of dialysis initiation) and late (91-365 days) PD experience.

**Results:** 27507 adult recipients with allograft failure started dialysis during the study period. There was no significant difference in early PD utilization between pre-PPS and post-PPS period in either immediate change called “step change” (0.3% increase; 95%CI: -1.95%, 2.54%; p=0.79) or rate of change over time called “slope change” (0.28% increase per year; 95%CI: -0.16%, 0.72%; p=0.18). Subgroup analyses revealed a trend toward higher PD utilization in post-PPS period in for-profit and large-volume dialysis units. There was a significant increase in PD utilization in post-PPS period in those units which had low PD experience in the pre-PPS period (2.2% increase; 95% CI: 1.31, 3.22; p=0.01). Similar findings were seen for the late PD experience.

**Conclusions:** PPS did not significantly increase the utilization of PD in patients initiating dialysis after allograft failure.
Effect of PPS on late PD experience in patients with allograft failure

SA-PO663
Characteristics of Registered Research in Peritoneal Dialysis, Past and Present
Martin L. Li,1 Ankush Bajaj,1 Uttam Bhetuwal,2 Ankur Shah,1,2 Brown University Warren Alpert Medical School, Providence, RI;1 Rhode Island Hospital, Providence, RI.

Background: Recent national policy changes and the continued growth of peritoneal dialysis (PD) as a therapy for end-stage kidney disease has renewed interest in this modality. The objective of this study was to describe the current landscape of PD clinical trials to assess trends and gaps in clinical research.

Methods: An advanced search was completed through ClinicalTrials.gov, yielding 248 abstracts. Descriptive statistics and Fisher exact tests were used for statistical analysis.

Results: Most studies were completed (197, 79.4%), did not indicate a phase (143, 57.7%), were academically sponsored (156, 62.9%), or conducted in Asia (88, 35.5%). There has been overall growth in PD clinical trials since 1995. Drug studies were more likely to be completed, industry-sponsored, or have surrogate as the primary outcome compared to device, procedure/behavioral, and other studies (17, 77.2%, 16, 72.7%, 71, 72.5%, respectively; p < 0.001; 2, 9.1%, 2, 9.1%, 5, 4.1%, respectively; p < 0.001; 13, 59.1%, 15, 68.2%, 78, 79.5%, respectively; p < 0.001).

Conclusions: Despite growth in PD research worldwide, more studies are being conducted outside the U.S., and static investment in U.S. government sponsored PD research risks not achieving the goal of increasing availability of home dialysis.

SA-PO664
Mobile Technology to Explore Real-Time Symptom Data and Physical Activity in People Receiving Peritoneal Dialysis
Brett Tara, Shilpa Jesudason,2 Paul N. Bennett,1 Thomas Wycherley,1 Katia Ferrat,1 University of South Australia Allied Health & Human Performance Academic Unit, Adelaide, SA, Australia;1 Central Adelaide Local Health Network, Adelaide, SA, Australia.

Background: Fatigue is a frequent and debilitating symptom that contributes to poor quality of life for people receiving peritoneal dialysis (PD). The fatigue experience and factors that may influence it (e.g., mood and physical activity) are poorly understood for people receiving PD, in-part, due to the recall instruments typically used to assess fatigue. Mobile ecological momentary assessment (mEMA) is a survey method that captures data in real-time using mobile phone technology, which has not been trialled in this cohort.

The aim of this study was to explore the real-time fluctuations and associations between fatigue, mood and physical activity using mEMA.

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A Proof-of-Concept Study: Metoprolol Tartrate Is Readily Cleared by Peritoneal Dialysis

Ozant Helvacı,1 Dolunay M. Topuz,2 Emre Yasar,1 Salihı Yıldırım,1 Galip Güz,1 Şevki Akaydin,2 Gazi Üniversitesi Tıp Fakültesi, Ankara, Turkey; 1Gazi Üniversitesi Eczacılık Fakültesi, Ankara, Turkey.

Background: The dialyzability of cardioprotective β-blockers such as metoprolol and carvedilol is well-known. Even so, there is no consensus on the choice between metoprolol vs. carvedilol due to studies with conflicting results. The situation is worse for PD patients since the data on PD clearance of β-blockers is far more scarce. Furthermore, some authors have linked β-blockers to UF failure without a clear mechanism. In this proof-of-concept study, we aimed to develop a technique for determining the metoprolol tartrate (MT) level in the effluent and serum samples of PD patients. The completed version of the study will also include metoprolol succinate and carvedilol levels, which we expect to be the first study to investigate that phenomenon.

Methods: We selected nine patients on stable doses of MT at a resting pulse rate >70 mmHg. All predialysis samples were taken on the dry abdomen. Regardless of APD or CAPD status, an exchange with 1.36% glucose solution was done. After a 2-hour dwell time, post-dialysis blood samples and effluent samples were collected. In addition, pre- and post-pulses and ECCs were recorded. The blood samples were analyzed with the HPLC 1220® (Hitachi liquid chromatography) instrument. The peaks at 262 nm were recorded, and the AUC values were calculated based on the standard analysis. A similar process was followed for the effluent.

Results: The mean age was 38±11 years. Drug doses and baseline pulse rates were similar. Pre-PD levels were 134±66 ng/mL, and post-PD levels were 51±22 ng/mL. The average effluent drug concentration was 81±51 ng/mL, and the delta change between pre-post-dialysis was 60±11%. Patients on APD had numerically higher MT baseline and post-dialysis concentrations, but the difference was insignificant (p=0.190). Residual renal function and transporter types did not affect drug levels. Pre and post-dialysis pulse rates were statistically similar; no tachycardia event was observed.

Conclusions: We have shown that effluent has very high levels of MT. This might be the link to the so-called β-blocker-related UF failure. Furthermore, we have proven that PD readily clears MT. After the completion of the study with the addition of metoprolol succinate and carvedilol levels, we hope to facilitate the “β-blocker” debate in the field of peritoneal dialysis.

Peritoneal Dialysis Patients Exhibit Quantifiable Neurocognitive Impairment but Not Acute Ischemic Brain Injury: A Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging Study

Jessica McIntyre,1 Dickson Y. Wong,2 Michael Chiu,3 Christopher W. McIntyre,4 Arsh Jain.5 Western University Department of Medical Biophysics, London, ON, Canada; 2Western University Schulich School of Medicine & Dentistry, London, ON, Canada; 3Lawson Health Research Institute, London, ON, Canada.

Background: Patients receiving hemodialysis (HD) are known to suffer recurrent ischemic events such as carotid stenosis, which affects the vulnerable areas of the brain. These acute cerebral insults are associated with significant white matter (WM) injury, ultimately leading to neurocognitive impairment. PD patients are not subject to the equivalent circulatory stress as HD patients suggesting PD is relatively neuro-protective. Our study uses a unique imaging-based approach previously applied to a HD cohort to examine the acute intradialytic effects of PD.

Methods: Patients completed a neurocognitive battery (The Montreal Cognitive Assessment (MoCA), Trails Making Test (TMT), and Cambridge Brain Science (CBS)), an fMRI of resting state cerebrovascular calibers, and a proton magnetic resonance spectroscopy (“H-MRS, neurochemistry). Imaging and neurocognitive assessments were performed before PD exchange, with repeat imaging after 90 minutes of dwell time.

Results: 12 patients receiving PD were studied. Patient demographics included (mean±SD): 67±10 years of age, 75±20 male, 75% diabetic, dialysis vintage 18±10 months, ultrafiltration 0.58±0.36L, and PD exchange 8.3% with 2.5% and 91.7% with 66.7% and 1.9% with 0.9% saline. The prevalence rates of retinal hemorrhage, microaneurysms, and retinopathy were 25%, 30%, and 40%, respectively. The mean arteriolar and venular calibers were 63.2 and 78.5 mm, respectively, and the corresponding mean tortuosity was 37.7±3.6 and 37.2±3.0 mm. The mean FD was 1.49. After adjusting for age, sex, education, mean arterial pressure, and Charlson index, retinopathy was found to be negatively associated with 3MS scores (regression coefficient, -3.7, 95% confidence interval: -7.89 to -0.33, P = 0.03).

Conclusions: Retinopathy, a condition common in patients undergoing PD, was associated with global cognitive impairment.

Funding: Government Support - Non-U.S.

Table 1 Evaluation of retinal microvascular characteristics

<table>
<thead>
<tr>
<th>Retinopathy Characteristic</th>
<th>All</th>
<th>without Retinopathy</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area (mm²)</td>
<td>247.1±18.5</td>
<td>229.3±16.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Density (number/mm²)</td>
<td>6.3±1.7</td>
<td>7.1±2.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Width (mm)</td>
<td>212.0±20.2</td>
<td>207.2±19.8</td>
<td>0.19</td>
</tr>
</tbody>
</table>

Figure 1 Subgroup analysis of associations between retinopathy and 3MS scores.

SA-P0668

A Novel Mouse Model of Peritoneal Dialysis-Related Encapsulating Peritoneal Sclerosis

Juan Sun, Hui Peng. Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.

Background: Encapsulating peritoneal sclerosis (EPS) is a severe complication in patients undergoing peritoneal dialysis (PD), with a high mortality rate. However, the insufficiency of knowledge pertaining to the etiology of EPS hampers the development of effective pharmacotherapeutic treatment, and there is a deficiency in pre-clinical models that can recapitulate the progression of the human disease. Thus, we aimed to develop an efficient and realistic mouse model of PD-associated EPS that could mimic the disease characteristics observed in humans.

Methods: Eight-week-old male C57BL/6J mice received a daily intraperitoneal injection of a combination of 4.25% PD solution and SHS (containing 0.1% chlorhexidine gluconate and 1.5% ethanol dissolved in saline), along with lipopolyaccharide administration once a week. And Saline group was given intraperitoneal injection of the same volume of 0.9% saline (daily) as the control. 3 weeks later, ultrasonic and histochemical examinations

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
were used to detect abdominal changes in mice, and then RNA sequencing (RNA-seq) was performed to uncover the potential molecules and signaling in the pathogenesis of EPS.

Results: In EPS group, 76.67% mice survived and all surviving mice developed significant and diffuse peritoneal adhesion at the end of experiment. Ultrasound and histopathological analyses demonstrated peritoneal thickening and extensive intra-abdominal adhesion. Combined with the immunohistochemical results of mice sacrificed at weeks 2 and 4, we revealed the dynamic process of adhesion formation in EPS models. Finally, the RNA-seq of peritoneal tissue showed marked fibro deposition and inflammatory cell infiltration dominated by macrophages in EPS group. These results observed in our mouse model were consistent with the characteristics of EPS patients.

Conclusions: Our novel mouse model of PD-associated EPS is efficient to replicate the key features of EPS occurred on patients, and provide a promising platform to investigate the molecular pathophysiology and treatment strategy of EPS.

SA-PO669

Optical System Shows Promise for Online Detection of Peritonitis in Peritoneal Dialysis Patients

Daniel Kushner,1 Tatiana Tanasaychuk,2 Jeffrey Perl,1,4 Isaac Teltebaum,2 Hezkiah Tsoory,2 Dimitry Zacharin,2 Ron Dayan,2 Victor Frajewicki,2 1Carmel Medical Center, Haifa, Israel; 2liberDi Ltd, Or Akiva, Israel; 3St. Michael’s Hospital, Toronto, ON, Canada; 4University of Toronto, Toronto, ON, Canada; 1University of Colorado, Denver, CO.

Background: Peritoneal Dialysis (PD) is associated with significant patient morbidity and mortality. Prompt peritonitis diagnosis and treatment is crucial and may be limited by the lack of early patient or care partner recognition of peritonitis signs and symptoms thereby delaying clinical presentation and treatment and adversely impacting peritonitis treatment outcomes.

Methods: The Intelligent Dialysis Assistant (IDA), a new electronic automated ambulatory PD exchange device (part of liberDi’s Digital Dialysis Clinic) provides aseptic PD exchanges. The IDA is fitted with an inline WBC sensor that can transmit online detection of white blood cells (WBC) in the PD effluent and aid in the early diagnosis of peritonitis. To check the capabilities of the sensor in-vitro, we created PD solutions with a range of 150–160000 cells/µL to mimic PD effluent peritonitis conditions.

Results: The sensor installed in the IDA (part of liberDi’s Digital Dialysis Clinic) was able to detect the different concentrations of white blood cells in the solution (from 150 through 160000 cell/µL), with a high linear correlation (R² = 0.98).

Conclusions: A point-of-care testing system for detecting peritonitis using a sensor is a promising approach that may improve the prompt diagnosis and treatment of peritonitis in PD patients. The ability of the installed sensor in the IDA to detect low concentrations and volumes of white blood cells suggests that maybe a reliable tool to detect peritonitis in the PD effluent and will require validation via further clinical studies.

Funding: Commercial Support - liberDi

SA-PO670

The Effect of Far-Infrared Therapy on the Cardiovascular and Infection Events in Peritoneal Dialysis Patients

Chih-Ching Lin,1,2 Taipei VGH PD Team; 1Taipei Veterans General Hospital Department of Internal Medicine, Taipei, Taiwan; 2National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan.

Background: Long-term peritoneal dialysis (PD) may be associated with cardiovascular (CV) and infection complications. A previous case report has shown that far-infrared (FIR) therapy may improve abdominal discomfort due to encapsulating peritoneal sclerosis in PD patients. Since there is little information concerning this issue, we conducted this study in order to evaluate the possible effects of FIR therapy on the CV and infection events of PD patients.

Methods: A total of 99 PD patients were enrolled and randomly divided into FIR and control groups. WS TY101 FIR emitter (WS Far Infrared Medical Technology Co., Taipei, Taiwan) was used to conduct the FIR therapy. The irradiating power density was set at 20 mW/cm² and the top radiator was set at 20 cm above the abdomen. Both groups underwent FIR therapy for 40 minutes twice daily during the first and last exchange of each PD session for 1 year. The outcome measures include (1) CV events such as 3P-MACE (3-point major adverse cardiovascular events [consisting of non-fatal stroke, myocardial infarction, and CV death]), coronary artery disease (CAD), and hospitalized heart failure (HHF) and (2) infection events such as pneumonia and peritonitis.

Results: Peritonitis was found to be statistically significant (hazard ratio (HR)=0.418, P=0.017) while two combinations of events were also found to be significant (CV and infection events [HR=0.338, P=0.007] & CV events and peritonitis [HR=0.336, P=0.012]). The survival curves showed that the FIR group had a slower occurrence of CV and infection events, as well as CV events and peritonitis, than the control group. The log-rank tests for both CV and infection events & CV events and peritonitis showed a significant difference (P<0.005, 0.007, respectively) between the two groups.

Conclusions: FIR therapy may significantly lower the risk of CV and infection events, as well as CV and peritonitis events.

Funding: Government Support - Non-U.S.

SA-PO671

Impaired Sodium Dipping Is Associated with Poor Blood Pressure Control in Patients on Peritoneal Dialysis

Washington A. Freire Filho, Ana Teresa P. Vieira, Edilene Maria dos Santos, Luiza K. Araujo, Benedito J. Pereira, Hugo Abensar, Zita M. Britto, Rosilene M. Elias. Universidade de Sao Paulo Hospital das Clínicas, Sao Paulo, Brazil.

Background: Overhydration is often found in patients on peritoneal dialysis (PD). There is no clear association between fluid overload and hypertension in this population. Since short dwells are associated with decreased sodium removal because of peritoneal sodium sieving, we hypothesized that impaired sodium dipping may be associated with worse blood pressure (BP) control.

Methods: This is a cross-sectional analysis of prevalent patients on PD. We evaluated sodium dipping (dialysate sodium dipping after 1 hour with 4.5% glucose bag), fluid overload (excess extracellular volume a 0.39 measured by bioimpedance spectroscopy) and BP control (high BP was defined as office-measured values > 140/90 mmHg).

Results: 47 patients (age 52±18 years, 53% men) were included. Overhydration was found in 62% of patients and high BP in 34% of patients; sodium dipping < 5mmol/L was found in 57% of patients. (Table 1) These patients were characterized by a higher percentage of high BP (81.3% vs 18.8%, p=0.018), despite similar use of antihypertensive drugs, and no difference in overhydration status, membrane transport profile, cycles/ volume PD prescription, ultrafiltration volume, and residual renal function. Sodium dipping < 5mmol/L remained significantly associated with high BP in a fully adjusted model (HR 11.8, 95% CI 2.0-68, p=0.006).

Conclusions: The association between lower sodium dipping and poor BP control suggests that dialytic sodium removal should be included as an important parameter of PD adequacy.

Table 1

<table>
<thead>
<tr>
<th>Trait</th>
<th>Na dipping ≥ 5 mmol/L</th>
<th>Na dipping &lt; 5 mmol/L</th>
<th>p</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess free water/Total body water</td>
<td>0.38 (0.12)</td>
<td>0.39 (0.16)</td>
<td>0.99</td>
<td>1.00</td>
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<tr>
<td>Sodium BUN mL/L</td>
<td>121 (67)</td>
<td>157 (25)</td>
<td>0.007</td>
<td>0.63 (0.38-1.00)</td>
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<td>Sodium Na, mmol/L</td>
<td>140 (3)</td>
<td>144.13</td>
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<td>Residual K+V</td>
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<td>1.29 (0.36)</td>
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<td>Ultrafiltration, mL</td>
<td>556 (187)</td>
<td>628 (400)</td>
<td>0.579</td>
<td>0.66 (0.38-1.17)</td>
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<td>Use of antihypertensive, %</td>
<td>69.3</td>
<td>76.4</td>
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<tr>
<td>Causes of antihypertensive, %</td>
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<td>0.2</td>
<td>0.037</td>
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<td>2</td>
<td>10.59</td>
<td>9.53 (0.4)</td>
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<td>2.3</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO672

CA-125 Is a Good Biomarker of Overhydration in Peritoneal Dialysis Patients
Ana C. Martins, Gonçalo F. Pimenta, Rita Calça, Patricia Matias. Centro Hospitalar de Lisboa Ocidental EPE Hospital de Santa Cruz, Carnaxide, Portugal.

Background: Volume management in peritoneal dialysis (PD) patients is crucial due to the impact of fluid overload on cardiovascular and non-cardiovascular morbidmortality. Clinical examination itself has a poor diagnostic accuracy for minor deviations from normohydration, highlighting the necessity for supplementary tools. The aim of this study was to evaluate the association between serum biomarkers (CA-125 and NT-proBNP) and volume status, assessed through bioimpedance analysis, upon initiation of PD technique and follow-up.

Methods: Single-centre observational cross-sectional study including PD patients that started technique between 2017 and 2023. Demographic and clinical data were collected from electronic records. Parameters evaluated were clinical examination, serum biomarkers, bioimpedance and dialysis adequacy.

Results: A total of 79 patients (51 male) were included with a median age of 59 (IQR 23) years. Baseline (T0) PET showed 77.2% high or high-average transporters. Follow-up (T1) PETs were performed after a median of 18 months (IQR 19). All the patients started with continuous ambulatory peritoneal dialysis (CAPD). Median weekly Kt/V was 2.3 (IQR 0.7). The median residual renal function (RRF) and residual diuresis were 5.9 (IQR 4.9) mL/min/1.73m2 and 1.5 (IQR 1.1) L (5.1% anuric), respectively. Median CA-125 at T0 and T1 were 16.2 U/mL (IQR 17.8) and 13.4 U/mL (IQR 16.1), respectively, which were not statistically different. The median overhydration index at T0 and T1 was 1.55L (IQR 2.5) and 1.1L (IQR 2.3) (p=.001). There was a positive association between D/P of creatinine and CA-125 (r=.25, p=.03) and a negative association between weekly Kt/V and CA-125 (r=.25, p=.035), both at T0. There was also a positive association between NT-proBNP and CA-125 levels at T1 (r=.44, p<.001) and between NT-proBNP variation from T0 to T1 and the CA-125 variation from T0 to T1 (r=.35, p=.004). There was no association between the variation of hydration status and the variation of NT-proBNP and CA-125 levels.

Conclusions: Serum NT-proBNP and CA-125 show a positive correlation, which suggests these biomarkers might be used interchangeably in the evaluation of the patients’ hydration. Effective management of hypervolemia improves clinical outcomes. Prospective studies are needed to better understand the use of CA-125 as a surrogate marker of hypervolemia.

SA-PO673

CCL18-PITPNM3 Mediates Macrophage-Mesothelial Cross-Talk and Promotes Peritoneal Dialysis-Associated Peritoneal Fibrosis
Yuxiang Sun, Qiang Huang, Hui Peng. Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.

Background: Peritoneal dialysis (PD) is one of the replacement therapies for end-stage renal disease. After long-term PD/PD treatment, about 50% of patients will develop peritoneal fibrosis and ultrafiltration failure. Macrophages and metabolic reprogramming have been confirmed to play an important role in PD-related peritoneal fibrosis.

Methods: We performed scRNA-seq on peritoneal effluents from patients receiving PD treatment and explored the functions of specific cell types in the development of PD-related peritoneal fibrosis. By cell communication analysis, we interrogated crosstalk among different cell types in PD effluent. Then we used western blot, qPCR and seahorse to investigate the downstream pathway.

Results: We discovered that PD promoted interactions between macrophages and mesothelial cells. We also found that PD induced the M2 polarization of macrophages. CCL18 was identified to be the most significantly M2-type macrophage-secreted factor upregulated in LPD patients. Moreover, the increased concentration of CCL18 in the PD effluent of LPD patients was related to the high peritoneal transport. It was found that PITPNM3 was the most abundant and significantly elevated receptor for CCL18 in PD effluent of LPD patients. Knockdown PITPNM3 receptor ameliorated the M2-type polarization of macrophages and reduced the secretion of ILK in peritoneal fibrosis. Mechanistically, CCL18 stimulates the migration and invasion of mesothelial cells via the HK2 signaling pathway, so as to enhance the glycolysis and EMT of mesothelial cells and lead to PD-related peritoneal fibrosis.

Conclusions: PD promoted macrophage M2 polarization and increase CCL18 secretion. CCL18 binds to PITPNM3 in mesothelial cells activating the P38K-Akt-cMyc signaling pathway. In conclusion, CCL18-PITPNM3 could promote the expression of glycolysis enzyme HK2 by activating the P38K-Akt-cMyc signaling pathway.

SA-PO674

Mesothelial Extracellular Vesicles Promote Fibroblast Activation via Delivering of Integrin-Linked Kinase in Peritoneal Fibrosis
Qiang Huang, Yuxiang Sun, Hui Peng. The Third Affiliated Hospital of Sun Yat-sen University Department of Nephrology, Guangzhou, China.

Background: Varieties of cell-cell communications among peritoneal cells play a significant role in peritoneal fibrogenesis induced by peritoneal dialysis (PD). Extracellular vesicles (EVs) have been confirmed to involve in intercellular communication by transmitting various molecules. However, their roles and functional mechanisms in peritoneal fibrosis remain to be determined.

Methods: We performed combined analysis of PD effluent-derived EV proteomics and peritoneal single-cell RNA sequencing to determine the cell source of PD effluent-derived EVs. We blocked mesothelial EVs secretion via GW4869 or shRab27a, and injected mesothelial EVs into mice treated with PD fluid. We detected the percentage of ILK+ EVs in PD effluent by flow cytometry.

Results: Using integrative analysis of EV proteomics and single-cell RNA sequencing, we characterized the EVs isolated from PD patient’s effluent and revealed that mesothelial cells are the main source of EVs in PD effluent. We demonstrated that transforming growth factor-β1 (TGF-β1) can substitute for PD fluid to stimulate mesothelial cells releasing EVs, which in turn promoted fibroblast activation and peritoneal fibrogenesis. Blockade of EVs secretion by GW4869 or Rab27a knockdown markedly suppressed PD-induced fibroblast activation and peritoneal fibrosis. Mechanistically, injured mesothelial cells produced EVs containing high level of ILK, which was delivered to the fibroblasts and activated them. Clinically, the percentage of ILK-positive EVs in PD effluent correlated with peritoneal dysfunction.

Conclusions: Our study highlights that peritoneal EVs mediate communications between mesothelial cells and fibroblasts to initiate peritoneal fibrogenesis. Targeting EVs or ILK could provide a novel therapeutic strategy to combat peritoneal fibrosis.
SA-PO675

Intraperitoneal Pressure Induces Peritoneal Dialysis-Related Peritoneal Fibrosis and "Stampede" Phenomenon Through CD44 Signaling

Yu-Wei Chen,1,2 Cheng-hsien Chen,3,5 Mai-Szu Wu,2,3 Yung-Ho Hsu,1,3

1Graduate Institute of Clinical Medicine, College of Medicine, Taipei Medical University, Taipei, Taiwan; 2Taipei Medical University Shuang Ho Hospital Center of Urology and Kidney, Taipei Medical University, Taipei, Taiwan.

Background: Peritoneal dialysis (PD) is a widely used sustainable kidney replacement therapy. Prolonged use of peritoneal dialysis fluids is associated with mesothelial-mesenchymal transition, peritoneal fibrosis, and eventual ultrafiltration (UF) failure. However, the impact of intraperitoneal pressure (IPP) on the peritoneum remains unclear.

Methods: In this study, we employed a mouse PD model and human Met-5A cells to investigate the influence of pressure on the peritoneum and mesothelial cells. We utilized repeated, chronic infusion of glucose-free phosphate-buffered saline (PBS) to increase IPP and examined its effects.

Results: We observed that increased IPP induced peritoneal fibrosis and upregulated the expression of cluster of differentiation 4 (CD44) in mesothelial cells (Figure 1). Pressurization led to a mesenchymal phenotype, the expression of fibrotic markers and inflammatory factors, increased cell proliferation, and cell migration in Met-5A cells. The mouse PD model and human peritoneum equilibrium tests showed a positive association between higher IPP and both increased small solute transport and decreased net UF. Treatment of CD44 neutralizing antibodies prevented pressure-induced phenotypic changes in mesothelial cells, while a CD44 inhibitor oligo-fucoidan ameliorated pressure-induced peritoneal thickening, fibrosis, and inflammation in PD mice.

Conclusions: Our findings suggest that IPP plays a crucial role in peritoneal fibrosis in PD. CD44-mediated mesothelial changes and inflammation are involved in these processes. The experiments of CD44 blockade showed its potential as a therapeutic approach for PD-related peritoneal fibrosis and UF failure.

Funding: Government Support - Non-U.S.

Background: Inflammatory responses in the peritoneum contribute to peritoneal dialysis (PD)-associated peritoneal fibrosis. Previous studies showed that FG4592 (Roxadustat) suppressed inflammation in renal ischemia-reperfusion injury, alcohol-induced alcoholic liver disease. To date, FG4592 has become widely used for the treatment of anemia in patients undergoing dialysis. However, the role of FG4592 in the progression of peritoneal fibrosis has not been clarified. In this study, we used a PD rat model to investigate the effects of FG4592 on PD-associated peritoneal fibrosis.

Methods: A rat model of peritoneal fibrosis was induced via intraperitoneal injection of 4.25% PD fluid at a dose of 100mL/kg daily for 4 weeks. To investigate the effect of FG4592 on peritoneal fibrosis, rat were intraperitoneally injected with FG4592 at 1mg/kg per day. Rats were randomly divided into three groups: rats injected intraperitoneally with saline equivalent to the amount of PD fluid were defined as the control group (n=6), rats injected with 100mL/kg PD fluid were defined as the PD group (n=6) and rats injected with 100mL/kg PD fluid plus FG4592 were defined as PDF+FG4592 group (n=6). After 28 days of PD treatment, PET was performed on each rat before the rats were killed. The parietal and visceral peritoneal tissues were collected for Masson’s thichrome staining, western blotting and real-time PCR.

Results: Compared with the PD group, those of the PDF+FG4592 group showed increased net ultrafiltration volume. Masson’s trichrome staining showed that those of the PD group showed thickness of the submesothelial compact zone, and the histological change was accompanied by decreased peritoneal transport of glucose and sodium, and increased peritoneal transport of creatinine and albumin. In contrast, administration of FG4592 prevented the thickening of the peritoneum and improved the peritoneal transport function presenting as increased transport of glucose and sodium, and decreased transport of creatinine and albumin. Injection of 4.25% PD fluid significantly increased the mRNA levels of IL-1β, TNF-α and MCP-1 in the visceral peritoneum, and treatment with FG4592 effectively decreased their expression. Results of western blotting demonstrated that FG4592 inhibited the formation of fibronectin, collagen I and vimentin at protein levels.

Conclusions: FG4592 alleviates the development of peritoneal fibrosis in a rat model of PD.

SA-PO676

FG4592 Ameliorates Peritoneal Dialysis-Associated Peritoneal Fibrosis

Qimei Luo, Xianrui Dou. Shunde Hospital of Southern Medical University, Foshan, China.

Background: Inflammatory responses in the peritoneum contribute to peritoneal dialysis (PD)-associated peritoneal fibrosis. Previous studies showed that FG4592 (Roxadustat) suppressed inflammation in renal ischemia-reperfusion injury, alcohol-induced alcoholic liver disease. To date, FG4592 has become widely used for the treatment of anemia in patients undergoing dialysis. However, the role of FG4592 in the progression of peritoneal fibrosis has not been clarified. In this study, we used a PD rat model to investigate the effects of FG4592 on PD-associated peritoneal fibrosis.

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Conclusions: FG4592 alleviates the development of peritoneal fibrosis in a rat model of PD.
SA-P0677

Matrix Metalloproteinase-10 Deficiency Has Protective Effects Against Peritoneal Inflammation and Fibrosis via NFXβ Pathway Inhibition

Hideki Yokoi,1 Takuya Ishimura,1 Akira Ishii,1,2 Hiroiyuki Yamada,1,3 Naohiro Toda,1,2 Keita M. Pori,1,4 Shoko Ohno,1 Yukiko Katay,1 Takaya Handa,1,2 Akio Ishikawa,1 Sayaka Sugioka,1 Haruo Nishio,1 Motoko Yanagita,1
1Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; 2Department of Primary Care Emergency Medicine, Graduate School of Medicine, Kyoto University, Osaka, Japan; 3Department of Nephrology, Kansai Electric Power Hospital, Osaka, Japan; 4Department of Nephrology, Osaka Electric Power Hospital, Osaka, Japan; 5Department of Nephrology and Dialysis, Tazuke Kofukai Medical Research Institute, Kitano University, Osaka, Japan; 6Institute for the Advanced Study of Human Biology

Background: One of the most common causes of discontinuation of peritoneal dialysis is impaired peritoneal function. However, its molecular mechanisms remain unclear. We have previously demonstrated that MMP (matrix metalloproteinase)-10 gene expression is significantly increased by microarray analysis of peritoneal fibrosis mice, but its function has not been elucidated yet.

Methods: Chlordexione glycinate (CG) was intraperitoneally injected to wild-type and MMP-10 knockout mice to elucidate the role of MMP-10 on peritoneal injury. We also examined function of peritoneal macrophages and mesothelial cells obtained from wild-type and MMP-10 knockout mice, and human MPP-10-overexpressing RAW 264.7 cells and MeT-5A cells. In addition, we investigated MMP-10 expression on human peritoneal biopsies from patients with peritoneal dialysis and peritoneal permeability determined by peritoneal equilibration test (PET).

Results: MMP-10 was expressed in positive cells for WT1, a mesothelial marker, and also for MAC-2, a macrophage marker, in the thickened peritoneum of both mice and patients. Serum proMMP-10 levels were well correlated with peritoneal permeability, indicated by D/P Cr. Peritoneal fibrosis, inflammation, and high peritoneal permeability induced by CG were all ameliorated by MMP-10 deletion, with reduction of CD31-positive vessels and VEGF-A-positive cells. Expression of Ccl2, Ifng, and Il6 and phosphorylation of NFκB at p65 in WT55 were suppressed in both MMP-10 knockout macrophages and mesothelial cells in response to lipopolysaccharide (LPS) stimulation. Overexpression of MMP-10 in RAW 264.7 and MeT-5A cells upregulated mRNA expression of pro-inflammatory cytokines with phosphorylation of NFκB subunit p65. Conclusions: Inflammatory responses induced by MMP-10 are ameliorated by MMP-10 deletion and that systemic deletion of MMP-10 ameliorates peritoneal inflammation and fibrosis caused by MMP-10-induced NFXβ activation of peritoneal macrophages and mesothelial cells.

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

SA-P0678

Peritoneal Endothelial Hyaluronan in Gloycex Is Decreased in Peritoneal Dialysis Patients Treated with Conventional Solutions

Keisuke Tawada,1 Akimasa Asai,1 Hiroshi Kinashi,1 Makoto Yamaguchi,1 Masashi Mizuno,2 Masataka Banshodani,3 Takui Ishimoto,1 Hideki Kawanishi,1 Yusuke Ito,1 (Aichi Ika Daigaku, 1Department of Biomedical Science, University of Padova, Padova, Italy; 2Bogem, Institute of Molecular Biology and Genetics, Ariano Irpino, Italy; 3Department of Translational Medical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy; 4Department of Biochemistry and Molecular Genetics, University of Colorado, Denver – Anschutz Medical Campus, Aurora, CO; 5Department of Medicine, University “G. d’Annunzio” of Chieti-Pescara, Chieti, Italy; 6Iperboreal Pharma Srl, Pescara, Italy; 7Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden.

Background: Long exposure to high glucose in peritoneal dialysis (PD) can lead to peritoneal fibrosis (PF), reduce the life span in ultrafiltration capacity. Transforming growth factor-beta (TGF-beta) plays a crucial role in PF, and it is influenced by the hyperglycemic state induced by glucose-based PD solutions. Now, new biocompatible PD solutions is being developed, incorporating two complementary approaches: reducing glucose and use osmotic-metabolic agents that offer metabolic benefits to counteract excessive local and systemic glucose exposure. One such agent is L-carnitine. This study aims to investigate the impact of L-carnitine and carnitine acetyletransfere (CrAT), a key enzyme in L-carnitine metabolism, on the modulation of TGF-beta’s pro-fibrotic effects.

Methods: Peritoneal CRAT overexpression in mesothelial cells (Mut5A) was obtained by a transfection of a plasmid encoding CrAT ORF. The expression of CrAT was assessed at both the gene and protein level using real-time PCR and Western blot. Metabolomic analyses were conducted on WT and CrAT-overexpressing cells. Wild-type (WT) and CrAT-overexpressing cells were also subjected to different concentrations of L-carnitine (50 µM and 2 mM) in the presence and absence of TGF-beta. The expression of markers associated with PF and inflammation was examined.

Results: CrAT overexpression was confirmed and unsurpassed hierarchical clustering analysis revealed marked differences in mRNA expression. Western blot analysis of CrAT overexpressing cells showed a significant increase in the expression of fibrotic and pro-inflammatory markers, alpha-SMA, vimentin, IL-6 and IL-1β. Conclusions: CrAT overexpression could provide valuable insights into the metabolic pathway, which L-carnitine metabolism effectively regulates transformation of fibrosis and inflammation in PD. Utilizing L-carnitine as an osmo-metabolic agent in PD solutions has the potential to significantly decelerate the advancement of PF.

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

SA-P0679

The Response of Mesothelial Cells to Fibrostrict Stress Is Influenced by Carnitine Acetytransferase (CrAT)

Valentina Masola,1 Luciano D’Apolito,2 Angelo D’Alessandro,2 Mario Bonomi,3 Giovannibattista Capasso,2 Francesco Trepiccio,2 Maurizio Ousso,1 Tommaso Prosdocimi,1 Jose C. Divino-Filho,1 Arturo Arduini,2 Department of Biomedical Science, University of Padova, Padova, Italy; 3Bogem, Institute of Molecular Biology and Genetics, Ariano Irpino, Italy; 4Department of Translational Medical Sciences, University of Campania “Luigi Vanvitelli”, Naples, Italy; 5Department of Biochemistry and Molecular Genetics, University of Colorado, Denver – Anschutz Medical Campus, Aurora, CO; 6Department of Medicine, University “G. d’Annunzio” of Chieti-Pescara, Chieti, Italy; 7Iperboreal Pharma Srl, Pescara, Italy; 8Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden.

Background: The epithelial-to-mesenchymal transition (EMT) of MCs is an early mechanism of peritoneal dysfunction in peritoneal dialysis (PD). Plasminogen activator inhibitor-1 (PAI-1) is initially known as an inhibitor of fibrinolysis. WT and TGF-beta-induced EMT, peritoneal thickening and an expression of markers of oxidative stress were investigated. In mouse PD model, Tiplaxtinin (20 µg/kg) administration resulted in a decrease in peritoneal thickness and fibrosis and an increase in ratio of L/V. Tiplaxtinin administration also prevented the induction of oxidative stress in human peritoneal mesothelial cells (HC) and reduced the expression of TGF-beta and inflammation in PD. Utilizing L-carnitine as an osmo-metabolic agent in PD solutions has the potential to significantly decelerate the advancement of PF.

Conclusions: PAI-1 plays a role in peritoneal EMT and fibrosis, and modulation of PAI-1 expression/activity in MCs could be a novel strategy to prevent peritoneal fibrosis in PD patients.

Funding: Government Support - Non-U.S.

SA-P0680

Role of Plasminogen Activator Inhibitor-1 (PAI-1) on Phenotype Transition and an Induction of Oxidative Stress in Human Peritoneal Mesothelial Cells (MCs)

Duk-Hec Kang,1 Chor ho Jo,2 Dal-Ah Kim,1 Minsung Lee,1,2 Division of Nephrology, Ewha Womans University College of Medicine, Seoul, Republic of Korea; 1Hanyang Biomedical Research Institute, Hanyang University College of Medicine, Seoul, Republic of Korea.

Background: One of the most common causes of discontinuation of peritoneal dialysis (PD) is peritoneal fibrosis (PF), reduce the life span in ultrafiltration capacity. Transforming growth factor-beta (TGF-beta) plays a crucial role in PF, and it is influenced by the hyperglycemic state induced by glucose-based PD solutions. Now, new biocompatible PD solutions is being developed, incorporating two complementary approaches: reducing glucose and use osmotic-metabolic agents that offer metabolic benefits to counteract excessive local and systemic glucose exposure. One such agent is L-carnitine. This study aims to investigate the impact of L-carnitine and carnitine acetyletransfere (CrAT), a key enzyme in L-carnitine metabolism, on the modulation of TGF-beta’s pro-fibrotic effects.

Methods: Peritoneal CRAT overexpression in mesothelial cells (Mut5A) was obtained by a transfection of a plasmid encoding CrAT ORF. The expression of CrAT was assessed at both the gene and protein level using real-time PCR and Western blot. Metabolomic analyses were conducted on WT and CrAT-overexpressing cells. Wild-type (WT) and CrAT-overexpressing cells were also subjected to different concentrations of L-carnitine (50 µM and 2 mM) in the presence and absence of TGF-beta. The expression of markers associated with PF and inflammation was examined.

Results: CrAT overexpression was confirmed and unsurpassed hierarchical clustering analysis revealed marked differences in mRNA expression. Western blot analysis of CrAT overexpressing cells showed a significant increase in the expression of fibrotic and pro-inflammatory markers, alpha-SMA, vimentin, IL-6 and IL-1β. Conclusions: CrAT overexpression could provide valuable insights into the metabolic pathway, which L-carnitine metabolism effectively regulates transformation of fibrosis and inflammation in PD. Utilizing L-carnitine as an osmo-metabolic agent in PD solutions has the potential to significantly decelerate the advancement of PF.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents completing author.
**SA-P0681**

**Unveiling the Role of Mesothelial Cells in Methylglyoxal-Induced Peritoneal Fibrosis**

**Yu-Syun Wei, Pei-Shuie J. Tsai. National Taiwan University, Taipei, Taiwan.**

**Background:** Being one of the renal replacement therapies for end-stage kidney disease patients, peritoneal dialysis (PD) maintains the lives of about 11% of dialysis patients. However, morphological and functional changes in the peritoneum, which is called peritoneal fibrosis, is inevitable during long-term PD. PD can gradually progress into ultrafiltration failure and has a high correlation with encapsulating peritoneal sclerosis, a complication with high mortality. Despite the presence of glucose degradation products (GDPs) produced by heating glucose-containing dialysate is considered to be the key component to initiating PD, and methylglyoxal (MGO) is one of the most important GDPs; however, the mechanisms of how MGO induces PD, especially the involvement of mesothelial cells, is still unclear.

**Methods:** Human mesothelial cells (MeT5A), were cultured and treated with different concentrations of MGO. The viability and production of free radicals were evaluated first. Next-generation sequencing was then performed to assess the transcriptomic changes after MeT5A was treated with MGO for 6 hours and 24 hours. Differential expression genes (DEGs) and pathway enrichment analysis based on databases of KEGG and gene ontology (GO) were further analyzed.

**Results:** When compared with control MeT5A, 2009 and 2516 DEGs were detected, respectively, after 6 or 24 hours of MGO stimulation. GO enrichment analysis showed that most DEGs that appeared at 6 hours were related to extracellular matrix organization (p=0.01); while DEGs that appeared at 24 hours were related to extracellular matrix organization (p=0.00002), type I interferon signaling pathway (p=0.0002), wound healing (p=0.006), cell adhesion (p=0.01) and angiogenesis (p=0.01). Although epithelial-to-mesenchymal (EMT) was considered an important phenomenon in peritoneal fibrosis, genes that related to EMT (VIM, SNAI1, SNAI2, CDH1, and VIM) were not significantly changed under our experimental setup. Moreover, proteins that are known to activate fibroblasts trans-differentiation into myofibroblasts, except for TGFβ1, genes such as IL1B, PDGFα, PDGFβ, and PDGFδ were upregulated significantly.

**Conclusions:** Our study showed that when mesothelial cells were treated with MGO in vitro, they tend not to develop EMT but promoted pro-inflammation response and the activation of fibroblasts.

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

**SA-P0682**

**PPARα Modulator Ameliorates Methylglyoxal-Induced Peritoneal Fibrosis**

**Yutaka Shinoki, Ryu Tamura, Naoki Ishiuchi, Yousuke Osaki, Yujiro Maceoka, Kensuke Sasaki, Takao Masaki, Hiroshima Daigaiku Daigaikutai Iki Kagaku Kenkyuka, Hiroshima, Japan.**

**Background:** Peritoneal inflammation and fibrosis play major roles to the long-term maintenance of peritoneal dialysis. In this study, we investigated whether PPARα agonism ameliorates peritoneal inflammation and fibrosis in methylglyoxal (MGO) induced peritoneal injury in mice, as well as in cultured human peritoneal mesothelial cells (HPMCs) and THP-1 cells.

**Methods:** Peritoneal fibrosis was induced by intraperitoneal injection of MGO in male C57Bl6 mice for 4 weeks. The mice were fed normal chow diet with a specific PPARα modulator, pemafibrate (0.3 mg/kg), 3 weeks before MGO injection, and then peritoneal tissues were examined. In vitro study, HPMC and THP-1 cells stimulated with IFN-γ were examined with or without pemafibrate treatment.

**Results:** A reduced PPARα expression was observed in the peritoneum. Pemafibrate significantly decreased MGO-induced cell density and peritoneal thickening. In immunohistochemical staining, pemafibrate reduced the number of fibrosis markers α-SMA, TGF-β1, and FSP-1 positive cells and deposition of collagen I and III, the expression of the inflammatory cytokine TNF-α, and macrophage infiltration. In addition, pemafibrate improved the deterioration of the diastase-to-plasma (D/P) ratio of BUN and glucose reduced TGF-β1 expression in the diastase. In vitro studies, pemafibrate inhibited IFN-γ-induced activation of fibrosis markers (TGF-β1, fibronectin) in HPMC. In THP-1 cells, pemafibrate promoted anti-inflammatory M2 macrophage polarity and inhibited inflammatory M1 macrophage cytokine production, including IL-1β. Moreover, Pemafibrate suppressed not only AP-1 signaling pathway but also NLRP3 inflammasome and caspase-1 activation in HPMC.

**Conclusions:** The specific PPARα modulator, Pemafibrate ameliorates peritoneal fibrosis by inhibiting peritoneal inflammation.

**SA-P0683**

**The Role of Myocardin-Related Transcription Factor-Serum Response Factor Signaling in Peritoneal Mesothelial Cells**

**Daichi Kainoki, Norihiko Sakai, Yuta Yamamura, Keisuke Sako, Keisuke Horikoshi, Takahiro Yuasa, Taichiro Minami, Shiroi Nagakawa, Megumi Oshima, Shinnji Kitajima, Taisada Toyama, Akinori Hara, Miho Shimizu, Yusunori Iwata, Takashi Wada. Kanazawa Daigaiku Daigaikutai Iki Kagaku Kenkyuka, Kanazawa, Japan.**

**Background:** Peritoneal membrane failure is a critical complication of long-term peritoneal dialysis treatment. Peritoneal fibrosis has been known to be involved in the development of peritoneal membrane failure. Therefore, clarifying the mechanisms of peritoneal fibrosis is important. Thus far, myocardin-related transcription factor (MRTF)- alpha (αMRTF) and beta (βMRTF) signaling is known to drive the development of fibrosis. Focal adhesion (FA) and lysyl oxidase (LOX) family mediating collagen cross-linking are also known to contribute to the development of organ fibrosis. However, the involvement of MRTF-SRF signaling in the expression of LOX components and LOX fibrosis is still unclear. In this study, we investigated the contribution of MRTF-SRF signaling to the expression of FA components and LOX family using peritoneal mesothelial cells (PMCs).

**Methods:** Mouse primary PMCs were stimulated with transforming growth factor (TGF)-β1, and caspase-1 activation in HPMC. Moreover, a βMRTF and LOX siRNA was transfected into peritoneal mesothelial cells (PMCs). In addition, the expressions of FA components were also reduced with CCG-1423. Taken together, TGF-β1, induced the expression of Col1α1, LOX family and FA components dependent on MRTF-SRF signaling in PMCs.

**Conclusions:** MRTF-SRF signaling may contribute to the development of peritoneal fibrosis through TGF-β1-induced FA components and LOX family in PMCs.

**Funding:** Veterans Affairs Support, Government Support - Non-U.S.

**SA-P0685**

**Histone Lactylation Facilitates Peritoneal Mesothelial Cell Senescence and Promotes Peritoneal Dialysis-Associated Fibrosis**

**Fang Yu, Xiaoyue Wang, Qingli Cai, Yanzi He, Keohong Chen. Daping hospital, Army Medical Center, Army Medical University, Chongqing, China.**

**Background:** Peritoneal fibrosis (PF) is a serious clinical complication in patients undergoing long-term peritoneal dialysis (PD). Recently, histone lactylation has been found to increase with glycolysis and intracellular lactate levels, leading to chronic organ damage. Here, we investigated the role and mechanism of histone lactylation in PD-associated fibroblast differentiation and PD-induced peritoneal fibrosis (PF).

**Methods:** Mouse models of PF were constructed by 4.25% glucose peritoneal dialysate combined with methylglyoxal. We used a lactylation enhancer (rotonea) and a lactylation inhibitor (oxamute) to validate the effects of histone lactylation in vivo and in vitro. The peritoneal fibrous layers and cultured peritoneal mesothelial cells (PMCs) were analyzed for the senescence, fibrosis, glycolysis, and histone lactylation levels. We generated DeR2 (a senescent marker) knockout mice to verify the effects of histone lactylation by clearing senescent cells. Single-cell RNA sequencing (scRNA-seq) was used to characterize the heterogeneity of PMCs clusters under different lactylation intervention conditions.

**Results:** We found that lactate and glycolysis levels were significantly higher in the PF group compared to the control group, and immunoprecipitation results also showed enhanced levels of histone lactylation modifications in the PF group. In vitro, we also confirmed that PMCs exhibited enhanced levels of lactate and lactation in response to stimulation by high glucose, while we found an increased expression of cell senescence marker (P16, P21, and DeR2) and senescence-associated secretory phenotype. Then we found that PMCs senescence was significantly enhanced in the lactation-enhanced group, while the lactylation-inhibited group alleviated PMCs senescence. In the PF model of DeR2 knockout mice, compared with the wild group, the peritoneal thickness and the expression of fibrotic markers were significantly reduced. The transcriptomic analysis with scRNA-seq revealed that activation of senescent-related pathway in PMCs clusters of PF group, whereas the senescence-related pathway was down-regulated in the lactation-inhibited group. The results indicated that histone lactylation may promote PF through PMCs senescence.

**Conclusions:** Histone lactylation may play a vital role in the progression of PD-associated fibrosis by promoting PMCs senescence.

**Funding:** Government Support - Non-U.S.
group, no degradation of the elastin or no elastin fragments in submesothelial tissue was observed. Mean, anisotropic cell swelling, peritoneal edema, and increased collagen matrix expression observed in the PDF group were significantly suppressed in PDF-MMP-12 inhibition group.

Conclusions: The results suggest that MMP-12 induced by PDF instillation could be associated with local microinflammation in the peritoneal tissue, suggesting that MMP-12 may be an therapeutic target to relieve peritoneal damage.

SA-PO686
An Unusual Dietary Cause of Hyperphosphatemia and Hypocalcemia Mimicking Tumor Lysis Syndrome
Alvin G. Kwon, Melissa Balcer, Hanny Sawaf. Cleveland Clinic, Cleveland, OH.

Introduction: In healthy individuals, high dietary phosphate intake is rarely emphasized since there is no correlation proven between phosphate intake and serum inorganic phosphate concentration. Hyperphosphatemia has a variety of etiologies other than traditionally focused cellular shifts. High phosphorus could cause more acute kidney injury (AKI) events and acute phosphate nephropathy can cause AKI in rare cases. Additionally, COVID-19 infection can alter the physiology of phosphate regulation and the severity of AKI. Here we present a patient with COVID-19 infection and sudden onset severe hyperphosphatemia and hypocalcemia in the setting of AKI who was revealed to have a substantial dietary intake of phosphate that improved with the improvement of AKI.

Case Description: The patient is a 52-year-old male who presented with shock in the setting of COVID-19 pneumonia. Further laboratory tests found that he had severe hyperphosphatemia (10.0 mg/dL), hypocalcemia (6.5 mg/dL), and AKI with a serum creatinine that peaked at 8.53 mg/dL. Ionized calcium was also low at 0.86 mmol/L and his uric acid level was elevated at 11.1 mg/dL. These electrolyte derangements initially raised concern for tumor lysis syndrome (TLS). However, there was no evidence of malignancy on physical examination or imaging. It was noted after further history taking that the patient drank 2 liters of soft drinks daily. This unusual diet in the setting of severe AKI likely led to hypocalcemia. The patient’s renal function improved with the improvement of his shock. The resolution of the patient’s AKI also normalized his hyperphosphatemia and hypocalcemia.

Discussion: In the setting of AKI, dysregulation of the phosphate transporter may interfere with phosphate balance. Although hyperphosphatemia is commonly seen in patients with severe AKI, a dietary cause of severe hyperphosphatemia leading to hypocalcemia is not well recognized. This patient’s phosphate intake through soda alone was 300-400 mg/day and phosphorous from food additives is absorbed at a much higher rate than natural sources. This intake likely precipitated a sudden hyperphosphatemia in the setting of the patient’s AKI which resulted in hypocalcemia, mimicking TLS. Further studies investigating hyperphosphatemia being the cause of hypocalcemia in instances other than TLS should be followed.

SA-PO687
Intravenous Ferric Carboxymaltose-Induced Severe Hyperphosphatemia
Mohammad Gul Yousef Khan, Shahtha A, Herz Allah, Gurwant Kaur. Penn State Health Milton S Hershey Medical Center, Hershey, PA.

Introduction: Hyperphosphatemia (HP) is a rare and severe adverse effect of some intravenous (IV) iron formulations. Here, we present a case of a patient with severe HP after receiving IV ferric carboxymaltose (FCM) due to renal phosphate wasting with high Urine fractional excretion of HP (40%).

Case Description: A 19-year-old female was initially evaluated in the clinic for iron deficiency due to heavy menstrual bleeding. She received one dose IV FCM because of inability to tolerate oral medications due to gastraparesis. A few days later she had severe generalized bone pains along with weakness, fatigue, nausea, chills, and headache. Labs showed isolated low serum phosphorous (S. PO4) of 1.9 mg/dl (normal 2.5-4.5 mg/dl). She was started on oral potassium-phosphate (K-PO4). Due to persistent HP and symptoms, she was admitted for further management. At the time of admission, labs revealed persistent HP. Remaining serum electrolytes were within normal range. Urine FEP was >55% with high 24-hour PO4 in the urine of 2.305g/24 hours (0.400-1.300). This favored renal PO4 wasting. Fibroblast growth factor (FGF-23) was 58 pg/ml (normal range was <59 pg/ml as per Mayo Clinic lab). She was managed with IV as well as oral PO4 supplements. She was discharged on oral PO4 supplements along with calcitriol. Follow up clinic visit within 1 month showed that her S.PO4 levels normalized to 4 mg/dl. She was able to come off oral PO4 supplementation. This further supports that it was a short-term effect from IV FCM use.

Discussion: HP has been reported with the use of IV iron preparations, more commonly with IV FCM as compared to other IV formulations. IV FCM induced HP is typically associated with increase in FGF-23 which causes increase in urinary phosphate excretion and suppression of 1,25(OH)2D concentration. Common symptoms include generalized weakness, fatigue, bone, and muscular pain. It is recommended to measure S. PO4 in patients who present with the above-mentioned symptoms. Measuring FEP or Urine fractional excretion of PO4 and Periods 4 and 5, respectively (Figure 1).

Conclusions: After consumption of sodium oxide participants had an increase in urine oxalate excretion, as expected, but they also had an increase in urine citrate excretion. The association between oxalate and citrate excretion may not be completely driven by dietary intake.

Funding: NIDDK Support

SA-PO688
The Association Between Urine Oxalate and Citrate May Not Be Diet Driven
Megan Prochaska, Fredric L. Coe, Elaine M. Worcester. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: Higher urine oxalate excretion has been associated with higher urinary citrate excretion and the magnitude of the association is larger in non-kidney stone patients compared with kidney stone patients. The mechanism for this association may be due to simultaneous dietary intake oxalate and citrate in fruits and vegetables or transporter linkage of SLC26A6 and NaDC1 in the kidney.

Methods: Eleven participants, including 3 kidney stone patients, were admitted to the clinical research center and given sodium oxalate. Timed pre-sodium oxalate (1) and post-sodium oxalate (6) urine samples were collected every hour. Urine composition was measured and excretion rates of oxalate and citrate calculated at each period. Mean and standard error were graphed per period and mixed methods longitudinal models were generated to compare change over time versus pre-oxalate value (Period 1) of oxalate and citrate excretion.

Results: Eight of the 11 participants were women with mean age 54 years. Urine oxalate and citrate excretions were higher than pre-oxalate (Period 1) at Periods 4 to 6, and Periods 4 and 5, respectively (Figure 1).

Conclusions: After consumption of sodium oxide participants had an increase in urine oxalate excretion, as expected, but they also had an increase in urine citrate excretion. The association between oxalate and citrate excretion may not be completely driven by dietary intake.

Funding: NIDDK Support

SA-PO689
Quantitative Assessment of Overall Acid-Base Balance in Humans

Background: Kidney stones are common and understanding mechanisms contributing to stone formation is important in developing effective prevention and treatment strategies. This study aimed to investigate the impact of various predictors on urine pH and acid-base homeostasis, which play a significant role in kidney stone formation.

Methods: Kidney stone patients and non-kidney stone patients provided 24-hour urine collections while at home and eating a free choice diet. A pH titration analysis was performed and acid-base parameters were measured in the urine to assess acid-base balance. Basic statistics and linear models were developed to characterize change in urine acid-base chemistry as a function of demographic and urine factors.

Results: There were 246 participants with mean age 54 years, 133 female, and 190 kidney stone patients. In multivariate analysis, higher age was associated with lower urine pH (<0.005 year, p<0.001) but there was no association by sex. In separate multivariate models, male sex was associated with lower acid excretion (-0.6 meq/mM creatinine, p<0.001) and lower urine anions (-0.5meq/mM creatinine, p<0.01) compared with female. In separate multivariate models, higher age was associated with higher urine creatinine (0.02 meq/mM creatinine per year, p<0.001) and higher titratable acidity (0.01 meq/mM creatinine per year p<0.001).

Conclusions: This study provides valuable insights into the relationships between demographic factors and urine acid-base chemistry. The association between age and sex with urine pH, urine anions, acid excretion, and titratable acidity underscores the importance of age and sex as factors in acid-base balance. This may also suggest different mechanisms for kidney stone formation in older adults and between men and women and is consistent with known data that stone types may change with aging and there are differences between men and women.

Funding: NIDDK Support
SA-PO690

Nephrolithiasis as a Manifestation of Primary Hyperaldosteronism Secondary to Adrenal Adenoma
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Introduction: The primary hyperaldosteronism has been considered a rare cause of secondary hypertension with a prevalence up to 12%. The variability of presentation of this syndrome is too wide and sometimes it is not the usual one. The following is a case of a patient who started with hypertension and recurrent kidney calculi due to primary hyperaldosteronism caused by an adrenal adenoma.

Case Description: A 33 years-old male with no significant medical history who presented to hospital due to hypertensive episodes. Outpatient laboratory tests were performed and hypokalemia plasma renin activity was reported and 0.39 and aldosterone at 20 Primary hyperaldosteronism was suspected. After that the patient begins with intermittent episodes of lower abdominal pain, irritated to right groin and hematuria. Laboratory tests creatinine 0.77 urea 21 Na 145 k 2.5 A renal Doppler ultrasound was performed and reported bilaterally renal calculi the intrarenal circulation was normal. The patient presented again in the emergency room due to abdominal pain and a well-defined hypodense nodular image towards the left adrenal gland was found in the abdominal tomography related to adenoma and multiple intrarenal stones microcysts and simple cysts were observed with presence of free intravesical stones. The patient received medical management and lithotrity was performed after 1 month a laparoscopic radical left adrenalectomy was performed without complications.

Discussion: There are few cases reported in the literature of patients with primary hyperaldosteronism and recurrent nephrolithiasis. It has been reported that chronic mineralocorticoid administration and primary hyperaldosteronism facilitate renal calculus excretion. This case alerts us of the importance to remember the renal physiology of calcium in hyperaldosteronism and it is one of the most variable presentations and for which the patient will seek medical attention quickly.

SA-PO691

Characterization of a Cohort with Kidney Stones and Enteric Hyperoxaluria
Han Ro,1 Ryan Tatton,2 Stephen R. O'Neill,2 Ramila A. Mehta,3 John C. Lieske,1 Mira T. Keddis.1 Mayo Foundation for Medical Education and Research, Rochester, MN; 2Mayo Clinic, Scottsdale, AZ.

Background: Enteric hyperoxaluria (EH) is a risk factor for kidney stones. The relationship between risk factors and the natural history remains poorly defined. To address this knowledge gap, we created an EH patient registry.

Methods: The electronic medical record at all 3 Mayo Clinic sites was searched to identify patients with a known cause of EH, 24-hour urine oxalate (Uox) ≥40mg, and history of kidney stones. Symptomatic stone events were defined by the presence of renal colic, stone passage associated with urinary tract infection or hematuria, or procedure for stone removal.

Results: We report on data from the first 74 abstracted patients. The largest group of 34 (46%) had bariatric surgery (29 (85%) of these were Roux-en-Y Gastric Bypass (RYGB)), 20 (28%) inflammatory bowel disease (IBD), 11 (15%) pancreatic insufficiency, 5 (7%) short bowel syndrome, 1 (1%) celiac, and 1 (1%) other fat malabsorptive conditions. Mean age at first stone diagnosis was 48.6 ± 14.1 years and BMI 31.6 ± 8.7 kg/m². EH diagnosis was on average 8 years after first stone event and mean Uox was 65.3 ± 30.9 mg/24 hr. Follow-up after EH diagnosis was available for 60/74 patients, 78% of whom had a prior stone event (average n=4, 45% ≥2 events). Those with bariatric surgery were more likely to be female (p = 0.002), have a higher BMI (p = 0.001), and experience asymptomatic kidney stones before surgery (p = 0.02). After a median follow-up of 3 years, the 5-year cumulative stone event rate after EH diagnosis was 52.9% (Figure) and did not differ by EH cause.

Conclusions: EH patients experience a high rate of stone recurrence of up to 53% at 5 years regardless of underlying etiology. RYGB is the single most common cause, however other conditions associated with fat malabsorption are also common. These preliminary data strongly support continued efforts to develop a robust EH patient registry to identify specific phenotypic features that are associated with stone disease risk to inform study design for novel therapeutics.
SA-PO694
Calcitriol-Mediated Hypercalcemia in Mesothelioma
Fnu Parveen. Baylor College of Medicine, Houston, TX.

Introduction: Hypercalcemia (hyperca) is common in several hematological and solid organ malignancies however hyperca has rarely been reported in mesothelioma. We report an unusual case of calcitriol mediated hyperca in mesothelioma.

Case Description: An 80-year-old gentleman with stage IV chronic kidney disease was admitted for severe hyperca. Serum calcium (Ca) corrected for hypoalbuminemia 15 mg/dL. He was diagnosed with right lung mesothelioma two months prior followed by first cycle of nivolumab/ipilimumab (Nivo/Ipli) a month prior. He had mild hyperca 6 months prior to mesothelioma diagnosis which progressed despite stopping vitamin D and Ca supplementation. Workup shown in Table 1. Initial imaging revealed concern for lytic lesions of pelvis however subsequent workup including serum free light chains, serum and urine protein electrophoresis, bone and PET scan were negative for plasma cell dyscrasias. Further Imaging revealed 2.3cm left renal mass suspicious of renal cell carcinoma (RCC) however PET scan did not show any uptake into the kidneys. After acute treatment of hyperca the patient continued treatment with immunotherapy(IT) to which he responded.

Discussion: Hyperca from malignancy occurs from either tumor secretion of parathyroid hormone-related protein or tumor production of calcitriol etc. Calcitriol induced hyperca from Nivo/Ipil has also been reported. In our case calcitriol mediated hyperca from mesothelioma is the most plausible etiology. Even though calcitriol levels prior to IT are not available hyperca developed prior to starting IT. Workup of hematologic features hyperca was negative and PET scan was negative. Finally his Ca levels improved with further IT and improvement in mesothelioma. Although FDG uptake in RCC has a lower sensitivity and Nivo/Ipil can also treat RCC we believe the time-course of events makes mesothelioma the most plausible etiology.

Table 1

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>14.3</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>2.6</td>
</tr>
<tr>
<td>Corrected Calcium (mg/dL)</td>
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<td>Ionized Calcium (mg/dL)</td>
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<td>Phosphorus (mg/dL)</td>
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<td>PTH (pg/mL)</td>
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<tr>
<td>1,25-Hydroxyvitamin D (ng/mL)</td>
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<td>Serum and Urine Protein Electrophoresis</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

921
Consider PJP as a potential differential diagnosis. When evaluating a renal transplant patient presenting with hypercalcemia, it is crucial to recognize PJP as a potential cause. In this report, we present a case of refractory hypercalcemia resulting from PJP in a renal transplant recipient, highlighting the need for effective recognition and management.

**Case Description:** A 57-year-old male with a history of renal transplant, currently on immunosuppressive therapy, who was admitted to the hospital with fever and general malaise. Laboratory findings revealed marked hypercalcemia (15.6 mg/dL) with suppressed parathyroid hormone (PTH) levels. Extensive infectious investigations, including urinalysis, chest x-ray, computed tomography (CT) of the chest, abdomen, and pelvis, blood cultures, viral panel tests yielded no significant findings. Despite administration of isotonic saline, calcitonin, and bisphosphonates, the patient’s hypercalcemia remained unresponsive. Further laboratory studies revealed normal PTH-Related Protein (14 pg/mL), elevated 1,25 dihydroxy vitamin D (133 pg/dL), and normal 25-dihydroxy vitamin D (52 ng/dL). Due to persistent fever in an immuno-suppressed individual, an extensive infectious investigation was conducted, including tests for various viruses and pathogens. A diagnosis of PJP was achieved with a positive PCR test for PJP returned positive. The patient was promptly initiated on systemic steroid and atovaquone therapy targeting PJP. Serum calcium returned to normal after completion of therapy.

**Discussion:** Hypercalcemia in renal transplant patients with PJP results from a granulomatous-like mechanism. Macrophages and monocytes in granulomas play a vital role by producing 1-alpha hydroxylase, converting calcidiol to calcitriol, the active form of vitamin D. Calcitriol stimulates increased calcium absorption in the intestines and kidneys and calcium mobilization from bone tissue, leading to hypercalcemia. Therefore, when evaluating a renal transplant patient presenting with hypercalcemia, it is crucial to consider PJP as a potential differential diagnosis.

**SA-PO696**

**Refractory Hypercalcemia: Unmasking Pneumocystis jirovecii Pneumonia in a Renal Transplant Recipient**

Wern Lyn Ng,1 Lillian Sangha,1 Benjamin Ravichander,1 Evelyn J. Calderon Martinez,1 Lay She Ng,2 Gabriela M. Calderon Barahona,1 Jia Yi Tan,1 Seema Sharma Gautam,1 Irina Mishagina,1 UPMC Harrisburg, Harrisburg, PA; 2 Mayo Clinic Minnesota, Rochester, MN; 3 New York Medical College, Newark, NJ.

**Introduction:** Refractory hypercalcemia in renal transplant recipients is a challenging consequence of Pneumocystis jirovecii pneumonia (PJP). Accurate diagnosis is crucial, as PJP can present subtly, leading to increased mortality rates. In renal transplant patients, hypercalcemia frequently accompanies PJP and serves as a vital diagnostic clue. In this report, we present a case of refractory hypercalcemia resulting from PJP in a renal transplant recipient, highlighting the need for effective recognition and management.

**Methods:** A retrospective observational study was performed on patients from three hospitals in Korea who were treated with denosumab between November 2016 and December 2021. We compared the mean percentage change in serum phosphate, calcium, and PTH levels from baseline to six months post-denosumab treatment. Among the 1156 patients (median age, 70.0 years; 89.2% female) included in this study, 10 069 (87.9%) had an estimated glomerular filtration rate (eGFR) over 60 mL/min/1.73 m² and comprised the preserved kidney function group. Patients with an eGFR under 60 mL/min/1.73 m² (n = 1 517) comprised the reduced kidney function group.

**Results:** One month after denosumab administration, serum calcium (preserved kidney function group: -3.15%; reduced kidney function group: -6.35%) and phosphate levels (preserved group: -10.9%; reduced group: -9.56%) decreased and serum PTH levels increased (preserved group: +123.54%; reduced group: +216.93%). However, all parameters returned to baseline six months after treatment. Six months after denosumab treatment, a higher rate of hypocalcemia was observed in the reduced kidney function group relative to that of the preserved kidney function group (4.5% and 8.3%, respectively, p < 0.001).

**Conclusions:** One month post-denosumab treatment, serum phosphate and calcium levels significantly decreased and PTH levels increased; however, these changes were transient. When using denosumab in reduced kidney function patients, close monitoring and replacement of calcium and vitamin D are required.

**Hypocalcemia at baseline and 6 months after denosumab treatment**

**SA-PO697**

**Neonatal Hypocalcemia and Maternal Hypercalcemia: Exploring the Potential Connection to Parathyroid Adenoma and CaSR Mutations**

Jhao-Jhuang Yi,1 Hae Min Park,1 Minhwa Lee,1 Seong Jin Kim,1 Ji Cho,1 Hyun Su Lee,1 Myeong Hae Kang,1 Ji Ho Kang,1 Hyunjae Kwon,1 Ju Jin Hyeog,2 Lay She Ng,3 Wern Lyn Ng,1 Tae-hyung Lee,1 Yeonghwan Kim,1 Gabriel M. Calderon Barahona,1 Jia Yi Tan,1 Seema Sharma Gautam,1 Irina Mishagina,1 UPMC Harrisburg, Harrisburg, PA; 2 Mayo Clinic Minnesota, Rochester, MN; 3 New York Medical College, Newark, NJ.

**Background:** This study aims to investigate the relationship between neonatal hypocalcemia and maternal hypercalcemia, and to explore potential genetic predispositions related to parathyroid adenoma and CaSR mutations in mothers.

**Methods:** Neonates presenting with late-onset (≥2 days) hypocalcemic tetany or seizures, low serum total calcium, high serum phosphorus, and inappropriate low or normal iPTH levels suggestive of hypoparathyroidism were prospectively enrolled. Further research is warranted to understand the genetic basis and optimize management strategies for both conditions.

**Results:** Seven full-term newborns (six males, one female) and their mothers were enrolled. All newborns were diagnosed with transient hypoparathyroidism secondary to maternal hypercalcemia. To investigate the cause of maternal hypercalcemia, maternal serum calcium, phosphorus, iPTH levels, and parathyroid scans were assessed. Five mothers were found to have parathyroid adenoma, and one was confirmed to have a CaSR loss-of-function genetic mutation. All newborns were treated with oral calcium gluconate combined with cholecalciferol or calcitriol. After approximately one month of treatment, serum calcium and phosphate levels normalized, and the iPTH-Ca correlation was restored. Following parathyroidectomy in mothers with parathyroid adenoma, serum calcium levels normalized, but elevated iPTH levels persisted for months. The mother with the CaSR loss-of-function mutation exhibited a similar trend in serum calcium and iPTH levels.

**Conclusions:** This study underscores the importance of evaluating maternal calcium homeostasis in cases of neonatal hypocalcemia and highlights a potential genetic association between neonatal symptoms and maternal parathyroid adenoma and CaSR mutations. Further research is warranted to understand the genetic basis and optimize management strategies for both conditions.

**SA-PO698**

**Trends in Serum Parameters Levels According to Renal Function Following Denosumab**

Jin Hyeog Lee, Yeonji University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea.

**Background:** Osteoporosis and chronic kidney disease (CKD) are major risk factors for fracture. Denosumab is widely used to treat osteoporosis in patients with CKD; however, its effect on phosphate, calcium, and parathyroid hormone (PTH) levels has not been fully elucidated.

**Methods:** A retrospective observational study was performed on patients from three hospitals in Korea who were treated with denosumab between November 2016 and December 2021. We compared the mean percentage change in serum phosphate, calcium, and PTH levels from baseline to six months post-denosumab treatment. Among the 1156 patients (median age, 70.0 years; 89.2% female) included in this study, 10 069 (87.9%) had an estimated glomerular filtration rate (eGFR) over 60 mL/min/1.73 m² and comprised the preserved kidney function group. Patients with an eGFR under 60 mL/min/1.73 m² (n = 1 517) comprised the reduced kidney function group.

**Results:** One month after denosumab administration, serum calcium (preserved kidney function group: -3.15%; reduced kidney function group: -6.35%) and phosphate levels (preserved group: -10.9%; reduced group: -9.56%) decreased and serum PTH levels increased (preserved group: +123.54%; reduced group: +216.93%). However, all parameters returned to baseline six months after treatment. Six months after denosumab treatment, a higher rate of hypocalcemia was observed in the reduced kidney function group relative to that of the preserved kidney function group (4.5% and 8.3%, respectively, p < 0.001).

**Conclusions:** One month post-denosumab treatment, serum phosphate and calcium levels significantly decreased and PTH levels increased; however, these changes were transient. When using denosumab in reduced kidney function patients, close monitoring and replacement of calcium and vitamin D are required.

**Hypocalcemia at baseline and 6 months after denosumab treatment**

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

**Underline represents presenting author.**
also impairs the function of the Parathyroid hormone. Loricre is quite popular among the general population of African population because of its assumed anti-oxidant properties and this case report highlights the significance of physician’s knowledge regarding its chronic use and but life-threatening complication of hypocalcemia.

### Table 1: Laboratory analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range</th>
<th>Findings</th>
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<tbody>
<tr>
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<td>0.6-1.0</td>
<td>Creatinine 0.6 mg/dL</td>
</tr>
<tr>
<td>Magnesium (mg/dL)</td>
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<td>Magnesium 2.5 mg/dL</td>
</tr>
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<tr>
<td>Alanine (mg/dL)</td>
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<td>Alanine not detected</td>
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<td>6-10</td>
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<tr>
<td>Pitt (mg/kg/hour)</td>
<td>0.5-1.0</td>
<td>Pitt 0.5 mg/kg/hour</td>
</tr>
</tbody>
</table>

**SA-PO700**

### Years of Hypomagnesemia due to an HNF1B Mutation

I. Kim, Prakash S. Gudsoorkar. University of Cincinnati, Cincinnati, OH.

**Introduction:** Mutations in the hepatocyte nuclear factor 1B (HNF1B) are an inherited cause of renal malformation that is accompanied by magnesium wasting and a distal tubular dysfunction like Gitelman syndrome. We describe a patient in late adulthood who has hypomagnesemia and an HNF1B mutation.

**Case Description:** A 39-year-old female presented with intractable nausea and loose stools. She denied any family history of kidney disease. Her laboratory findings revealed a magnesium of 1.0 mg/dL and a potassium of 3.3 mg/dL. Her FeCa was < 0.1% and FeMg was 5.6%. She reported multiple visits to her PCP for IV magnesium infusions twice per week in addition to oral supplementation. She otherwise denied any symptoms of paresthesia or numbness. Genetic testing was performed and revealed a deficiency in HNF1B. She was started on amiloride in an effort to decrease magnesium supplementation. Her subsequent visit revealed a magnesium of 1.4 mg/dL. Renal ultrasound also revealed an innumerable amount of bilateral renal cysts, one of which was 59.4 mg. Gitelman syndrome (GS) is the most common form of familial renal magnesium wasting. The 24-hour urine calcium/creatinine ratio is 85 mg/g. The upper limit for the urine calcium/creatinine ratio in adults is about 200 mg/g. The lower limit of normal for calcium excretion is unknown. A spot urine calcium/creatinine ratio of < 0.1% and a FE of Magnesium < 10 mg/day is considered normal. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients.
SA-PO704
The Drug that Keeps Giving: Hypomagnesemia Fixed by SGLT2 Inhibitor
Ahmed Abdallah,1 Fatima Ayubi,1 Ahmed Elkalashy,2 Md R. Hasan,2 Praveen K. Errabelli,1 Mauriik Lathiya,1 Manisha Singh,1 Nithin Karakala,1 Joseph H. Holthoff,3 University of Arkansas for Medical Sciences, Little Rock, AR; 3Arkansas College of Osteopathic Medicine, Fort Smith, AR; 4Mayo Clinic Health System Albert Lea, Albert Lea, MN.

Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are widely used in patients with kidney disease to improve clinical outcomes. They are known to increase serum magnesium levels. There are rare case reports of these helping treat hypomagnesemia with or without urinary losses of magnesium. We present a case report to add to this data in treating refractory hypomagnesemia with a significant improvement in serum magnesium levels.

Case Description: A 72-year-old frail woman with a past medical history of type 2 diabetes mellitus and gastric bypass surgery presented to the emergency department with complaints of worsening fatigue and refractory chronic hypomagnesemia. The patient had experienced generalized weakness, tremors, and reduced appetite for many months. The patient had known chronic hypomagnesemia, hypokalemia, hypocalcemia, and alkalosis, thus a concern for Gitelman syndrome. She was prescribed oral supplemental mag without significantly improving serum magnesium levels. Her home medications included metformin and pantoprazole. At the time of presentation, the patient had normal vitals, though she was very frail, demented, and resting tremors in her hands. serum magnesium was 0.9 mg/dL. The pantoprazole was discontinued, and oral and intravenous magnesium supplementation was started with a slight improvement in the serum magnesium levels to 1.2 mg/dL. Next, amiloride was added. However, she developed diarrhea likely secondary to the magnesium salts, which added to her gastric losses and inability to tolerate oral repletion. The fractional excretion of magnesium (FeMg) was 69% consistent with renal magnesium wasting, but the genetic tests for Gitelman came back negative. Subsequently, we added an SGLT2 inhibitor with marked improvement in serum magnesium levels to 2.3 mg/dL and complete resolution of tremors.

Discussion: In patients with significant urinary magnesium wasting, supplementation often fails to improve serum magnesium levels. Clinical trials have shown that SGLT2 inhibitors can improve hypomagnesemia in diabetic patients with urinary magnesium wasting. However, data on their efficacy in nondiabetic patients with hypomagnesemia is scarce. SGLT2 inhibitors may be considered in patients with intractable hypomagnesemia, representing a possible new tool in this challenging clinical disorder.

SA-PO705
Urinary Phenotyping in Mesoamerican Nephropathy
Amin Oomastia,1 Faisal M. Badri,1 Ali M. Al-Rashed,1 Marvin A. Gonzalez,2 Dorothea Nitsch,3 Neil Pearce,3 Ben Caplin,1 The Colt/KMC CKDu Study Group. 1University College London, London, London, United Kingdom; 2Research Centre on Health, Work and Environment at National Autonomous University of Nicaragua, Leon, Nicaragua; 3London School of Hygiene & Tropical Medicine, London, United Kingdom.

Background: Mesoamerican nephropathy (MN) is a leading cause of CKD in Central America. Studies suggest an underlying tubulointerstitial nephritis with coexisting electrolyte wasting in affected individuals. The Colt-MRC cohort is a community-based study in Nicaragua, which recruited individuals at risk of MN, measuring serum creatinine (Cr) and collecting questionnaire data and biosamples at annual study visits for 7 years. In this sub-study, we aimed to compare the urinary phenotype of individuals from the cohort representing a possible new tool in this challenging clinical disorder.

Methods: We compared concurrent serum and urine samples from EKI cases pre and post decline in eGFR to two samples from HC matched for age, sex, community and post decline, with healthy controls (HC) and those with established MN (eMN).

Results: FE of all electrolytes were raised in the eMN group, but serum Na and Mg were lower. MCP1 was significantly raised in cases in the visit post EKI compared to pre-EKI, HC and eMN. See Table 1.

Conclusions: Urinary MCP1 levels are higher in cases after incident EKI versus HC and eMN, suggesting acute inflammation at the onset of MN that subsequently subsides. Participants with eMN had raised FE of all measured electrolytes, a common feature of EKI due to hyperfiltration and subsequent nephron mass. However, they also had lower serum Na and Mg, with 50% exhibiting clinical hypomagnesemia, which is not a feature of CKD and suggests ongoing impairment of tubular function in established MN.

Funding: Private Foundation Support, Government Support - Non-U.S.
hypervolemia to prompt timely evaluations/interventions. Fluid AG assignments for patients are used to calculate a Fluid Clinical Quality Score (CQS) for each HD clinic. This analysis investigated if Fluid CQS was meaningfully associated with FO hospitalizations.

Methods: Fluid AG scoring assigns patients into groups representing a low-to-high FO risk based on the presence of post-HD hypertension coupled with excess interdialytic fluid gains, missed/shortened treatments, unchanged/increased estimated dry weights, and/or multiple blood pressure medications. Fluid CQS Score was calculated based on percent of patients in AGs with the median scoring 5, top decile scoring 10, and bottom decile scoring 1. Data on the Fluid CQS and the average rolling 12-month hospitalization rate considering exposure time were collected from 9/2022- 2/2023. FO hospitalization rate was averaged for each level of the Fluid CQS.

Results: Among patients treated at 2,705 clinics, we observed an inverse relationship between higher Fluid CQS scores and lower FO hospitalization rates ($R^2 = 0.93$). Average FO hospitalization rate was 25% lower at clinics with a Fluid CQS score of 10 vs 1 (0.16 vs 0.12 FO admissions/patient year at clinics with a Fluid CQS score of 10 vs 1, respectively). Consistent trends were observed during each month individually.

Conclusions: Fluid CQS appears to be meaningfully correlated with FO outcomes observed at a clinic and can be viewed as a surrogate marker of the management of fluid control. Further investigations are needed to understand the effectiveness of interventions being performed based on Fluid AG for individual patients.

Funding: Commercial Support - Fresenius Medical Care

Figure 1: Association between Fluid Clinical Quality Score (CQS) and fluid-overload hospitalizations

SA-PO709

Hypertension, Hypokalemia, and Psychosis: A Case Report of Ectopic ACTH Production from Pulmonary Carcinoid Tumor

Amara Sarwal, Siddhartha Kakani, Josephine Abraham. University of Utah Health, Salt Lake City, UT.

Introduction: Pulmonary carcinoid tumours are a rare cause of ectopic ACTH [1]. Herein, we present a case of ectopic ACTH production presenting as acute psychosis due to a pulmonary carcinoid tumor.

Case Description: 63 year old male with rheumatoid arthritis and hypertension presented to the Emergency Department with erratic behavior and altered mental status. Initial workup revealed profound hypokalemia to 1.8 mmol/L, sodium of 152 mmol/L, bicarbonate at 34 mmol/L and serum creatinine at 1.02 mg/dL. Urine toxicology was positive for marijuana. He was also found to be hypertensive at 152/101. Patient noted excessive sweating for 1.5 years along with weight loss of 20 pounds in the last month. Contrast imaging of the abdomen did not reveal any masses in the adrenals, although did note bilateral adrenal hyperplasia. Hyperaldosteronism was ruled out. 24 hour cortisol was 9948 ug/d with elevated ACTH of 229 pg/mL. Patient’s behaviour was thought to be due to acute psychosis from the hypercortisolism, and he was started on ketonozole with improvement in symptoms. Contrasted imaging of the chest revealed a 1.9cm right upper lung nodule that had been stable since 2020. Unfortunately, patient developed PJP pneumonia, causing a delay in surgical resection. Patient underwent wedge resection a month later, with pathology revealing 1.4cm well differentiated carcinoid tumor with positive ACTH immunostaining.

Discussion: Metastases in pulmonary neuroendocrine tumors have been reported at <15% of cases[1]. >80% of cases of pulmonary carcinoids are curative with surgery [1]. Our patient had a nodule that had been unchanged for years prior to presentation. After ruling out any other causes for ectopic ACTH, we decided to pursue further evaluation of the lung nodule.

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

Poster/Saturday
**SA-PO710**

**Dare to Diurese: Lymphedema in a Patient with Spina Bifida**

Maheen Khan, Neey Patel, Yashvi Pethani, Martin Brigham, Adrian P. Sequeira. LSU Health Shreveport, Shreveport, LA.

**Introduction:** Evaluation of edema is a common part of medical practice. While there are myriads etiologies that can cause edema, diuretics are cornerstone of management and have the potential to be overused. We present one such case in a patient with lymphedema from Spina Bifida. Fortunately, the patient presented with primary lymphedema compared to healthy individuals[2]. Lymphedema praecox, the most common form of primary lymphedema, has its onset between age 2 and 35 and has a female to male ratio of 10:1.[3]

**Case Report:** A 28-year-old female with past medical history of spina bifida presented to the ED with worsening lower extremity swelling and light-headedness. Prior evaluation by PCP endocrinologist, and cardiologist were unremarkable. She was on lasix 80 mg twice a day, metolazone 2.5 mg twice a day, spironolactone 50 mg daily and 80 mEq of sodium level of 151 mEq/L, a urine output of 6.5 L/day, and a urine specific gravity on admission suggested presence of ADH effect which argues against GDI. Second, low copeptin level was suggestive of VWS. The copeptin level is expected to be within reference range in GDI or elevated in the setting of cardiacogenic shock. Finally, absence of anterior pituitary axis dysfunction would make CDI very less likely. In conclusion, urine chemistry and copeptin level are essential in the diagnosis of polyuria in pregnancy.

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**SA-PO711**

**Therapeutic Plasma Exchange-Related Hypotension: A Comparison of Replacement Fluids**

Andrew Yanik,1 Amara Sarwal,1 Jamie P. Dwyer,1 Srinivasan Beddhu,2 Robert E. Boucher,1 Josephine Abraham.1 University of Utah Health, Salt Lake City, UT.

**Background:** Therapeutic plasma exchange (TPE) is used to remove specific pathogenic entities or replace substances that are physiologically lacking. TPE requires replacement fluid administration due to plasma losses, and the most common replacement fluids are albumin and saline. A recent report shows the effect of different replacement fluids on TPE-related hypotension. This study aimed to compare TPE-related hypotension between groups receiving partial-saline and 100% albumin.

**Methods:** This is a retrospective, single-center study from the University of Utah. Patients who were 18 years old or older and had diagnoses necessitating TPE were considered eligible participants. 2272 TPE sessions were performed in 333 patients from 1/1/2020 and 3/3/2023. All patients before 3/1/2022 received partial saline, and all patients after this received 100% albumin. Episodes of TPE-related hypotension were investigated and compared between groups using logistic regression models to relate TPE group to the incidence of each type of hypotensive event, with adjustment for SBP, DBP, and indication for TPE.

**Results:** The mean age of the patients was 50.5 years and 48.6% were male. The partial-saline group accounted for 1432 sessions and the 100% albumin group account for 840. Hypotension occurred in 32.4% of TPE sessions in the partial saline group, and 31.7% in the albumin group (OR=1.01, 95% CI 0.83-1.23, p=0.865). When analyzing individual criteria of hypotension between the partial saline and albumin groups, respectively, the results show: 4.82% vs 2.86% (SBP <90 mmHg OR=1.70, 95% CI 1.03-2.78, p=0.035), 16.13% vs 11.31% (MAP <65 OR=1.39, 95% CI 1.05-1.83, p=0.02), 21.37% vs 22.26% (SBP drop >20 mmHg OR=0.98, 95% CI 0.7-1.3, p=0.84), and 3.64% vs 5.30% (SBP drop >40 mmHg OR=1.74, 95% CI 1.00-3.03, p=0.05). When analyzing the composite of an SBP drop below 90 mmHg, MAP <65, and SBP drop >40 mmHg, events occurred in 19.41% and 14.05% of the partial saline and albumin groups, respectively (OR=1.41, 95% CI 1.09-1.80, p=0.007).

**Conclusions:** Partial saline recipients are significantly more likely to have a hypotensive event. This may reflect support for using 100% albumin as replacement fluid during TPE, reinforcing the physiological rationale for this replacement fluid.

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**SA-PO712**

**Differentiating Vasopressin Withdrawal Syndrome from Gestational and Central Diabetes Insipidus: A Learning Case Study**

Panupong Hansrivijit,1,2 Annie Liu,1 Pui Susan W. Cheung.1,3 Massachusetts General Hospital, Boston, MA; 1Brigham and Women’s Hospital, Boston, MA.

**Introduction:** Differentiating vasopressin withdrawal syndrome (VWS) from gestational diabetes insipidus (GDI) and central diabetes insipidus (CDI) in a pregnant woman is challenging. Prolonged administration of exogenous vasopressin can lead to negative feedback on endogenous anti-diuretic hormone (ADH) production from the posterior pituitary gland. CDI can occur following a shock leading to pituitary injury and usually co-exists with anterior pituitary axis deficits given their enriched blood supply. Finally, GDI is mediated by placenta-derived vasopressinase which degrades endogenous ADH and exogenous vasopressin. GDI typically presents in the 2nd and 3rd trimesters and can persist up to 6-8 weeks post-partum. A baseline urine analysis and serum copeptin level is a useful tool in the diagnosis of polyaury in pregnancy.

**Case Description:** A 32-year-old, 24-week pregnant female was admitted to the Intensive Care Unit for peripartum cardiomyopathy requiring Impella device placement. She was diagnosed on phenylephrine and vasopressin for hypertension on hospital day (HOD) 1. On HOD13, vasopressin was stopped, and she became polyuric with nine liters of urine output leading to some issues with the Impella device. Urine osmolality was 100 mosm/kg. Vasopressin was then restarted with resolution of polyuria. Nephrology was then consulted on HOD22 with a urine output measured at 1500 mL/hour. Vasopressin was successfully discontinued on HOD22 with a bridge using desmopressin. Eventually, desmopressin was completely stopped on HOD37 (16 days after delivery).

**Discussion:** This patient’s presentation favors VWS over GDI. First, the urine specific gravity on admission suggested presence of ADH effect which argues against GDI. Second, low copeptin level was suggestive of VWS. The copeptin level is expected to be within normal range in GDI or elevated in the setting of cardiacogenic shock. Finally, absence of anterior pituitary axis dysfunction would make CDI very less likely. In conclusion, urine chemistry and copeptin level are essential in the diagnosis of polyaury in pregnancy.

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**SA-PO713**

**Running Dry: The Thirsty Journey of Postpartum Diabetes Insipidus**


**Introduction:** Diabetes insipidus (DI) is a rare complication of pregnancy, occurring in 1 in 30,000 pregnancies. Diagnosing DI during pregnancy can be challenging due to physiological changes, which increases the degradation rate of vasopressin.

**Case Description:** A 28-year-old female G2P1A0 with a trichorionic triamniotic pregnancy at 27-37 weeks gestation, was admitted to the hospital due to preterm premature rupture of membranes (PPROM) and later developed preeclampsia. After an emergent cesarean section, she developed acute respiratory distress syndrome requiring endotracheal intubation, was treated for hyperthyroidism and transfused with one packed red blood cells. On day 6 following delivery, the patient developed polyuria, no polydipsia reported while sedated on mechanical ventilation. Laboratory investigations showed normoglycemia, normocalcemia, hypokalemia, hypomagnesemia, hyperthermia (serum sodium level of 151 mEq/L), a urine output of 6.5 L/day, and a urine specific gravity of 1.005. Total placenta weight was found to be 770 g (normal 500-680 g in a full-term pregnancy). Treatment with synthetic analogue 1-deamino-8-D-arginine vasopressin decreased urine output, increased urinary osmolality, and normalization of sodium levels. The patient was discharged from the hospital with no signs of DI or additional complications. Endocrinological follow-up confirmed that there were no underlying metabolic disorders.

**Discussion:** This case highlights the diagnostic complexity of transient diabetes insipidus in the postpartum period. It is a rare complication that can occur following pregnancy in patients with pre-existing medical conditions. Diagnosing DI during pregnancy can be challenging due to physiological changes, which can make interpreting results difficult. A high index of suspicion for vasopressinase-induced DI should be considered in the presence of risk factors such as preeclampsia, hepatic dysfunction, and multiple gestation.

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**SA-PO714**

**Arginine Vasopressin Deficiency in the Hypoxic Brain**

Leanna V. Ritchie, Abdul Basit, Lyle W. Baker. Mayo Foundation for Medical Education and Research, Jacksonville, FL.

**Introduction:** Hypernatremia is an electrolyte disorder most commonly related to limited access to water or suppression of the thirst regulatory mechanism. Hypernatremia is defined as being in excess of the normal range of sodium (serum sodium level of 140-145 mEq/L) in response to elevated serum sodium from the posterior pituitary gland to bind with V2 receptors in the distal tubules and collecting ducts in the kidney to facilitate water reabsorption. If this phenomenon is interrupted, termed arginine vasopressin deficiency (AVD), a patient may present with hyponatremia and polyuria. The most common etiologies of AVD are secondary to infiltrative disease, primary or secondary tumors and traumatic brain injury.

**Case Description:** Here presented is a case of a 58 year old female with a past medical history remarkable for hypertension, diabetes, seizure disorder and obesity who presented to the hospital after cardiac arrest. The patient had asystole and achieved return of spontaneous circulation after 1 hour of advanced cardiac life support. Following ROSC, the patient developed hypernatremia with hyperosmolar state. GT had unexpected global hypoxemic brain injury. The patient had absent brainstem reflexes. The patient developed acute kidney injury secondary to renal ischemia and was started on continuous veno-venous hemofiltration (CVVH). Despite renal replacement therapy the patient developed hypernatremia with polyuria. Initially free water balance were initiated, however the patient developed refractory hypernatremia. Renal replacement therapy was discontinued. Urine osmolality was 259 mOsm/kg, consistent with AVD. The patient’s urine volume was...
SA-PO715

Spontaneous Development of Diabetes Insipidus in a Healthy Female: A Rare Case of Central Diabetes Insipidus in the Nephrology Clinic
Allison Mitchell, Hania Kassem. The University of Texas Medical Branch at Galveston Development Office, Galveston, TX.

Introduction: Diabetes Insipidus (DI) is a rare complication resulting from vasopressin (AVP) deficiency [central (CDI)] or AVP resistance [nephrogenic (NDI)] leading to polydipsia, polyuria, and hyponatremia. We present a case of CDI in the nephrology clinic setting including diagnosis, imaging, and treatment.

Case Description: A 46-year-old female presented to nephrology clinic with polydipsia and polyuria that began 3 months prior. Her primary complaints were extreme thirst requiring consumption of approximately 20L of water over 2 to 3 days with large volume urination every hour. Initial laboratory findings were consistent with diabetes insipidus: high-normal sodium (Na) of 145, creatinine of 0.55mg/dL, low urine osmolality of 140 mOsm/kg, and low serum AVP (which resulted 2 weeks later). Due to high suspicion for CDI, patient was started on a trial of oral desmopressin 0.1mg daily which was increased over two weeks to desmopressin 0.2mg BID. Patient subsequently improved with resolution of symptoms and labs showing: normal serum Na (140 mmoL/L) with improved urine osmolality (494 mOsm/kg). MRI brain showed diffuse thickening of the pituitary infundibulum in the absence of posterior pituitary bright spot and a small meningioma over the left anterior temporal lobe supporting a diagnosis of Langerhans cell histiocytosis (LCH). Patient was referred to neurology and oncology for further evaluation.

Discussion: LCH is a rare disorder characterized by abnormal proliferation of Langerhans cells, histiocyte-like cells, of unknown cause. This disorder is rarely seen in adults (1-2 per million) and is twice as likely to be diagnosed in males. LCH affects the central nervous system by affecting the pituitary infundibulum leading to the initial presentation of DI. An elevated serum Na along with dilute urine in a patient with polyuria and polydipsia was strongly suggestive of DI, which led to the decision of work up and treatment without requiring a confirmatory water deprivation test. Desmopressin dosing titration required close monitoring with patient counseling about decreasing fluid intake once urine output decreases and being aware of the signs of hyponatremia. This was a unique case in the outpatient nephrology setting of a rare disease in an unlikely patient demographic.

SA-PO716

A Deep Dive into Diabetes Insipidus
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Introduction: Central diabetes insipidus (DI) is a disease caused by absent antidiuretic hormones production, leading to symptoms of polyuria and polydipsia. Head trauma is a typical cause of central DI. We present a case of new onset partial central diabetes insipidus where recurrent scuba diving was considered a likely trigger.

Case Description: A 58-year-old female presented with polyuria, nocturia, and thirst for one month that started after an annual scuba diving trip. Past medical history was notable for anxiety. She was recently prescribed bupropion prior to these symptoms. Physical exam was unremarkable, serum sodium 145 mmoL/L, serum osmolality 305 mOsm/Kg, 24-hour urine volume >2.8 L, and urine osmolality 180 mOsm/Kg. She was empirically started on DDAVP to relieve nocturia symptoms and scheduled for a water deprivation test. Nocturia symptoms improved immediately after started DDAVP. Water deprivation test (Figure 1) showed mild elevations of urine osmolality with water deprivation and substantial increase of urine osmolality with DDAVP administration indicative of partial central DI. An MRI was performed, showing an absent neurohypophysis on T1 sequence. According to the patient, a previous head MRI was normal. On further review of the patient’s social history, she went on annual scuba diving vacations for many years.

Discussion: To our knowledge this is the first report of central DI associated with scuba diving. Previous studies have shown that recreational diving can cause a reduction of 20% central blood flow, decompression while ascending can also cause brain injury. We hypothesize that repeated exposure to such hypoxic conditions may have caused injury to the posterior pituitary, with potentially some injury associated with each dive until eventually enough posterior pituitary function was affected, resulting in dysfunction of antidiuretic hormone production or release.

Figure 1. Water deprivation test. Urine osmolality was measured each hour. DDAVP administered at hour 7.
Diagnosing Acute Intermittent Porphyria with SIADH
Mandy Hsu, 1 Abdul-Jawad Majedj, 1 Kevin C. Roe. 2 Penn State College of Medicine, University Park Program, State College, PA; 2Mount Nittany Medical Center, State College, PA.

Introduction: We present a case of acute intermittent porphyria (AIP) presenting with SIADH. AIP is a rare and often overlooked diagnosis. This case highlights the importance of considering AIP when a patient presents with SIADH. Delay in diagnosis led to increased treatment, multiple emergency department visits and hospitalizations, and unnecessary testing.

Case Description: A 20-year-old female with a history of anemia and anxiety presented with nausea, vomiting, and abdominal pain. She experienced symptoms for two months and underwent extensive evaluation and prior hospitalization. She described the pain as diffuse, inconsistent, and varying in severity. Prior evaluation included upper endoscopy, colonoscopy, CT scans, X-rays, gynecologic evaluation with pelvic ultrasound, and psychiatric consultation. Laboratory evaluation was consistently notable for hyperkalemia and hypocalcemia. Renal ultrasound was consistent with proteinuria consistent with proximal tubular injury. The patient required 11 liters of hypertonic saline (HTS) to maintain his serum sodium at near normal levels over a two week course. With on-going supportive management, he was weaned off HTS and transitioned to salt tablets which eventually were discontinued and the patient went on complete resolution.

Discussion: RSW shares several features with SIADH but this case highlights key differentiators. SIADH is regarded as a state of impaired free water excretion and low urine volumes with maintained volume status resulting from augmented release of arginine vasopressin (AVP) despite plasma osmolality (P-Osm) being elevated. RSW also exhibits impaired free water excretion but is accompanied by high urine volumes as a defect in tubular sodium reabsorption drives solute diuresis, an accompanying drop in serum sodium and hypovolemia. Cisplatin and Ifosfamide have been noted to cause proximal tubular dysfunction which can complete of his chemotherapeutic agents, yet the diagnosis may prove elusive as the initial work up time was 1.2 Liters. Once vasopressin was discontinued, the urine output increased to 120-130 mEq/L. Hyponatremia was first attributed to dehydration and anoxia treated with IV fluids, free water restriction and salt tablets. However, when euvolemia was achieved a low serum sodium (129 mmol/L) with inappropriately elevated urine osmolality (331 mOsm/kg) persisted. Once the diagnosis of SIADH was determined, a nephrology consultant recognized the association with AIP. Testing for urine porphobilinogens confirmed the diagnosis. The patient was transferred to a tertiary center to receive appropriate treatment with hemin infusion. Symptoms improved but evidence of SIADH persisted.

Conclusion: Early recognition of AIP is often difficult given the rarity of the disease and because the presentation is variable and nonspecific. Our case demonstrates how the presence of low urine sodium levels may help lead to a diagnosis of AIP. This diagnosis may have been missed had the potential cause of SIADH not been taken into consideration. Prompt diagnosis of AIP is important so that hemin therapy can be started to early manage future acute attacks and prevent long-term consequences, such as chronic neuropathic pain. Given that the patient had numerous differential diagnoses, it is important to consider the relationship between SIADH and AIP when presented with repeated unexplained abdominal pain, nausea, and vomiting. Teaching points: identify the underlying cause of hyponatremia when managing SIADH. AIP and SIADH have an established relationship. SIADH may result from damage to hypothalamus and hypothalamic-hypophyseal tracts in AIP. Fluid, Electrolyte, Acid-Base Disorders: Clinical - II

SA-PO719
Pressor Dose Vasopressin-Induced Acute Hyponatremia

Introduction: Vasopressin infusion is commonly used in intensive care unit for circulatory shock but has rarely been associated with hyponatremia. We describe a case of severe hyponatremia in a patient receiving vasopressin infusion that improved upon discontinuation.

Case Description: A 54-year-old, 74-kilogram male, with a history of intestinal bowel disease, was admitted to the intensive care unit for acute hypoxic respiratory failure due to adenocarcinoma lung disease, was admitted to the intensive care unit for acute hypoxic respiratory failure due to adenocarcinoma of the lung. Teaching points: identify the underlying cause of hyponatremia when managing SIADH. AIP and SIADH have an established relationship. SIADH may result from damage to hypothalamus and hypothalamic-hypophyseal tracts in AIP.

Case Description: A 92-year-old female with a history of hypertension, emphysema, and chronic renal failure, presented with a 12 day history of nausea, vomiting, and anorexia. Initial evaluation included a complete blood count, chemistries, and electrolytes which were significant for hyponatremia with a serum sodium of 122 mEq/L. Urine output was 500 mL without evidence of dehydration. Serum osmolality was 266 mOsm/kg and urine osmolality was 1200 mOsm/kg. Initial sodium was 127 mEq/L. Assessment revealed hypovolemia, hypotension, and a systolic blood pressure of 80 mmHg. Vasopressin was discontinued and a prompt diuresis and correction of hyponatremia was observed. The patient was discharged home in stable condition with a final sodium of 133 mEq/L.

Discussion: Vasopressin, at doses of 0.03 units/min, is a common medication given in the intensive care unit to support circulatory collapse. Vasopressin can exert antidiuretic effects through interaction with V2 receptors in the renal collecting duct cells by incorporation of aquaporin 2 channels allowing passive free water reabsorption across an osmotic gradient. This results in water intoxication with subsequent hyponatremia. In our patient, discontinuation of Vasopressin resulted in a prompt diuresis and correction of hyponatremia.

SA-PO720
Polyuric Hyponatremia: A Case of Salt Wasting
Manuel Urra, Ryan P. Flood. University of Colorado Anschutz Medical Campus, Aurora, CO.

Introduction: Renal salt wasting has been described in association with several chemotherapeutic agents, yet the diagnosis may prove elusive as the initial work up may reveal findings consistent with the much more common diagnosis of syndrome of inappropriate anti-diuretic hormone (SIADH). Here we described a case of renal salt wasting (RSW) associated with two chemotherapeutic agents and identify the key diagnostic features to differentiate RSW from SIADH.

Case Description: A 39 male with Stage IV testicular rhabdomyosarcoma undergoing inpatient chemotherapy with Etoposide, Ifosfamide and Cisplatin developed acute hyponatremia with a serum sodium drop from 134mEq/L to 123mEq/L under 48 hours. Urine studies revealed a urine sodium of 168mmol/L, urine potassium 18.4mmol/L, with a negative electrolyte free water clearance and a urine osmolality of 530mOsm/kg. Initial evaluation revealed RSW given inability to excrete free water further supported by a diagnosis of active malignancy. Additional evaluation revealed that the patient was polyuric with a daily urinary volume of six liters. Additionally, he was hypertensive with evidence of volume depletion on exam. Urinary evaluation revealed normocytic normochromia, glaucocytosis and BKd cells consistent with proximal tubular injury. The patient required 11 liters of hypertonic saline (HTS) to maintain his serum sodium at near normal levels over a two week course. With on-going supportive management, he was weaned off HTS and transitioned to salt tablets which eventually were discontinued and the patient went on complete resolution.

Discussion: RSW shares several features with SIADH but this case highlights key differentiators. SIADH is regarded as a state of impaired free water excretion and low urine volumes with maintained volume status resulting from augmented release of arginine vasopressin (AVP) despite plasma osmolality (P-Osm) being elevated. RSW also exhibits impaired free water excretion but is accompanied by high urine volumes as a defect in tubular sodium reabsorption drives solute diuresis, an accompanying drop in serum sodium and hypovolemia. Cisplatin and Ifosfamide have been noted to cause proximal tubular dysfunction which can complete of his chemotherapeutic agents, yet the diagnosis may prove elusive as the initial work up time was 1.2 Liters. Once vasopressin was discontinued, the urine output increased to 120-130 mEq/L. Hyponatremia was first attributed to dehydration and anoxia treated with IV fluids, free water restriction and salt tablets. However, when euvolemia was achieved a low serum sodium (129 mmol/L) with inappropriately elevated urine osmolality (331 mOsm/kg) persisted. Once the diagnosis of SIADH was determined, a nephrology consultant recognized the association with AIP. Testing for urine porphobilinogens confirmed the diagnosis. The patient was transferred to a tertiary center to receive appropriate treatment with hemin infusion. Symptoms improved but evidence of SIADH persisted.

Conclusion: Early recognition of AIP is often difficult given the rarity of the disease and because the presentation is variable and nonspecific. Our case demonstrates how the presence of low urine sodium levels may help lead to a diagnosis of AIP. This diagnosis may have been missed had the potential cause of SIADH not been taken into consideration. Prompt diagnosis of AIP is important so that hemin therapy can be started to early manage future acute attacks and prevent long-term consequences, such as chronic neuropathic pain. Given that the patient had numerous differential diagnoses, it is important to consider the relationship between SIADH and AIP when presented with repeated unexplained abdominal pain, nausea, and vomiting. Teaching points: identify the underlying cause of hyponatremia when managing SIADH. AIP and SIADH have an established relationship. SIADH may result from damage to hypothalamus and hypothalamic-hypophyseal tracts in AIP.

Case Description: A 92-year-old female with a history of hypertension, emphysema, and chronic renal failure, presented with a 12 day history of nausea, vomiting, and anorexia. Initial evaluation included a complete blood count, chemistries, and electrolytes which were significant for hyponatremia with a serum sodium of 122 mEq/L. Urine output was 500 mL without evidence of dehydration. Serum osmolality was 266 mOsm/kg and urine osmolality was 1200 mOsm/kg. Initial sodium was 127 mEq/L. Assessment revealed hypovolemia, hypotension, and a systolic blood pressure of 80 mmHg. Vasopressin was discontinued and a prompt diuresis and correction of hyponatremia was observed. The patient was discharged home in stable condition with a final sodium of 133 mEq/L.

Discussion: Vasopressin, at doses of 0.03 units/min, is a common medication given in the intensive care unit to support circulatory collapse. Vasopressin can exert antidiuretic effects through interaction with V2 receptors in the renal collecting duct cells by incorporation of aquaporin 2 channels allowing passive free water reabsorption across an osmotic gradient. This results in water intoxication with subsequent hyponatremia. In our patient, discontinuation of Vasopressin resulted in a prompt diuresis and correction of hyponatremia.
SA-PO723

Prevalence of Hyponatremia in Dengue-Infected Patients: Relationship with Systemic Inflammation
Juan Carlos Ayus,1 Kyung Min Lee,2 Daniel Caputo,3 Armando Negri,4 Carlos Eghi,5 University of California Irvine, Irvine, CA; 2Hospital Nacional Profesor Alejandro Posadas, El Palomar, Argentina; 3Universidad del Salvador Facultad de Medicina, Buenos Aires, Argentina.

Background: Dengue infection is becoming more prevalent worldwide and is associated with systemic inflammation. Systemic Inflammation is associated with non-osmotic release of ADH. Purpose: To evaluate the prevalence of hyponatremia in newly infected patients and its relationship with systemic inflammation.

Methods: Cross-sectional study in 375 patients with newly diagnosed dengue infection at Hospital Posadas in Argentina. Diagnosis was confirmed by IgM serology or PCR. Hyponatremia was defined as serum sodium concentration <135 mEq/L.

Results: Hyponatremia was present in 30.13% of the patients at admission. In multivariate logistic regression model, the OR for hyponatremia adjusting for age and sex was significant in the patients over 65 years, OR 6.034 (IC95 2.652-13.728) p=0.001. We also analyzed the relationship of hyponatremia with C-Reactive Protein (CRP). In multivariate logistic regression model adjusted for age, sex and CRP, OR for hyponatremia was significant in the group of patients with elevated CRP, OR 3.37 (IC95 1.439-7.895) p=0.005. We found a negative correlation between serum sodium and CRP (Spearman correlation coefficient r= -0.283; p<0.002).

Conclusions: 1. The prevalence of hyponatremia is high in newly infected patients with dengue; 2. Degree of hyponatremia correlated with severity of inflammation.

SA-PO724

A Case of Asymptomatic Isotonic Hyponatremia Following Transurethral Bladder Resection
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Introduction: Hyponatremia is a known, uncommon sequela of transurethral resection (TUR) of the prostate or bladder. This is usually attributed to perioperative fluid absorption of glucose used during bladder irrigation. However, a less observed occurrence of hyponatremia related to this procedure is due to fluid absorption after a bladder perforation.

Case Description: We present an 85-year-old male who experienced gross hematuria and was found to have a bladder mass requiring TUR of the bladder. During this procedure, the patient underwent bladder irrigation with glycine 1.5%. Subsequently, patient was initiated on continuous bladder irrigation (CBI) with normal saline solution. The morning of the surgery, his serum sodium level was 140 mEq/L. The post-procedure metabolic panel (drawn 12 hours after his TUR) was 130 mEq/L. This sodium was repeated 5 hours later, and was found to be 128 mEq/L (Figure 1). Serum osmolality, urine osmolality and urine sodium were 288 mosm/kg, 297 mosm/kg, and 132 mosm/L respectively. On physical exam, the patient was euolemic, and had a tender but soft abdomen. These findings were consistent with isotonic, euolemic hyponatremia. CT urethrogram was performed, which identified an anterior bladder perforation. CBI was discontinued, and he was started on a moderate fluid restriction. His serum sodium improved to 132 mEq/L in about 20 hours (Figure 1).

Discussion: Bladder perforation is an uncommon cause of acute isotonic hyponatremia, due to the retention and reabsorption of urine. Transurethral resection of prostate tissue has historically been associated with isotonic hyponatremia due to intraoperative glucose administration and absorption. Our patient likely had a mixed picture, with both causes contributing to the sodium level. This case highlights the importance of ruling out bladder perforation when hyponatremia is found after a TUR procedure.

SA-PO725

Severe Hyponatremia Following Melphalan Use: An Important Recognition
Allan Almousshef, Jad Tabbara, Laura Ferreira Provenzano. Cleveland Clinic, Cleveland, OH.

Introduction: Hyponatremia has been associated with adverse outcomes in various underlying diseases. In cancer patients, syndrome of inappropriate antidiuretic hormone (SIADH) has been a recognized complication of many chemotherapy agents. Melphalan has been reported to cause SIADH in the pediatric population. Still, no previous cases were reported in adults. Here we present a rare case of severe hyponatremia as a complication of melphalan chemotherapy.

Case Description: A 67-year-old female with a history of multiple myeloma achieving partial response on classical bortezomib regimen presented for an autologous stem cell transplant. The patient underwent a high dose of melphalan pre-conditioning regimen (200 mg/m2) 48 hours prior to the transplant. Serum sodium was 140 mmol/L before melphalan induction. The next day, the patient reported mild nausea. On the third day, serum sodium was 119 mmol/L repeatedly. Further workup showed serum osmolality of 253 mOsm/kg and normal renal function. Urine studies revealed a urine osmolality of 352 mOsm/kg and urine sodium of 41 mmol/L. No other associated symptoms were reported. The patient remained hemodynamically stable, and appeared euvolemic on the exam suggesting that SIADH as the etiology of hyponatremia. The decision was made to proceed with the transplant using only 1 L 0.9% Normal Saline for stem cell infusion. The repeat serum sodium level at 6 hours interval was 134 mmol/L, an increase of 15 mmol/L from the last measured level. Given this rapid correction was noted just after 48 hours of the development of hyponatremia, a re-lowering rescue strategy was applied with desmopressin and an infusion of dextrose 5% in water to avoid osmotic demyelination syndrome. The re-lowering strategy was stopped when serum sodium reached a level of 126 mmol/L, and the patient was then treated with fluid restriction (< 1 Liter/day) until serum sodium gradually increased to a normal level.

Discussion: Melphalan-induced SIADH is a rarely reported complication, particularly in adults. It has been hypothesized that alkyating agents, including melphalan, increase the release of anti-diuretic hormone, leading to hyponatremia. This case underlies the importance of monitoring sodium levels closely after melphalan infusion in adult cancer patients and avoiding high water and hypotonic fluids intake in patients receiving drugs that can trigger SIADH.

SA-PO726

Acute Peripartum Hyponatremia Due to Oxytocin
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Introduction: Medication-induced hyponatremia is common in hospitalized patients. In addition, the physiology of pregnancy predisposes to hyponatremia. We present a case of oxytocin-induced peripartum hyponatremia.

Case Description: A 40-year-old woman with diabetes and hypertension is admitted for induction of labor at 34 weeks of pregnancy for preterm rupture of membranes. Administration serum sodium (Na) was 136 mEq/L. Oxytocin was given as an infusion over 36 h at a maximum rate of 0.034 units/min and followed by a bolus of 30 units IV for postpartum bleeding. The first Na level after oxytocin started was 129 [Figure]. At hour 30 of the infusion, Na dropped to 123 and then reached a nadir of 116 an hour after the oxytocin was discontinued. Urine studies revealed osmolality 227 mOsm/L and Na 68 mEq/L. Fluid intake was restricted, urine output increased to 2000 mL/h for 6 h, and Na levels rapidly normalized over the next 20 h.

Discussion: Along with systemic vasodilation and arterial underfilling, pregnancy is characterized by a reset of the osmotic set point for antidiuretic hormone (ADH) release, predisposing to hyponatremia. Pregnancy-specific causes of hyponatremia include syndrome of inappropriate ADH from hyperemesis gravidarum, Sheehan syndrome, and oxytocin-induced hyponatremia. Oxytocin and ADH are cyclic nonapeptides that differ by only 2 amino acids and are synthesized by overlapping groups of neurons in the hypothalamic supraoptic and paraventricular nuclei. Both bind G protein-coupled receptors with significant overlap in affinity. This cross-reactivity gives oxytocin an ADH-like effect. While well described in the literature, oxytocin-induced hyponatremia is likely underrecognized. Nephrologists and obstetricians alike must be aware of this form of medication-induced hyponatremia, allowing for appropriate monitoring and prompt recognition to prevent the maternal and fetal morbidity associated with hyponatremia in pregnancy.

Figure 1: Serum Sodium (mEq/L) vs Postoperative Day (POD)
SA-PO727
A Rare Cause of Worsening Hyponatremia in Pulmonary SIADH
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Introduction: Primary adrenal insufficiency is a relatively rare entity with most cases in the United States secondary to auto-immune or genetic processes. Here we present a rare case of tuberculous adrenalitis presenting as worsening hyponatremia in a patient with SIADH.

Case Description: 50-year-old male from Mexico, with medical history of pulmonary tuberculosis and chronic hyponatremia (SIADH secondary to tuberculosis), presented with complaints of generalized weakness, nausea and vomiting for 4 days. Initial lab evaluation was significant for hyponatremia of 119. This was a significant change from patient’s previous mild hyponatremia readings in 130s which had responded to salt tablets and fluid restriction in the past. This led to further investigation into the cause of this worsening hyponatremia not responsive now to salt tablets or fluid restriction. Labs were significant for low cortisol with no increase seen with ACTH stimulation test, suggestive of primary adrenal insufficiency, subsequently confirmed by high ACTH. Imaging revealed interval worsening of pulmonary tuberculosis with left upper lobe opacity, scattered patchy opacities and tree-in-bud nodularity in lingula, left lower lobe and right upper lobes. Bilateral adrenal hyperplasia and retroperitoneal adenopathy were noted on abdominal CT scan. Patient was re-started on RIPE therapy and hydrocortisone and fludrocortisone supplementation requiring higher doses due to RIPE. Patient’s symptoms improved and sodium stabilized in 130s after therapy initiation.

Discussion: Adrenal insufficiency generally appears in tuberculosis cases after 90% glandular destruction. Most patients with active disease have bilateral adrenal enlargement seen on imaging and biopsy is generally not required in cases with evidence of extra-adrenal tuberculosis. This case was unique as there was clear evolution in the cause of worsening hyponatremia with worsening infection. It also highlighted the importance of investigating worsening of chronic hyponatremia in patients with pulmonary tuberculosis. Lastly, it should be highlighted that even with treatment of the infection, adrenal function rarely seems to return to normal likely due to anatomical destruction of the gland, emphasizing the importance of early detection and medication compliance in this disease.

SA-PO728
The Prevalence of Hyponatremia in the United States
David A. Woolley,1 Bhupinder Singh,2 University of Oregon, Eugene, OR; Nephcentric LLC, Phoenix, AZ.

Background: Hyponatremia (serum sodium [corrected for hyperglycemia] < 135 mmol/L) is the most common electrolyte abnormality. Hyponatremia prevalence has been estimated in high risk settings (e.g. 15% - 30% in hospitalized patients) using more recent data, while data regarding overall prevalence date back to surveys conducted prior to 2005. Using data from a nationally representative sample, we estimate the overall prevalence of hyponatremia in the US adult population using pooled data from population-based cross-section samples from 1999 – 2020, providing an analytic sample nearly 4-fold larger than used in previous estimates.

Methods: NHANES (National Health and Nutrition Examination Survey) produces national estimates that are representative of the total noninstitutionalized civilian US population. Typically conducted every 2 years, each cycle provides a nationally representative cross-sectional survey of approximately 10,000 persons, more than half of whom are adults providing serum samples. Multiple cycles can be combined to provide estimates with even greater precision. This study used pooled NHANES data from 1999 – 2020 (n = 55,731) to estimate the overall prevalence of hyponatremia across the general US adult population, as well as by gender and age subgroups. Observed data were used in the primary analyses, with missing data imputed in secondary analyses.

Results: Overall prevalence of hyponatremia in US adults is estimated to be 2.05%. As shown in the table, prevalence is highest in women (p < 0.001) and increases with age (p < 0.001). Based on US census data, it is estimated that in 2022, 5,944,024 US adults had hyponatremia. Secondary analyses based on imputed data showed very similar results.

Conclusions: Approximately 6 million US adults had hyponatremia in 2022, a prevalence of about 2%. Prevalence was higher in women and increased with age. As the population ages, the prevalence of hyponatremia in the US will likely increase.

Funding: Commercial Support - NephCentric
Fluid, Electrolyte, Acid-Base Disorders: Clinical - II
Poster/Saturday

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

**SA-PO730**

**Risk Factors of Under-Correction in Severe Hyponatremia: A Post Hoc Analysis of the SALSA Trial**

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1Hallym University Yongdong Sacred Heart Hospital, Hwasung, Gyeonggi, Republic of Korea; 2Seoul National University Seoul Metropolitan Government Bundang Medical Center, Dongjak-gu, Seoul, Republic of Korea; 3Seoul National University Bundang Hospital, Seongnam, Republic of Korea.

**Background:** The under-correction of hyponatremia is a non-optimal correction, is insufficient to improve cerebral edema, associated with increased mortality. Few prospective studies have identified the individuals at high risk of under-correction under controlled hypertonic saline treatment.

**Methods:** We conducted a post hoc analysis of a prospective randomized controlled study – the SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic saline) trial in 178 patients with glucose-corrected serum sodium (sNa) ≤125 mmol/L. Six subjects without sNa values during the entire follow-up period were excluded from the study. Under-correction was defined as sNa of less than 5 mmol/L within 24 hours or sNa of less than 10 mmol/L or 130 mmol/L within 24-48 hours.

**Results:** Mean age was 72.8 years old and mean sNa concentrations were 118.2 mmol/L. Over 48-hour intervention period, mean changes in sNa were at 24 hours and 48 hours were 8.6 and 11.5 mmol/L, respectively. Twenty-six of 172 patients (15.1%) experienced under-correction (10 patients within 24 hours and 21 patients within 48 hours). The under-correction group received more amount of hypertonic saline (486 ml vs 952 ml, P<0.001) and had less urine output for 48 hours (4117 ml vs 2647 ml, P = 0.004). High levels of uric acid, serum calcium and creatinine and lower levels of body mass index, systolic blood pressure, uric acid, and albumin were associated with greater risk for under-correction.

**Conclusions:** Among patients with symptomatic severe hyponatremia under controlled hypertonic saline treatment, under-correction occurred in 15% and were associated with baseline patient’s information.

**SA-PO731**

**Response of Relowering Treatment and Clinical Significance in Severe Hyponatremia: A Post Hoc Analysis of the SALSA Trial**

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1Hallym University Youngdong Sacred Heart Hospital, Hwasung, Gyeonggi, Republic of Korea; 2Seoul National University Seoul Metropolitan Government Bundang Medical Center, Dongjak-gu, Seoul, Republic of Korea.

**Background:** Relowering treatment has been performed in overly rapid correction of hyponatremia and its response may be numerous. However, few studies evaluated response of relowering therapy and its relationship to prognosis in patients with treating hyponatremia.

**Methods:** One hundred seventy-eight patients with glucose-corrected serum Na (sNa) ≤125 mmol/L were included. Eighty-seven out of 178 patients (in total 207) underwent relowering treatment. Relowering regimen was 5% dextrose infusion of 10 ml/kg over 1 hour if sNa level increase ≤10 mmol/L or a 18 mmol/L within 24 or 48 hours, respectively. Patients with concurrent desmopressin use or without sNa level adjustment were excluded. Eighty-seven patients (age 73.1 years, male 43.7%, and mean initial sNa 117.0 mmol/L) were classified into responder group (RG) (a 2 mmol/L) (34/87) and non-responder (NRG) (<2mmol/L) (53/87) group according to decrease of sodium after treatment. Overcorrection was defined as increase in the sNa level by >12/18 mmol/L within 24-48 hours.

**Results:** Mean of sNa at time of relowering treatment and delta from initial sNa were 128.6 mmol/L and 11.7 mmol/L, respectively. Among 87 patients with relowering treatment, overcorrection occurred in 9/34 (26.5%) of RG and 27/53 (50.9%) of NRG patients. sNa levels dropped to 128.6 mmol/L and 11.7 mmol/L, respectively. Among receiving 3% hypertonic saline for 24 hours, his sodium continued to be below 106 mmol/L, even on blood gas analysis. In order to determine the initial sodium level upon admission and the rate of correction, we used the following formula: sodium assimilation = 2(Na)+ BUN+2.8+ Glucose/18+ EtoH/3.7 (Na: mmol/L, BUN: mmol/L, Glucose: mg/dL, EtoH: mmol/L) and the patient was given intravenous Lasix on a daily basis due to suspected hypervolemic hyponatremia in the context of liver cirrhosis. The sodium levels continued to improve slowly, reaching 140 on the eighth day of hospitalization.

**Discussion:** The patient in this case presented with critically low sodium below detectable range and severe symptoms, necessitating a precise plan of care for improving sodium promptly but also without overcorrecting. Using simple algebraic calculations involving the serum osmolality formula, the patient’s sodium was reliably estimated. This guided sodium correction without any episodes of overcorrection in this already critically ill patient.

**SA-PO733**

**Modified Formula to Predict a Change in Serum Sodium in Patient with Hyponatremia Requiring RRT**

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**Introduction:** Hyponatremia is a common and feared electrolyte imbalance encountered, but rapid correction of sodium is what most physicians dread. In patients with hyponatremia requiring RRT, controlling the rate of sodium correction can be challenging & often requires the use of a hypertonic solution to dilute the diuretic. Here we present a case of a patient with hyponatremia pending liver transplant, who was started on CVVHD & rather than using a hypertonic solution we used a slower diuresis flow rate to prevent rapid correction of sodium.

**Case Description:** 39 year old male with decompensated cirrhosis presented with acute, asymptomatic hypervolemic hyponatremia. Initial labs showed Na 120, S.Osm 273, U.Osm 328, U. Na 49, BUN 74, Creatinine 2.36, CO2 17, normal TSH & cortisol. Despite fluid restriction, hypertonic saline, furosemide & tolvaptan, his sodium did not improve and fluctuated between 120-124. He also developed worsening renal failure needing initiation of CVVHD. To avoid overcorrection of sodium, the following modified formula was used to predict the rate of correction. ([Dialysate Na (140) - Patient’s Na (120)] / [TBW 0.8 X patient’s weight [141]) X Dialysate flow rate (L/Hr) = Rate of sodium correction (~0.23mEq/L/Hr) In our patient we used Qd (Dialysate flow Rate) as 1.5L/hr to get 0.35mEq/L/hr as the rate of sodium correction His sodium corrected to 127 on day 1,131 on day 2 and plateaued at 134 on day 3.

**Discussion:** Rapid correction of hyponatremia in cirrhosis runs a higher risk of patients developing osmotic demyelination syndrome. On CVVHD there is a risk for rapid correction if adjustments like diluting the diuretic with a hypertonic solution to reduce the dialysate sodium are not made. The above formula helps us adjust the diuretic flow rate accordingly to predict the rate of sodium correction and therefore prevent an overcorrection of hyponatremia. Various factors can affect the serum sodium in patients on CVVHD like IV infusions, insensible losses, etc. which explains why there wasn’t an exact correction of sodium as predicted in this patient. However by setting an upper limit of correction with the above diuretic flow rate formula we were able to avoid overcorrection of hyponatremia. If predicted change in hourly serum sodium is higher, consider adding hypertonic solution to avoid overcorrection.

**SA-PO734**

**Urea for the Treatment of Hyponatremia: A Two-Center Experience**

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**Background:** Oral urea is an effective treatment for hyponatremia, especially in patients with the syndrome of inappropriate antidiuresis (SIAD). However, data are limited and no predictors for treatment response have been identified. Here, we report our experience on efficacy, safety and tolerance of oral urea in the treatment of hyponatremia.

**Methods:** Retrospective study including hospitalized patients at the Erasmus Medical Center, The Netherlands and the University Hospital Basel, Switzerland who received oral urea for hyponatremia (plasma sodium (pNa) <135 mmol/l) between August 2018 and September 2022. The primary outcome was the rise in pNa until discontinuation of urea and/or discharge. The secondary outcomes included the risk of overcorrection (rise in pNa >10 mmol/l in 24h) and urea discontinuation due to side effects. Linear regression analyses were performed to identify predictors for pNa rise.

**Results:** In 138 patients (median age 69, 53% males, 92% SIAD) 159 urea treatment episodes (median dose 30 g/d) were identified. Concomitant fluid restriction (median 1L/24h) was prescribed in 88%. Under urea, pNa rose from 127 mmol/l (IQR 123–129) to 132 mmol/l (IQR 129–141, p=0.027). Urea was discontinued in 27% of the cases (median dose 30 g/d) and urea normalization was achieved in 47% of the cases. Higher baseline pNa and more liberal fluid intake were associated with a lower pNa rise (<0.7 mmol/L, 95%CI 0.8 -0.6 and <0.4 mmol/L, 95%CI 0.6-
to 0.2, respectively). In contrast, longer treatment duration and higher estimated glomerular filtration rate were associated with a greater pNa rise (0.3 mmol/L, 95% CI 0.1 to 0.4 and 0.2 mmol/L, 95% CI 0.1 to 0.4, respectively). Patients who reached normalization were treated significantly longer than those who did not (median 6 vs 3 days). Overcorrection occurred in 6 patients (4%, rise 13 ± 2 mmol/L in 24h). Urea was discontinued in 12 patients (9%) due to poor palatability and/or gastrointestinal symptoms. No treatment-related serious adverse events, including osmotic demyelination syndrome occurred.

Conclusions: In this largest cohort reported to date, oral urea effectively corrected hyponatremia with a relatively low rate of overcorrection and side effects. Higher baseline pNa and more liberal fluid intake were associated with a lower pNa rise, whereas longer treatment and higher eGFR were associated with a greater pNa rise.

SA-PO735

Serum Osmolality Testing and Preserved GFR Are Associated with Improved 30-Day Mortality in Severely Hyponatremic Patients

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Background: Despite UK guidelines advocating paired osmolalities and urinary sodium, inadequate investigation of hyponatremia is common. Although many hospitals suggest serum osmolality as an initial test, it is unclear whether this approach improves outcomes. We have built a logistic regression model to explore the association between serum osmolality (sOsm) testing status and mortality in severely hyponatremic patients. We also examined renal function to identify if this conferred greater risk.

Methods: We analyzed sodium values on admission from 87,174 patients in a large UK tertiary hospital. We extracted U/E, measured osmolalities, age, and blood glucose. Since we wanted to isolate the effect of the sOsm test, it was important to control for its value. In the absence of a measured osmolality, we therefore derived a calculated osmolality using the first glucose and urea available within 24h. We validated this by regressing 753 measured and estimated osmolalities (R2 = 0.6958, p < 0.0001). 30-day mortality was modeled with covariates ‘Serum Result’, ‘sOsm value (calculated if measured not available)’, ‘age’, ‘GFR’ and an interaction term identifying if testing was associated with improved mortality when sodium was <126mmol/L.

Results: Testing for serum osmolality in patients with sodium values <126mmol/L was associated with lower 30 day mortality (coefficient -1.527, p<0.001), as was preserved eGFR (p=0.01) and younger age (p<0.001). Of 1187 patients with Na<126mmol/L, just 39.4% received a sOsm test within 7 days of admission.

Conclusions: In this large hospital cohort, a low proportion of patients received a serum osmolality when severely hyponatremic. Performing serum osmolality testing is associated with lower 30 day mortality. Patients with impaired renal function were at increased risk. Not being able to identify patients who were admitted for palliation or identifying further clinical predictors of mortality were important limitations. The inclusion of sOsm calculated may provide a valuable tool for identifying patients who are at risk of overcorrection but who do not have measured osmolality. 30 day mortality was modeled with measured osmolalities in place of the calculated value to model the impact of the test itself on outcomes, a technique which could be used on other datasets. The results of this analysis have led to the adoption of an electronic alert to prompt sOsm testing, the impact of which will be measured in 3 monthly intervals.

SA-PO736

Chronic Hyponatremia Is Independently Associated with Mortality at Each Stage of CKD

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Background: Prior studies have shown hyponatremia is associated with mortality among patients with CKD. What is not clear is whether or not hyponatremia is a marker of underlying disease severity or if hyponatremia is associated with mortality independent of the severity of the underlying CKD and other comorbid conditions. The objective of this study is to determine if chronic hyponatremia (> 90 days duration) is independently associated with mortality and secondary outcomes at all stages of CKD.

Methods: All adult patients with CKD with chronic hyponatremia (cases) and without chronic hyponatremia (controls) between 2012 and 2018 were eligible for inclusion. The analysis included 25,944 cases and 25,944 matched controls. The analysis is based on a large retrospective study performed at a tertiary academic medical center. The participants were selected from a research network used to identify cohorts. The follow-up time was 5 years after CKD diagnosis. Primary outcome was mortality. Secondary outcomes were cerebrovascular, cardiovascular, infectious, thrombotic and neurodegenerative outcomes. All outcomes were analyzed as time to event using Kaplan-Meier analysis and summarized as hazard ratios. Subgroup analysis was performed for each CKD stage.

Results: The analysis included 25,944 cases and 25,944 matched controls. The mean age for cases was 66.3 (SD 15.8) and 65.9 (SD 16) years in controls. Patients in the cases group had higher chances of death (HR: 2.11, 95% CI: 2.05-2.18, p<0.001), stroke (HR: 1.92, 95% CI: 1.82-2.02, p<0.001), sepsis (HR: 4.17, 95% CI: 3.99-4.36, p<0.001), and stroke (HR: 1.92, 95% CI: 1.82-2.02, p<0.001). Subgroup analysis was performed for each CKD stage.

Conclusions: At each of stages of CKD, 1 and 2 collectively, 3, 4 and 5, chronic hyponatremia is independently associated with morbidity and mortality.

SA-PO737

Overcorrection in the Management of Hyponatremic Patients

[Na+] >125 mmol/L Following Emergency Department Admission

Shruti Korg, George N. Cortisidis, Sanjeev Gupta, James Beck. Westchester Medical Center, Valhalla, NY.

Background: Hyponatremia (HN) is the most common electrolyte abnormality. Treatment of a low serum sodium [Na+] level needs to be gradual to avoid overcorrection (OCx). We studied patients who were overcorrupted and why.

Methods: Patients admitted to Westchester Medical Center via the Emergency Department from 2019 - 2022 with [Na+] >125 mmol/L were included. An OCx is defined as [Na+] correction > 8 mmol/L in 24 hours. Slowing or reversing the OCx is considered a reversal. The use of hypertonic saline (HTS), serum and urine osmolality (UOs), urine sodium, and the duration were recorded.

Results: 477 patients were studied per the inclusion-exclusion criteria. 43% were on HN-associated medications averaging 1.83 (+/− 0.89) per patient with loop diuretics the most common. Cirrhosis was the most common HN-associated chronic disease, and renal consultation was requested in 58% (275/477). OCx occurred in 89 (19%) of patients, with a higher odds ratio (OR) in patients with UOs<300 (OR 3.9) and in whom HTS was administered (OR 4.5). Psychoactive medications were more common in OCx versus diuretics (27 vs 8%) and chronic diseases less likely in OCx (31.5 vs 60%). The rate of OCx was 9.2 +/- 0.6 mmol/L in 24 hours. Reversal of treatment was seen in 50% of OCx and risk was increased in patients with UOs <300 (OR 4.3) and HTS (OR 9.4).

Conclusions: OCx is associated with predictors UOs and HTS. Patients presenting with Na<125, on psychoactive medications, and lacking HN-associated chronic diseases should prompt an immediate renal consult to adequately assess HN physiology, underscore the need for UOs, and assess the selection of empiric fluids. While many of these findings are in general associated with HN, this study also highlights their association with OCx.

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

Underline represents presenting author.

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 477)</th>
<th>Controls (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66.3 (15.8)</td>
<td>65.9 (16)</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>54%</td>
<td>52%</td>
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<tr>
<td>BMI (kg/m²)</td>
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<td>25.4 (4.1)</td>
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<tr>
<td>Smoking (yes)</td>
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<td>30%</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>30%</td>
</tr>
<tr>
<td>HN (yes)</td>
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<td>100%</td>
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Table 2: Adequate Correction vs Overcorrection

<table>
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<tr>
<th>Correction</th>
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<th>Overcorrection (n = 220)</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>121.6 (14.0)</td>
<td>218.3 (14.0)</td>
<td>&lt;0.001</td>
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<tr>
<td>Overcorrection</td>
<td>209 (15.0)</td>
<td>209 (15.0)</td>
<td></td>
</tr>
</tbody>
</table>

Length of stay (days)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (n = 477)</th>
<th>Controls (n = 477)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of stay</td>
<td>12.13 (13.30)</td>
<td>9.58 (11.84)</td>
</tr>
</tbody>
</table>
SA-PO738

Use of Copeptin to Diagnose Nephrogenic Diabetes Insipidus Secondary to Hypercalcaemia
Olivia R. Drummond, Adrian J. Baudy. Tulane University School of Medicine, New Orleans, LA.

Introduction: Diabetes insipidus (DI) is a condition characterized by polyuria caused by inadequate antidiuretic hormone (ADH) activity. Differentiating between central and nephrogenic DI is usually accomplished by an indirect water deprivation test, which is effective, however inconsistencies in sample collecting can confound results. An emerging method of determining the etiology of DI is through the measurement of Copeptin, a moiety which is cleaved off the pre-ADH molecule and is a surrogate marker for ADH levels. Here, we discuss a case of a nephrogenic DI, in which a Copeptin level was used to assist in diagnosis.

Case Description: A 23-year-old woman presented to the hospital with abdominal pain and vomiting. She was found to have necrotizing pancreatitis and a calcium of 16 mg/dL. She was treated with IV fluids, calcitonin and zoledronic acid. An ultrasound and sestamibi scan revealed a parathyroid adenoma. The patient then developed hypernatremia up to 167 mmol/L with urine osmolality of 130 mosmol/kg, despite daily fluid resuscitation. Workup for differentiating central from nephrogenic DI included TSH, cortisol, MRI brain which were unrevealing. The patient had no response to DDAVP 0.1 mcg or 2 mcg subcutaneously. However, with a higher dose of 4 mcg, the urine osmolality increased to 307 mosmol/kg and sodium decreased by 2 mmol/L. Given the incomplete response to DDAVP, nephrogenic DI was diagnosed and treated with a thiazide diuretic and D3W until her sodium normalized. Copeptin levels returned at more than double the upper limit of normal, confirming the diagnosis of nephrogenic DI. This further confirmed hypercalcaemia as the culprit and parathyroidectomy was planned after discharge.

Discussion: Copeptin can be a useful tool in differentiating nephrogenic DI from central DI. Response to DDAVP or water deprivation tests are widely used, however in our patient, as in many cases, the results were difficult to interpret as the lab collection times and urine output measurements were inconsistent. An elevated copeptin level provided a simplified way to assess the patient’s level of ADH and confirm the diagnosis of nephrogenic DI. ADH is an unstable molecule and degrades quickly, thus cannot easily be measured directly. However, copeptin is a stable, surrogate marker for ADH levels and can be measured alone or in combination with water deprivation.

SA-PO739

From Shock to Sprinklers: A Rare Case of Polyuria in the ICU
Juan P. Moreno-Ortiz, Hiba Hamdan, Dana Sheely, Shubha Ananthakrishnan.
UC Davis Health, Sacramento, CA.

Introduction: Arginine vasopressin deficiency (AVD), previously known as central diabetes insipidus, is most commonly idiopathic, a result of a tumor, neurosurgery, or trauma. Here, we present a case of massive polyuria caused by transient vasopressin deficiency in an ICU patient after discontinuation of therapeutic vasopressin used for septic shock.

Case Description: A 56-year-old man with a history of COPD, AIDS, R ear Squamous Cell Carcinoma, was admitted for COPD exacerbation. His course was complicated by respiratory failure requiring mechanical ventilation and septic shock due to R e infection, managed with vasopressin. When stopped after two days, urine output went from an average of 1.5 to a peak of 8.2 L/day, associated with serum sodium rise from 130 to a peak of 148 mmol/L. Urine osmolality reached a nadir of 57 mosmol/kg and sodium copeptin level was 3 mmol/L. Concerned for AVD, IV vasopressin was restarted and desmopressin was trialed, both resulting in resolution of polyuria, urine osmolality peaking at 547 mOsm/kg, and normalization of serum sodium. Oral desmopressin was initiated. ACTH, AM Cortisol, LH, TSH and prolactin levels were normal. Brain MRI did not reveal structural abnormalities. After eight days of serum sodium 135-145 mmol/L and urine output 2-3L/day, desmopressin was tapered off and patient was discharged. Sodium levels off desmopressin 12 days later were stable. Further review of his chart revealed a similar presentation following cessation of vasopressin during a hospitalization for septic shock five years prior, resolving without intervention.

Discussion: Vasopressin is released by the posterior pituitary gland in response to thirst, hyperosmolality, and hypotension. Analogs are used to treat catecholamine-resistant shock, and abrupt cessation has been reported to lead to transient AVD. Neurosurgical and cardiothoracic surgical patients have been reported to be at risk. We present a case of AVD in sepsis. Prior case series have proposed downregulation of V2 receptors as a mechanism for the polyuria and hypernatremia, however, a low normal copeptin level in the face of hypernatremia suggests that suppression of endogenous arginine vasopressin is a more likely process. Given the recurrent nature of AVD in this patient, future research is needed to identify predisposing factors.

SA-PO740

Unintended Consequences: Severe Hyponatremia and Metabolic Alkalosis Following Baking Soda Ingestion for Urine Drug Screen Evasion
Manasawee Tanarayaku,1,2 Thiratest Leetsutpornsri,1 Witina Techasatian,1 Chinnawat Arayangkool,3 Noppawat Aiumtrakul,1 Mohammad I. Khan,1 Abhisest H. iztutsu,1,3 University of Hawai‘i at Manoa John A Burns School of Medicine, Honolulu, HI, 1Hawaii Residency Programs Inc, Honolulu, HI, 2Queen’s Medical Center, Honolulu, HI.

Introduction: Baking soda, also known as sodium bicarbonate, has various uses such as cleaning and treating conditions like metabolic acidosis and acid reflux. However, baking soda overdose can lead to fatal adverse events. We report a case of severe hyponatremia caused by intentional abuse of sodium bicarbonate to alter a urine drug screening (UDS) test result.

Case Description: We report a case of an individual found unconscious in a courthouse restroom. Initial findings revealed hypoglycemia to 55mg/dL and seizure activity upon EMS arrival. The patient was encephalopathic, prompting intubation. Formal laboratory tests showed critical hyponatremia, hypokalemia and metabolic alkalosis with Na+=180, K+=2.4, Cl-=111, CO2=50, pH in blood gas=7.56. Further information was obtained from the patient’s mother, revealing that the patient likely ingested baking soda with water before the UDS in an attempt to manipulate the test results. Interestingly, the initial UDS on admission returned negative for methamphetamine, but a repeat test done two days later resulted positive. The nursing staff also found white powder in the patient’s bag. After mixing the powder with vinegar, bubbles were observed, raising suspicion of a baking soda ingestion. Sodium correction using D5W and LR, was initiated along with antimicrobial drugs in conjunction with serial lab monitoring to ensure that sodium levels were appropriately lowered. Unfortunately, the patient deteriorated further with development cerebral edema and brain herniation.

Discussion: Metabolic alkalosis occurs from an accumulation of HCO3- or an inability to eliminate excess HCO3-. This case involved a patient with severe hyponatremia and metabolic alkalosis due to excessive alkali intake from baking soda, presenting with seizures and encephalopathy. The initial blood gas indicated an acute metabolic alkalosis with respiratory compensation. Cytotoxicity resulting from seizure and fluid shifts from rapid changes in sodium levels can explain the cerebral edema. Notably, a simple test demonstrating the reaction between vinegar and baking soda can be done to confirm the substance and may change the clinical course.

SA-PO741

A Man with Serum [Na+] 163 mM Who Is Not Thirsty
Ethan Orley-Shirrit, Alan Segal, MMP Nephrology, Maine Medical Center, Portland, ME.

Introduction: Lack of thirst sensation is a rare cause of hypertonicity, as thirst is the main defense to maintain isotonicity and normal intracellular volume. Hypertonicity is sensed by osmoreceptor cells, which control thirst and ADH release. The ability to sense/act on thirst is both necessary and sufficient to prevent dehydration, with ADH playing a supportive role by increasing the kidney water absorption. We present a case of a patient who developed hypertonicity due to an acquired injury resulting in defects in both thirst (resulting in hypodipsia) and ADH release (resulting in reduced water retention).

Case Description: A 60-year-old man with a history of CHF, DM, HTN and CKD (GFR 1.9 mg/dL) was admitted for cardiac shock. He was managed with diuresis and discharged with Torsemide and water/salt restrictions. During the admission, [Na+] increased from 132 to 154 mM. Four days after discharge, he was re-admitted when follow-up laboratory tests showing serum [Na+] of 163 mM and urine osmolality of only 369 mosmol/L. Surprisingly, he did not complain of thirst. He was treated with D5W, reduced Torsemide dose, and daily water consumption of ~ 2.5 L. Within two days, serum [Na+] corrected to 144 mM. CT head did not show a brain lesion (cardiac defibrillator precluded MRI). A transient resumption of Torsemide and liberation of water consumption led to an immediate worsening of hyponatremia. He was discharged with serum [Na+] of 147 mM and instructions to keep strict water intake of ~3 L per day. To date, the patient is isotonic.

Discussion: Our patient developed severe hyponatremia, which—although initially prompted by water restriction and Torsemide—was maintained by a remarkable lack of thirst sensation and urine concentration defect. Most of the patients with this rare condition, are young and have an identified CNS etiology (e.g. tumor), whereas our patient was 60 years old without a brain lesion. We conclude that our patient developed hypertonicity due to a rare combination of lack of thirst (hypodipsia) and partial arginine vasopressin deficiency and was treated successfully with an increased water intake.
SA-PO742

Unusual Polydipsia-Polyuria Syndrome, Hypernatremia, and Hypercoperpetinemia: What Is the Diagnosis?

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1University of Vermont Larner College of Medicine, Burlington, VT; 2East Tennessee State University, Johnson City, TN; 3University of Vermont Medical Center, Burlington, VT.

Introduction: Polydipsia-Polyuria Syndrome (PPS) can represent central diabetes insipidus (DI), nephrogenic DI or primary polydipsia (PP). Correct differentiation is crucial; Copeptin assay is useful. We describe PPS, hypernatremia, and hypercopeptinemia: Is this a new syndrome?

Case Description: A 76-yr female with Alzheimers disease was evaluated for dizziness, fatigue, incessant thirst, and chest pain. She was drinking excessively even from public faucets and had increased very wet diapers. The daughter restricted water intake at home. Vitals signs were stable. Chest radiograph and non-contrast head CT were non-diagnostic. She received IV D5W and drank to thirst. Sodium normalized (Figure A). BUN trajectory was a near mirror image (Figure B). Chest radiograph and non-contrast head CT were non-diagnostic. She received IV D5W and drank to thirst. Sodium normalized (Figure A). BUN trajectory was a near mirror image of Na trajectory (B). Incessant thirst persisted. Copeptin was 79.7 (>1.3) pmol/L. She was discharged with a diagnosis of PP and a Psychiatric referral.

Discussion: Does our patient have partial nephrogenic DI from AKI, drug-induced SIADH (?Sertaline), and/or PP, or a combination thereof? Hypernatriemia on admission probably reflected true water deficit following forced restriction of water intake at home by the daughter in the few days preceding the admission. Follow up would require a delicate balance of controlled water intake. Psychiatry management of suspected PP could include behavioral therapy, health education, relaxation techniques and positive reinforcement. Her dementia could be a barrier. Recent evidence supports a role for GLP-1 agonists in PP. Several unanswered diagnostic and therapeutic questions around PPS remain and call for further research.

SA-PO743

Identification and Characterization of a Novel CASR Mutation Causing Familial Hypocalciuric Hypercalcemia

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Background: Although familial hypocalciuric hypercalcemia type 1 (FHH1) is primarily caused by monoallelic mutation in calcium-sensing receptor (CASR) gene, the characterization of the newly-identified CaSR mutation linked to clinical response to calcimimetics remains limited.

Methods: A 45-year-old male presenting with hypocalciuric hypercalcemia, hypophosphatemia, and inappropriately high parathyroid hormone (PTH) had a good response to cinacalcet (total serum calcium from 12.5 to 10.1 mg/dL). Sanger sequencing of CASR, GNAS1, and AP2N1 genes was performed in this family. The simulation model used was to predict the function of the identified mutant. The in vitro studies including immunoblotting, immunofluorescence, cycloheximide chase study, Calbryte™ 520 calcium (Ca2+) detection, and half-maximal effective concentration (EC50) were examined.

Results: The patient was identified to carry a de novo heterozygous CASR I554N mutation, located in the cysteine-rich domain (residues 542–612) crucial to affect the ligands (Ca2+) binding. This missense mutation was pathogenic based on the different software prediction models and ACGME criteria. The simulation model showed CASR I554N mutation decreased its binding energy with Ca2+. Human CASR I554N mutation attenuated the stability of CASR protein, reduced the expression of p-ERK 1/2, and blunted the intracellular Ca2+ response to gradient extracellular Ca2+ (eCa2+) concentration. EC50 study also showed calcimimetics rescued the function of CASR I554N mutation.

Conclusions: This novel CASR I554N mutation decreases CASR stability and its binding affinity with Ca2+. Its correction of blunt response to eCa2+ by calcimimetics may support the therapeutic effect of cinacalcet for this patient.

Funding: Government Support - Non-U.S.
Conclusions: Both imaging and clinical genetic scoring have the potential to inform ADPLD-patients on their risk of developing symptomatic disease. Hereby, the combination of female sex, PRKCSH-disease, and rapid progression of hepatomegaly is associated with the greatest odds of PLD-related hospitalization.

Funding: Government Support - Non-U.S.

SA-PO745

Outcomes of Foam Sclerotherapy for Large Kidney/Liver Cysts using Multi-Stage (Same/Next Day) and Multiple Sequential Procedures

Cassie Howe, Ryan Helland, Adriana Gregory, Timothy L. Kline, Lisa E. Vaughan, Vicente E. Torres, Marie C. Hogan. Mayo Clinic Minnesota, Rochester, MN.

Background: We have been performing sotradecol foam sclerotherapy (SFS) outpatient procedures to ablate liver/kidney cysts. SFS has led to substantial reductions in Targeted Kidney & Liver Cyst (TKCV/TLCVs), total kidney/liver volumes (TKV/TLV), improved QOL, & augments cyst volume reduction in addition to tolvaptan (kidney cysts) & octreotide (liver cysts). We examined efficacy in individuals with multiple large cysts who opt to undergo multiple or multi-stage SFS (same day or 2 consecutive days).

Methods: Kidneys & liver were segmented using a deep-learning algorithm & cysts segmented using semi-automated segmentation software, pre & post SFS. Wilcoxon tests assessed Δ% TKCV & TLV pre/post SFS. Median Δ% TKCV/TLV were calculated (per-patient) by taking median Δ% of targeted cysts within patient & compared to outcomes from single stage cyst procedures.

Results: For multiple liver procedures (n=15) median Δ% TKCV/TLCVs was -76.5% [IQR, -90.3%, -42.8%, P<0.001] & ΔTLV % -1.9% [IQR, -7.4%, 0.4%, P=0.11] (Fig 1). For patients undergoing multiple kidney procedures (n=16), median % ATKCV was -88.8% [IQR, -95.1%, -82.0%, P<0.001] & Δ% TKV -13% [IQR, -23.8%, -4.9%, P<0.001]. Only 5 had multi-stage liver procedures; median Δ% TLCV post SFS -73% [IQR, -93%, -71%, P=0.06], & only 2 underwent multi-stage kidney procedures; median Δ% TKCV -52%[IQR, -73.5%, -31%, P=0.5].

Conclusions: Multiple SFS procedures led to substantial reductions in TKCV/TLCV/TKV/TLV; data on patients who underwent multi-stage procedures were sparse, but still demonstrated positive results. SFS is feasible & convenient for patients seeking ablation of multiple cysts in a single 1 or 2 day session. Multiple & multi-stage SFS appear to be effective for patients with high cyst burden mainly due to a limited number of large cysts, with good patient satisfaction.

Funding: NIDDK Support, Private Foundation Support

SA-PO746

The Clinicopathological and Genetic Characteristics of Autosomal recessive polyscyctic kidney disease presenting in adulthood

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a rare ciliopathy that causes massively enlarged kidneys and pulmonary hypoplasia in perinatal children, frequently leading to fetal demise. In the survivors, ductal plate malformation often causes congenital hepatic fibrosis and Caroli disease. However, the spectrum of presentation and disease varies considerably.

Methods: We examined the clinicopathological characteristics of PKHD1-defined ARPKD. Genetic testing was performed using whole exome sequencing.

Results: Three unrelated families (4 adult individuals) were identified to harbor disease-causing PKHD1 variants sequenced by the Irish Kidney Gene Project. The average age of initial presentation was 16.5 ± 18.6 years. In family (1), we identified biallelic PKHD1 variants (NM_138694.4:c.2702A>C;p.N901T & c.107C>T;p.T36M) in a female patient with congenital hepatic fibrosis and non-enlarged cystic kidneys, during the evaluation of elevated creatinine. She had gradually progressed into ESKF at 53 years of age. In family (2), the renal-limited phenotype of PKD was identified in two siblings. No liver involvement was identified. The two siblings developed a homozygous missense variant in the PKHD1 gene, NM_138694.4:c.5221G>A;p.V1741M. Patients progressed to ESKF at ages 36 and 40 years, respectively. In family (3), the index patient presented with predominant hepatic phenotype - recurrent cholangitis, portal hypertension, and Caroli disease at clinical disease-onset aged 48 years. A liver biopsy was performed and demonstrated marked liver fibrosis with numerous multifocal cystic dilatation of intrahepatic ducts. She was found to have multiple small bilateral kidney cortical cysts with impaired function. At the last assessment, aged 61 years, she developed slowly progressive kidney insufficiency, with a serum creatinine of 201 µmol/L and creatinine clearance of 23 ml/min about 15 years after her presentation. Exome-sequencing revealed pathogenic biallelic PKHD1 variants (NM_138694.4: c.6067T>C; p.W2209R and c.333delG; p.G113DF*4).

Conclusions: While ARPKD is remarked with early-onset and high disease mortality, these cases illustrate disease heterogeneity, and PKHD1-defined ARPKD is not merely a pediatric disease.

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

Underline represents presenting author.
SA-P074 An Updated Analysis of the Irish Kidney Gene Project Registry Elhussein A. Elhassan, 1,2 Sahin Sahin,3 Susan M. McAnallen, 1, 2 Dervla M. Connaughton, 1, 2 Kendrah O. Kidd, 3 Anthony J. Bleyer, 4 Gianpietro Cavallari, 2 Katherine A. Benson, 2 Peter J. Conlon. 1, 2 Beaumont Hospital, Dublin, Ireland, 3 Royal College of Surgeons in Ireland, Dublin, Ireland, 4 Western University School of Medicine & Dentistry, London, ON, Canada; 5 Wake Forest University School of Medicine, Winston-Salem, NC.

Background: Over 700 genes have been implicated in monogenic nephropathies (MN), a significant cause of chronic kidney disease (CKD), but their prevalence is often underestimated. Diagnosing MN can personalize clinical management with better-informed choices of therapies and targeted disease surveillance and influence prognosis and genetic counseling for patients and their families. Herein, we provide an update on the diagnostic yield of various technologies (exome sequencing, targeted gene panel, and MUC-1 sequencing) and immunostaining utilized by the Irish Kidney Gene Project (IKGP).

Methods: All results from the multidisciplinary genetic kidney clinic between January 2014 and March 2023 were analyzed in a single cohort study. All clinic visit records were analyzed for clinical and genetic factors associated with solved cases. Using the guidelines of the American College of Medical Genetics and Genomics, pathogenic or likely pathogenic variants were evaluated as disease-causing.

Results: Over 700 genes have been implicated in monogenic nephropathies (MN), a significant cause of chronic kidney disease (CKD), but their prevalence is often underestimated. Diagnosing MN can personalize clinical management with better-informed choices of therapies and targeted disease surveillance and influence prognosis and genetic counseling for patients and their families. Herein, we provide an update on the diagnostic yield of various technologies (exome sequencing, targeted gene panel, and MUC-1 sequencing) and immunostaining utilized by the Irish Kidney Gene Project (IKGP).

Conclusions: The use of broad genomic strategies had a high success rate, especially in the presence of familial history.

SA-P0748 Incompletely Penetrant Variants Underlie the Familial Variability in Disease Progression in Adults with ADPKD Elhussein A. Elhassan, 1, 2 Katherine A. Benson, 2 Stephen Madden, 2 Francesca Ciurlì, 2 Valeria Aiello, 2 Anna Vella, 2 Francesca Montanari, 1 Carlotta P. Cristalli, 2 Gaetano La Manna, 2 Irene Capelli, 2 Gianpietro Cavallari, 2 Peter J. Conlon. 1, 2 Beaumont Hospital, Dublin, Ireland, 3 Royal College of Surgeons in Ireland, Dublin, Ireland, 4 IRCSS Azienda Ospedaliero-Genetic Diseases: Cystic - Genetic Analysis and Extrarenal Manifestations.

Background: Although familial variability is one of the most prominent characteristics of autosomal dominant polycystic kidney disease (ADPKD), its molecular causes remain unknown. We hypothesize that co-inheritance of additional PKD1 or PKD2 variants with a pathogenic inactivating variant may contribute to familial disease progression.

Methods: Family members with clinically diagnosed polycystic kidney disease were recruited. Primary disease-causing variants were identified using ADPKD targeted next-generation sequencing panel. Additional variants (AV) were investigated using the criteria listed below: 1) allelic frequency <0.01; 2) missense variants in exonic or splicing regions, and 3) SIFT and PolyPhen predicted to be detrimental to protein formation variants were included. All AVs were deemed as variants of uncertain significance. We compared the progression to end-stage kidney failure (ESKF) between families with AV (at least one member with an additional ADPKD variant per family) and families with only primary variants.

Results: A total of 115 families with ADPKD (338 individuals, 55.9% female, 53.8% progressed to ESKF) were included; 60 different truncating PKD1 variants, 37 non-truncating PKD1 changes, and 7 PKD2 variants. 31 (26.9%) families (52 individuals) had at least one patient with AV. Among these families, those with non-truncating PKD1 variants and AV had a lower mean age of ESKF than families without additional variants (46 ± 10.1 vs. 52.35 ± 11.6; p = 0.041). The mean age of ESKF was not different between families with truncating PKD1 and PKD2 variants based on AV. 47.8 ± 8.4 vs. 47.3 ± 9.2 and 61.3 ± 3.5 vs. 67.3 ± 11.6, respectively, in a multimatrix Cox mixed-effects model (adjusted for sex, early-onset of hypertension, early-onset urological events, and primary ADPKD variants), we identified an independent effect of the additional variants on familial disease progression [multivariate shared frailty model p = 0.0015].

Conclusions: Our findings suggest that familial variability in ADPKD may be explained by co-inheritance of additional damaging variants, particularly in families with PKD1 non-truncating variants.

SA-P0749 ADPKD Comorbid Conditions at a PKD-Focused Center Allen Chao, Ying Gao, Diana Etwaru, Meyecon Park. University of California San Francisco, San Francisco, CA.

Background: We are a center providing multidisciplinary care to patients with autosomal dominant polycystic kidney disease (ADPKD). We sought to evaluate the prevalence of common co-morbid conditions in our patient population.

Methods: We used the Epic System’s electronic medical record (EMR) at our institution to perform a search for clinical data on patients with ADPKD seen in our health system. We used the following ICD-10 codes: hypertension (I10, I15.1, N28.89), flank pain (R10.0, G89.29), hematuria (R31.0, R31.1, R31.9, R32.1), pancreatic cysts (D49.0, K66.2, K67.8), abdominal hernia (K45.0, K42.9), brain aneurysm (Q28.3, I17.9, I17.1, I17.4, I17.1, I86.79), nephrolithiasis (N20.0), liver cysts (Q44.6, K76.89), urinary tract infection (UTI, N39.0), liver transplant (Z94.4), and family history of PKD (Z84.1). We performed chart review to validate data on a subset of patients.

Results: 556 unique patients were identified out of a total of 3561 nephrology clinic visits at our center since 2011. The median age was 48 years old [IQR 35-62]. 301 patients (54.1%) were women. A majority of patients identified as White (302, 54.3%), 42 (7.6%) Black, 95 (17.1%) Asian, 62 (11.2%) LatinX, and remainder Other race categories. The mean (SD) systolic blood pressure (SBP) obtained from office visit measures was 133.3±17.8 mmHg and mean (SD) diastolic blood pressure (DBP) was 77.0±11.4 mmHg. The median [IQR] estimated glomerular filtration rate (eGFR) was 60.0 [38.5, 93.0] ml/min/1.73 m². Median [IQR] urine albumin to creatinine ratio was 19.5 [8.6, 97.9] mg/g. 63 (11%) patients had received a kidney transplant. Co-morbidities are shown in the Figure. We found that brain aneurysm was inaccurately coded due to automatic generation of a diagnosis of cerebral aneurysm when ordering magnetic resonance angiography (MRA) at our center; only 22 out of 74 patients with screening had a true positive brain aneurysm after chart review.

Conclusions: EMR data can identify ADPKD patients for both coordinated care and research purposes. Further efforts to quality control true positive cerebral aneurysm coding at our center are needed.


Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with a variety of extrarenal manifestations. Previous studies reported a prevalence of pericardial effusion (PE) in ADPKD of up to 35% in U.S. cohorts. Our study is the first to evaluate systematically the prevalence and determinants of PE in a non-U.S. ADPKD cohort.

Methods: Clinically stable ADPKD patients from a specialized outpatient clinic were reviewed retrospectively. Magnetic resonance imaging and computed tomography scans were investigated regarding the presence of PE (≥4mm). Imaging findings were linked to clinical characteristics.

Results: 268 out of 286 ADPKD patients had imaging suitable for evaluation of PE. We detected PE with a mean size of 6.8±3.1mm in 17 patients (8.2%). The prevalence of autoimmune diseases was higher in patients with PE (11.8% versus 2.1%, p=0.022). Overall, we observed a clear female preponderance with a prevalence of PE of 7.8% in females (5.8% in male patients). PE dimension was generally larger in patients with known PE etiology other than ADPKD. Presence and size of PE were not associated with signs of rapidly progressive disease, ADPKD genotype, patient age, body mass index, medications, and other parameters. Exploratory investigation of individual characteristics of patients with PE by regression tree analysis suggested renal functional impairment, sex, and proteinuria as candidate variables.

Conclusions: The prevalence of PE in our cohort was up to four times lower than previously reported and showed a clear female preponderance. The low prevalence of PE compared to recent U.S. data may point to an unknown environmental factor as a cause of PE in ADPKD. Furthermore, a PE size >10mm deserves further attention, as they may have additional non-ADPKD related pathologies.

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

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SA-P0751
Polygenic Effects on the Risks of Intracranial Aneurysms Among Patients with ADPKD
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Background: Patients with autosomal dominant polycystic kidney disease ADPKD are at an increased risk of intracranial aneurysms (IA). Although there is an ongoing debate on who to screen, current strategies do not provide a personalised evaluation on risk of development and progression of IA. In this study, we aimed to identify the association of risk of IA in patients with ADPKD and genome-wide polygenic scores (PGS).

Methods: All adult ADPKD patients enrolled in the Irish Kidney Gene Project who underwent cerebral imaging screening for IA were included. Using previously published array SNP genotyping data, we created PGS for six traits (hypertension (HTN), albuminuria, total kidney volume (KV), intracranial aneurysm (IA), and stroke, and glomerular filtration rate (GFR)). Using PRSice2 software, PGS were calculated, and each trait was quantified categorically into three groups (high PGS >70%, average PGS 31%–70%, and low PGS <30%). To identify potential IA-specific risk factors, the polygenic effects of each trait were compared between patients with and without IA using logistic regression.

Results: A total 226 participants (mean age 57.1 ± 14.4 years, 59.7% female) were assessed for IA-specific genetic risk stratification. 213 (88%) patients had hypertension, and 140 patients progressed to kidney failure at mean age 49.4 ± 10.4 years. Family history of IA was confirmed in 75 (33.1%) patients. Forty-seven (20.8%) patients had intracranial aneurysms, with 31.9% having multiple IA. Compared to the average (31%–70%) PGS distribution for each trait, the distribution of high or low PGS did not have a differential impact on the risk of IA development in patients with ADPKD.

Conclusions: Our current method did not identify a significant polygenic effect for the risk of IA in ADPKD patients, possibly due to the small sample size. To test this hypothesis, a larger study would be needed.

SA-P0752
Prevalence and Characteristics of Intracranial Aneurysms and Cerebral Hemorrhage in Patients with Autosomal Dominant Polycystic Kidney Disease in the Japanese Nationwide Database
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Background: Selective screening for cerebral aneurysms in patients with autosomal dominant polycystic kidney disease (ADPKD) is recommended worldwide. In this study, we analyzed data from a cohort of Japanese patients with ADPKD, for which universal screening is recommended. We describe the prevalence and characteristics of intracranial aneurysms and cerebral hemorrhage in patients with ADPKD.

Methods: We examined the nationwide registry data of 4447 patients with ADPKD who held a new certificate of medical subsidy from the Japanese Ministry of Health, Labor, and Welfare from 2015 to 2017. We investigated the screening rates and risk factors for intracranial aneurysms, and prevalence of intracranial aneurysms and intracranial hemorrhage in patients with ADPKD. To analyze the diagnostic rate of intracranial aneurysms, we also compared the prevalence of intracranial aneurysms between patients who received MRI and those who did not.

Results: Overall, 693 patients (15.6%) had intracranial aneurysms, and 256 (5.8%) had intracranial hemorrhage. The MRI screening rate for intracranial aneurysms in patients with intractable diseases was 78.2%. The prevalence of intracranial aneurysms in patients who underwent MRI increased to 19.2% (odds ratio [OR] = 9.33) compared with that in patients who did not (2.5%). The prevalence of intracranial aneurysms in MRI-screened patients was 22.6% in patients aged ≥ 50 years, 19.4% in patients with hypertension, and 21.5% in female patients. Hypertension (OR = 1.46, P = 0.002), age ≥ 50 years (OR = 1.39, P < 0.001), female sex (OR = 1.52, P < 0.001), and CKD stages 4–5 (OR = 1.29, P = 0.005) were risk factors associated with intracranial aneurysms. Female sex was found to interact with age and was not a risk factor for intracranial aneurysms in patients under 50 years of age but was a risk factor for intracranial aneurysms in those over 50 years of age (P < 0.05 for the interaction).

Conclusions: Screening with MRI improved the diagnostic rate of intracranial aneurysms in patients with ADPKD, which is particularly important for attributes at risk for intracranial aneurysms such as patients aged ≥ 50 years, with hypertension, female sex, and CKD stages 4–5.

SA-P0753
Targeted Genetic Testing with Broad Panel Informs Secondary Genetic Factors in Polycystic Kidney Disease
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Background: Currently, a major obstacle in autosomal dominant polycystic kidney disease (ADPKD) research is the low number of African American (AA) patients in clinical studies and lack of studies evaluating a potential interaction of APOL1-related nephropathy with ADPKD. In this pilot study, we aimed to identify the causal and secondary variants in a cohort including AA patients.

Methods: Genetic testing was performed using a commercially available next-generation sequencing-based 382 gene kidney disease panel. Pathogenic (P), likely pathogenic (LP) variants and variant of uncertain significance (VUS) were reported. Demographic data and urine protein creatinine ratio (UPCR) were obtained from electronic medical reports.

Results: Genetic testing was performed for 13 ADPKD patients (9 men and 4 women, mean age 56±10 yrs, Table 1). Five individuals were found to have heterozygous PKD1 mutations (2 with P variants, 1 with LP variant, 2 VUSs). Two individuals were found to be heterozygous for a PKD2 P variant. Six individuals had no identified P, LP variants or VUS in PKD1 or PKD2. There were 5 AA patients and all have APOL1 renal risk variants. Mean UPCR of AA patients were significantly higher than European American patients (2.1±5.2 vs 0.57±0.95 g/g, p=0.035). Of these AA patients, one had two APOL1 risk alleles (G1/G2), one with homozygous G1/G1 and 3 had heterozygous APOL1 G0/G1 risk allele.

Conclusions: Genetic testing was performed using a commercially available next-generation sequencing-based 382 gene kidney disease panel. Pathogenic (P), likely pathogenic (LP) variants and variant of uncertain significance (VUS) were reported. Demographic data and urine protein creatinine ratio (UPCR) were obtained from electronic medical reports.

SA-P0754
“Genotype-First” Approach to Analyzing the Diversity and Prevalence of Genes in a Cohort of Cystic Disease Patients
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Background: Cystic kidney diseases are one of the most prevalent forms of renal failure diseases. Variants in PKD1 and PKD2 reportedly comprise 93% of genetic causes of cystic kidney diseases with variants in other genes (i.e. IFT44, GANAB, etc) accounting for a small proportion. As variants in these less common genes lead to milder or atypical presentations, a “phenotype-first” approach to identifying cases with genetic causes of cystic kidney diseases with variants in other genes (i.e. IFT44, GANAB, etc) accounting for a small proportion. As variants in these less common genes lead to milder or atypical presentations, a “phenotype-first” approach to identifying cases with genetic testing with broad panel informs secondary genetic factors in polycystic kidney disease.
variants were identified in PKD1/2, of which 67% were private to a single case. Behind PKD1 (0.96%, n=357), PKD2 (0.47%, n=304) and UPK1B (0.22%, n=171) comprised small but significant proportions of the positive cases. Findings in each of the remaining cystic genes (ALG9, GANAB, SEC63, PRKCSH) had prevalence < 1.0%.

Conclusions: This study, representing the largest real-world experience, provides new insights into the prevalence of cystic disease causing variants using a “genotype-first” approach. While our observation of private mutations in PKD1/2 is consistent with prior reports, we showed that PKD1/2 were etiologically implicated in a smaller proportion of cases than has previously been reported. These new insights into the genotypic profile of cystic disease will have important implications for clinical practice, given the prognosis and implications for management differ greatly between PKD1/2 and the other 22 autosomes. We filtered for frequency (<0.5% in a control cohort of 15440 cancer patients within 100kGP and was found to be 0.35%).

Methods: In a phenotype-first approach, ICD9/10 codes and other diagnoses of kidney cysts have been employed to identify ADPKD and kidney cyst populations in the MCBB. WES data associated with these groups are being screened for likely causative variants. In the genotype-first approach, we are screening for loss-of-function (LoF) and known pathogenic variants in the ADPKD genes in MCBB participants. Examination of clinical records and imaging will determine the cystic disease penetrance of these variants.

Results: Using 15 renal/hepatic cyst related ICD codes, we identified a total of 1,093 individuals in the MCBB (2.08%). Of these, 184 were coded as ADPKD (0.35% in the MCBB), 579 with other cystic kidney phenotypes (1.10%), 294 with a single cyst (0.56%), and 36 with just liver cysts (0.07%). Analysis of the MCBB for patients with positive imaging diagnosis and the ADPKD ICD codes (≥75) were also found with the ADPKD ICD codes. MCBB also contains 50 patients previously diagnosed with kidney cysts; 26 had cystic ICD codes. Utilizing CPT codes, we have found that 1,013 (92.7%) of these patients have available imaging data (MRI, CT, or ultrasound). Manual inspection is underway to verify the phenotypes, and genetic variants from 341 PKD/ciliopathy genes are being retrieved for these patients. LoF and known pathogenic variants in all ADPKD genes are also being identified in the whole MCBB for an additional genotype-first approach.

Conclusions: Population-based analyses can better explain the genetics of kidney cysts and penetrance of ADPKD genes, and the MCBB is ideally suited for this analysis.

Funding: NIDDK Support

SA-PO757

Recessive Variants in NEK1 and NEK8 Are Associated with Cystic Kidney and Kidney Stone Disease

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Background: ~9-20% of chronic kidney disease patients have a Mendelian genetic cause. Mice with bi-allelic deleterious variants in NEK1 and NEK8, encoding Nima-related serine/threonine kinases, develop adult-onset cystic kidney disease. In humans, bi-allelic NEK1 and NEK8 pathogenic variants are associated primarily with severe fetal/neonatal disease with multiple congenital anomalies including kidney malformations (14/16 congenital renal onset). It remains unclear if variants in these genes cause later onset kidney disease.

Methods: Variants in NEK1 (NM_001199397.3) and NEK8 (NM_178170.1) were detected by panel, exome or genome sequencing in ~5,857 families with cystic kidney or kidney stone disease (Boston Children’s Hospital), with renal/urologic disease patients (Genomics England), with suspected hereditary kidney disease (University of Chicago), or with clinical genetic testing identifying bi-allelic NEK1/8 variants (GeneDx, University of Iowa, University Medical Center, Groningen, Netherlands). We identified NEK1/8 variants in 27 families.

Results: Six families (seven individuals) with cystic kidney disease and/or kidney stone disease were identified with rare recessive variants in NEK1 (two) or NEK8 (four). Deleterious variants exhibited a population frequency (gnomAD genome database), 2x deleterious in silico prediction scores (PolyPhen2.0, MutationTaster, SIFT, CADD) and strong amino acid conservation in vertebrate orthologues. All NEK1 variants (p.Ala313Thr; p.Met646ValIleTer35; p.Ser909Cys) and four of five NEK8 variants (p.Tryn116Le; p.Bel700Phe; p.Ser224Cys; p.Arg294His) were novel, while one NEK8 variant p.Tryn116Lee was previously reported. Clinical phenotyping revealed cystic kidney disease (5/7), nephrolithiasis and/or nephrocalcinosis (3/7), nephromegaly (3/7), and chronic kidney disease (3/7). Age of kidney disease diagnosis ranged from age 5-18 years. In contrast, no deleterious bi-allelic variants were observed in exome data from 1,285 non-disease control subjects.

Conclusions: Recessive NEK1 and NEK8 variants were identified in individuals with non-congenital cystic kidney and kidney stone disease, suggesting a novel association between NEK1/8 variants and later-onset kidney disease.

Funding: NIDDK Support

SA-PO758

TMEM67 Allelic and Other Effects Drive Vast Phenotypic Heterogeneity A Wide-Spectrum Approach

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Background: Ciliopathies are genetically and phenotypically heterogeneous inherited diseases, impacting multiple organ systems, including kidneys. Kidney phenotypes include polycystic kidney disease (PKD) and renal cystic dysplasia, and genes associated with integrity/function of primary cilia. TMEM67 variants are found in several ciliopathies, with varying severity, including Meckel (MKS), Joubert syndrome (JBT), and nephronphthisis (NPHP). MKS is the most severe, including perinatal lethality, PKD, CNS defects, CHF, and polydactyly. Whereas NPHP, tubulointerstitial nephritis and cysts, is the mildest. It is currently unclear how TMEM67 variants cause such a diverse range of phenotypes and disease severity.

Methods: To investigate the pathogenesis, penetrance, and pathomechanisms of TMEM67 missense variants (19) across these diseases, we employed in vitro exogenous expression systems and patient derived cells to assess TMEM67 mutation/transfer capacity of the apical plasma membrane (glycosylation status/western blotting, surface immunolabeling/flow cytometry, and immunofluorescence [IF] imaging) and primary cilia transition zone [TZ; IF], and primary cilium protein composition [IF].

Results: All the MKS-associated TMEM67 missense variants that we assessed, are found in silico to be ≥2 deleterious (7/7), and abolish trafficking of TMEM67 to the cell surface and TZ, (1/1, patient cells). Whereas only a subset in the milder JBTs (7/13) and NPHP (2/5) diseases, are fully penetrant, and incompletely penetrant/mild and apparent neutral alleles are present (~31 – 60%, respectively). Interestingly, many of these variants exhibit hypomorphic or complete loss-of-function enhancing folding conditions, even for the fully penetrant variants found in MKS (~57%). In addition, absence of TMEM67 from the TZ, perturbs trafficking of other ciliary proteins, inversin and ARL13B.

Conclusions: Our preliminary studies assessing 19 TMEM67 variants (MKS, JBTs, and NPHP) have revealed that: 1) allele penetration correlates with disease severity to some degree (TMEM67 maturation/trafficking), 2) perturbed TMEM67 maturation/trafficking

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Multiple Unilateral Subcapsular Cortical Hemorrhagic (MUCH) Cystic Disease of the Kidney: First Case in Brazil of a Possible New Clinical Entity of Unknown Etiology

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Introduction: The occurrence of MUCH Cystic Disease of the Kidney was described in 14 patients from the USA, France, Canada and Japan by Yoshida et al. in 2019. We describe the first similar case in Brazil.

Case Description: A 36-year-old hypertensive Brazilian man was referred to our Nephrology Clinic due to nephrotic syndrome (NS) along with acute kidney injury requiring dialysis. An extensive investigation of systemic diseases associated with NS (viral serologies, syphilis, autoimmune diseases and neoplasms) was negative. Abdominal MRI showed multiple subcapsular cortical hemorrhagic cysts in the left kidney with normal right kidney. The cysts measured <1 cm on average, the biggest one 2 cm. The signal was hypointense on T1 and hyperintense on T2-weighted MRI suggesting hemorrhagic content. Biopsy of the right kidney revealed focal segmental glomerulosclerosis (FSGS), tip lesion variation, added to acute tubular necrosis in recovery phase. Complete remission of NS and recovery of renal function was achieved after 8 weeks of immunosuppressive treatment.

Discussion: Yoshida et al described 14 cases with distinctive renal image findings, similar to the presented. No patients had positive family history of kidney disease. 6 of them underwent genetic evaluation and results were negative for renal cystic disease. The characteristic of multiple, subcapsular, subacute hemorrhagic cysts suggest a different etiology from that of the classic APKD/1, ARKD or medullary cystic kidney disease. Whole genome sequencing is currently being performed. None of the patients previously described had NS nor FSGS, suggesting a non-causal association. These clinical and radiological findings might be features of a new non-inherited renal cystic disease.

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

Underline represents presenting author.

SA-P0759

Glomerulocystic Kidney Disease with Concurrent Thin Basement Membrane Disease in an Adult Male

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Introduction: Glomerulocystic kidney (GCK) is a rare condition that presents as progressive renal insufficiency and is typically found in pediatric patients with only a few cases described in adults. GCK is defined by the dilation of Bowman space to 2-3 times normal size and more than 5% of glomeruli are involved. Patients with GCK have rapid development of renal insufficiency in less than 1 year and most progress to ESRD. Most cases of GCK have been reported; however, GCK with concurrent TBMD has an even rarer occurrence.

Case Description: A 30-year-old Asian male patient with history of bilateral glaucoma and gout with no family history of renal disease was admitted for evaluation of deteriorating renal function and renal insufficiency. Foley catheter was placed with 900 ml of yellow urine suggesting urinary obstruction. Physical exam reveals no flank tenderness. Renal ultrasound showed increased echogenicity of the kidneys, without hydroureter. No renal stones, peripheric stranding, hydronephrosis, or cysts in organs were noted on CT. The patient underwent a renal biopsy with preliminary findings consistent with obstructive nephropathy. Patient’s renal function did not improve with foley insertion. GN serology was unremarkable. UA with 4-10/HPF RBC, 2+ Hb and 1+ protein. Biopsy was reviewed again with renal pathologist, and the findings were consistent with GCKD with concurrent thin basement membrane and chronic tubulointerstitial disease. The patient was started on hemodialysis and referred to genetics clinic. A pathogenic variant was detected in the COLA1 gene and heterozygous pathogenic variants in the ECHSl1 & ITPA genes.

Discussion: To our knowledge, this is the first case of GCK with concurrent TBMD with pathogenic variants of the COLA1, ECHSl1 and ITPA genes. A literature search has identified 5 main types of GCK: GCK in PKD, hereditary, syndromic, obstructive, and unclassified. The observed association between GCKD and TBMD suggests a potential shared etiology or prenatal development pathway. Further research is needed to understand the genetic basis and clinical implications of these rare conditions.

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

Underline represents presenting author.
and sporadic. Our case is most consistent with hereditary variant of GCKD. This has been reported in one case study by Hashimoto et al. in which no pathogenic mutations in genes had been identified. A pathogenic COL4A1 gene can lead to hereditary angiopathy with nephropathy, aneurysms, and associated with renal cystic lesions and basement membrane involvement as seen in our patient. GCKD with concurrent TBMD can present in adulthood. This case report highlights this rare presentation of GCKD.

SA-PO763

PAGE Phenomenon in a Crossed Fused Renal Ectopia: A Rare Phenomenon in a Rare Anomaly

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Introduction: PAGE phenomenon is rare. It occurs due to an external compression of the renal parenchyma, usually by subcapsular hematoma. Crossed fused renal ectopia (CFRE) is another rare finding. We present an unusual case of a young female with CFRE complicated by PAGE kidney due to pheochromocytoma.

Case Description: A 28 yo F with CFRE presented with Rt flank pain for 3 days. Pain was severe, radiating to the back, associated with nausea. She denied vomiting and headache. In the ED, she was found to have hypertensive urgency, BP 202/117, HR 103 bpm. PE was significant for RLQ tenderness with no rebound or rigidity. Blood work showed Hgb of 11.3 g/dL, CMP, including BUN and Cr were wnl. US of the abdomen showed diffuse echogenic appearance of the RI kidney with scattered cysts. CT Urogram showed large Rt retroperitoneal and subcapsular hematoma and a heterogenous right suprarenal mass. She was admitted to the ICU and was treated with Nicardipine drip. Urine catecholamines were significantly elevated. Patient was stabilized and was transferred to urologic oncology surgeon for intervention.

Discussion: PAGE kidney is rare and is commonly traumatic or iatrogenic. However, it can be caused by an adrenal mass. It carries high morbidity especially in patients with solitary kidney and CFRE. Urgent intervention is warranted to salvage the kidney.

SA-PO764

Case Report: Mosaic TSC2/PKD1 Contiguous Gene Deletion Syndrome

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Introduction: A rare overlap of tuberous sclerosis complex (TSC) and autosomal dominant polycystic kidney disease (ADPKD) can occur when large deletions impact the adjacent TSC2 and PKD1 genes, leading to TSC2/PKD1 contiguous gene deletion syndrome. We present a case of TSC2-PKD1 contiguous gene deletion syndrome with somatic mosaicism where initial genetic testing did not identify a pathogenic variant.

Case Description: A 21-year-old female patient was referred to the McMaster Kidney Genetics Clinic with clinical features consistent with TSC, including childhood epilepsy, multiple bilateral brain tubers, angiofibromas, ash leaf lesions, and bilateral kidney cysts. There was no family history of TSC or PKD. In childhood, she was diagnosed with bilateral renal angiomyolipomas (AMLs) on ultrasound. Her most recent creatinine was 0.75 mg/dL with eGFR of 117 ml/ min/1.73m². Magnetic resonance imaging of the kidneys at age 18 revealed numerous bilateral kidney cysts including complex heterogenous cysts in an atypical lopsided distribution (Mayo class 2) but no evidence of fat containing AML. Clinical genetic testing with capillary sequencing and multiplex ligation-dependent probe amplification (MLPA) for PKD1, PKD2, TSC1, and TSC2 did not identify a responsible pathogenic variant. A follow up cystic kidney disease gene panel was arranged which identified a deletion spanning exons 15-46 of PKD1 and exons 32-42 of TSC2 predicted to be in 35% of the patient’s circulating white blood cells, suggesting somatic mosaicism and a diagnosis of TSC2-PKD1 contiguous gene deletion syndrome.

Discussion: Through unexpectedly low read depths, next generation sequencing gene panels can identify deletions. However, detection of somatic mosaicism can be challenging as the variant allele frequency can be above the expected 50% for a heterozygous deletion. Patients with somatic variants may present atypically with more subtle phenotypic features than patients with classical pathogenic variants. Patients with TSC can have small kidney cysts, though their phenotype should be quite clinically distinct from ADPKD. Our case demonstrates an example of mosaic TSC2-PKD1 contiguous gene deletion syndrome and the improved sensitivity for somatic genetic variants with gene panel sequencing over traditional capillary sequencing and MLPA.
SA-PO765

Tolvaptan Use in Patients with Autosomal Dominant Polycystic Kidney Disease and Gilbert Syndrome

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Introduction: Jnacr therapy is contraindicated in patients with elevated liver enzymes. Gilbert’s syndrome, one of the most common genetic disorder, is characterised by mild fluctuating unconjugated hyperbilirubinemia. A search of the available medical literature did not identify any studies or information that evaluated the use of tolvaptan in patients with ADPKD and Gilbert’s syndrome. We present two cases with ADPKD and Gilbert’s syndrome, in whom treatment with tolvaptan was initiated.

Case Description: Case 1 was a 31-year-old male and Case 2 was a 34-year-old female sibling. They have rapidly progressive ADPKD and a family history of Gilbert’s syndrome. Blood testing for systemic markers of liver function were performed prior to and after initiation of Jinarc, continuing monthly thereafter. Their renal function was normal. Both patients received Jinarc 45 mg in the morning and 15 mg in the afternoon, and the dose was not increased during first 4 months of follow-up. A sustained urine osmolality (Uosm) of 280 mOsm/kg was achieved in both patients. Case 1 had Uosm between 65 and 138 mOsm/kg and Case 2 between 43 and 287 mOsm/kg. Case 1 had mild hyperbilirubinemia prior to tolvaptan initiation but no significant additional elevation of bilirubin was observed during treatment. Case 2 had an increase in bilirubin immediately after starting treatment but it remained < 2 ULN thereafter. The table presents the bilirubin values in both patients before and during tolvaptan therapy. All other parameters of potential hepatocellular injury, including hepatic transaminases, were within the normal range in the first 4 months.

Discussion: In two young adult siblings with rapidly progressive ADPKD and a benign Gilbert’s syndrome we cautiously started treatment with tolvaptan. We observed an isolated elevated serum bilirubin in the absence of the other criteria for hepatic injury. We feel that patients with Gilbert’s syndrome can also be considered for tolvaptan therapy. Still, safety studies in patients with impaired bilirubin glucuronidation are warranted.

Total and direct bilirubin presented for cases 1 and 2.

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<th>Case 1</th>
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<td>Total bilirubin, mg/dL</td>
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<td>Direct bilirubin, mg/dL</td>
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SA-PO766

Phenotypic Variabilities of Neonatal Autosomal Recessive Polycystic Kidney Disease

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Introduction: Autosomal Recessive Polycystic Kidney Disease (ARPKD) is caused by a mutation in the PKHD1 gene and is an inherited cause of chronic kidney disease in children. The most typical presentations in neonates are a history of oligohydramnios, massively enlarged kidneys, and the Potter sequence with pulmonary hypoplasia that can lead to respiratory insufficiency and perinatal death. Other renal manifestations include congenital hepatic fibrosis, cholangiostasis, and portal hypertension. A subset of ARPKD patients can have a predominant liver phenotype.

Case Description: We report the variable clinical manifestations of three cases of neonatal ARPKD. Case 1 is the male neonate with enlarged ventricles in the brain, atypical extra-renal manifestation, and confirmed diagnosis by genetic testing. Although he did not require renal replacement therapy in the neonatal period, he developed severe hypertension at 3 months. Case 2 was born with a history of oligohydramnios and required ventilator support for 3 days. His neonatal course was unremarkable and developed hypertension at 8 weeks of life. He received a renal transplant at 4 years of age. Case 3 is a full-term neonate who developed pulmonary hypoplasia, was on a high-frequency ventilator at birth, and required initiation of dialysis and nephrectomies in the neonatal period.

Discussion: It should be aware of variable presentations of ARPKD cases and some may require aggressive management of nephrectomies and dialysis in the neonatal period. Due to its multi-system effects, a multidisciplinary team of nephrologists, gastroenterologists, surgeons, and neonatologists help families of patients make informed treatment decisions.

SA-PO767

Discovery of a Novel Candidate Gene Implicated in X-Linked Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by typical imaging findings and a family history and ~90% of cases have a genetic explanation. In contrast, the underlying genetic basis of adult-onset sporadic cystic kidney disease remains incompletely elucidated, with ~30% of patients in our cohort remaining unexplained by variants in established cyst-related genes, leading to inconclusive diagnoses. These individuals were presumed to harbor potentially unreported mutations in novel candidate genes associated with PKD.

Methods: An NGS panel screening was conducted to analyze 69 known genes associated with renal cysts in adult patients with no familial history of the condition. Whole-genome sequencing was performed on 47 unrelated individuals who did not exhibit any pathogenic candidate variants, aiming to identify novel genes implicated in renal cyst formation.

Results: Candidate gene A, located on the X chromosome, exhibited missense variants found in three male patients aged 74 (PT570), 80 (PT698), and 58 (PT1216) years, respectively. These patients demonstrated renal function impairment with estimated glomerular filtration rates (eGFR) of 33.5, 21.8, and 20.2 mL/min/1.73m², respectively. Hypertension was a shared characteristic among all patients, while no complications associated with hepatic cysts were observed. The protein product of gene A was found to be expressed in the primary cilia of human renal tubules. Kidneys from 12-month-old male knockout mice lacking gene A exhibited vacuolation of tubular cells and tubular dilation, providing evidence that gene A is a novel causative gene involved in cyst formation.

Conclusions: Gene A is a newly discovered gene associated with PKD, demonstrating X-linked inheritance, which is uncommon in inherited cases of PKD. Further accumulation of cases is warranted for a more comprehensive understanding.

Funding: Government Support - Non-U.S.
SA-PO768
Determine the Pathogenic Mechanism Underlying Infantile ADPKD Caused by a Novel Monoallelic NEK8 Mutation
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Background: ADPKD is mainly caused by mutations in PKD1 and PKD2 that encode polycystins, PC1 and PC2, respectively. Current evidence suggests that the dosage of PCs in primary cilia controls the severity and progression of ADPKD. But the molecular mechanisms mediating the trafficking of PCs into primary cilia remain unclear. NEK8 is the only known protein kinase residing in primary cilia, in the Inversin compartment, and is associated with a syndromic ciliopathy when both alleles are mutated. Interestingly, a novel monoallelic NEK8 mutation (p.Arg45Trp) was recently identified in 3 Mayo families with early onset PKD without extrarenal manifestations. This finding suggests that the mutation selectively causes PKD, and thus represents a unique tool for investigating the molecular mechanisms specifically regulating renal cystogenesis.

Methods: Mutagenesis Transfection CRISPR/Cas9 Immunostaining Kinase assay

Results: To understand how p.Arg45Trp (R45W) affects NEK8, we inactivated Nek8 in IMCD3 cells, and then re-expressed wild type (WT) or R45W variant NEK8. Primary cilia in Nek8−/− cells were truncated but were rescued equally well by NEK8-WT and NEK8-R45W, which show comparable expression and stability. The level of GPR161 in cilia remained the same with or without Nek8. Yet, ANK56 as a binding partner of NEK8, lost its localization in Nek8−/− cilia, which was fully recovered by reexpressing NEK8-WT or R45W. These data suggest that the overall structure of primary cilia is not affected by the R45W mutation. However, we observed that PC2 levels significantly decreased in Nek8−/− null cilia; a defect rescued by NEK8-WT but not R45W, although the total protein level of PC2 appeared comparable. Our results indicate that the R45W mutation specifically impairs PC2 in cilia. Moreover, we showed that the autophosphorylation of NEK8-R45W was significantly decreased compared to NEK8-WT, implying a partial loss of kinase activity. This suggests that adequate NEK8 kinase activity is necessary for supporting the normal level of PC2 in cilia.

Conclusions: We found that a novel ADPKD variant of NEK8 (R45W) selectively repressed the ciliary level of PC2. In future, we will seek NEK8 partners in cilia that are specifically affected by this single-point mutation in NEK8. Our work will provide critical information to the understanding of PC trafficking in cilia and ADPKD etiology.

Funding: Other U.S. Government Support

SA-PO769
Molecular Testing in a Clinical Laboratory Cohort Reveals Significantly Increased Incidence of PKD1 Truncating Variants in ADPKD Patients with Pediatric-Onset vs. Adult Presentation
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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a multisytem disorder characterized by multiple kidney cysts and extrarenal features. PKD1 and PKD2 (likely) pathogenic (L/PATH) variants cause 95% of ADPKD. Although the majority of ADPKD cases present in adulthood, approximately 1-2% have onset before age 15. While severe presentation is usually associated with truncating PKD1 variants in adults, the variant spectrum in pediatric ADPKD cases is not well-established.

Methods: We reported on 235 individuals with typical, mild or atypical PKD with prenatal onset. Diagnosis cases primarily had L/PATH variants in PKD1 (69%) or PKD2 (16%), but also included HNF1B (2% adult, 16% pediatric), b-allelic PKD1D1 (1% adult, 7% pediatric) and GANAB (2% adult, 2% pediatric). Truncating PKD1 L/PATH variants were significantly enriched in both our pediatric (p-value<0.001) and adult (p-value=0.001) sub-cohorts. A statistically significant association was found between the age groups and variant spectrum in pediatric and adult cases in a retrospective study of 1582 cases referred for next generation sequencing multi-gene panel clinical testing for Cystic Kidney Disease (CKD). Testing included sequence and copy number analysis of PKD1, PKD2, PKD1D1 and other genes associated with renal cysts.

Results: The pediatric sub-cohort accounted for nearly one-third of cases tested. Our analysis revealed a diagnostic rate of 42% for the entire cohort and involved 13 genes (40% within adult and 46% within pediatric sub-cohorts – including ADPKD patients with prenatal onset). Diagnostic cases primarily had L/PATH variants in PKD1 (69%) or PKD2 (16%), but also included HNF1B (2% adult and 16% pediatric), b-allelic PKD1D1 (1% adult, 7% pediatric) and GANAB (2% adult, 2% pediatric). Truncating PKD1 L/PATH variants were significantly enriched in both our pediatric (p-value<0.001) and adult (p-value=0.001) sub-cohorts. A statistically significant association was found between the age groups and variant spectrum in pediatric and adult cases within the general population for cosegregation with disease and evidence of genetic variants. Family history (FH) was used to determine genetic predisposition.

Results: Forty patients with PKD were identified between December 2020 and December 2022. Twenty Seven were positive for a PKD1/PKD2 mutation, 7 of which had a variant of uncertain significance (VUS) of PKD1/PKD2. Seventeen of these 27 had a positive FH of PKD, while 8 were negative and 1 unknown. Three patients did not have a PKD1/PKD2 mutation, but tested positive for mutations COLA1A4, COLA4A and TCTC21B. Lastly, there were 3 patients with negative results, one of which is PCDH10.

Conclusions: Eighty Five percent of the patients in our cohort have a PKD1/PKD2 mutation or PKD1/PKD2 VUS, with some VUSs becoming pathogenic at a later time. However, 30% of these patients do not have a FH. The genetic study thus confirmed the diagnosis and helped predict their prognosis. The existence of heterogeneous PKD1 together with C4D4A mutation may be the culprit of the kidney cysts in patients with Alport syndrome. The patients with true negative results remain unclear, but the sequence data will contribute to the nationwide database and help identify the true variants. Our experience advocates that the benefit of genetic testing is imperative to detecting and identifying true causative variants and that this can provide prognostic information for patients with ADPKD.

SA-PO771
Elucidating the Genetics of Unresolved PKD in a Large Unselected Cohort

Background: We reported on 255 individuals with typical, mild or atypical PKD from an unselected cohort of 174,172 individuals with exome sequencing. Variants in 11 known cystic genes (PKD1, PKD2, PKC1, PKD2C8, A1CSQ, DAB1, GANAB, HNP1, HNF14, PKD1, PRKCS, and SEC63) were identified in 76.5% of these individuals, leaving 55 with no candidate causal variant.

Methods: The 55 individuals with unresolved genetics consisted of 37 with typical, 6 with mild and 12 atypical PKD. We expanded the analysis to include 121 cystic genes identified by the Kidney Cystic and Ciliopathy Disorders Gene Curation Expert Panel in an attempt to identify candidate causal variants. Exome sequencing combined with EHR was leveraged to identify rare variants from these genes in these individuals. Variants were evaluated in the general population for cosegregation with disease and evidence of PKD in carriers.

Results: 47/55 individuals had at least one rare variant (MAF<0.001) including 13 with protein truncating variants in the 121 genes. Two unrelated individuals, one with mild and one with atypical PKD had the same BCCI frameshift variant: His141TrpTer16 (10:58766953:TTC). Another with typical PKD is a carrier of two missense variants in BBS2. This individual has several unaffected 1st degree relatives who are carriers of one the variants of BBS2. Additional efforts are underway to determine other candidate variants as well as their penetrance.

Conclusions: Genetic variants in genes other than PKD1 and PKD2 may play a significant role especially in atypical and mild PKD. Exome sequencing in an unselected cohort is a powerful approach to demonstrate the phenotypic and genetic variability of PKD and in determining penetrance.
Background: ADPKD is genetically heterogeneous and primarily due to mutations in PKD1 or PKD2. Complex inheritance with biallelic PKD1 or digenic PKD1 and PKD2 mutations (s.a. complex genetic) has been reported in a small number of families. Here, we report the prevalence and genotype-phenotype correlation of patients with complex genetic from the extended Toronto Genetic Epidemiology Study of PKD.

Methods: All study patients underwent PKD1 and PKD2 mutation screening by targeted Next-Generation sequencing (NGS) and multiplex ligation-dependent probe amplification in mutation-negative cases. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF ≤1%) deleterious variants. Phenotypic data were collected and compared to those of patients with PKD1 or PKD2 mutations.

Results: We found genetic complexity in 47/993 (4.7%) of families with an ADPKD diagnosis. Preliminary results from 44 of 53 patients in these families suggest that patients with a protein-truncating (PT) and a non-truncating (NT) PKD1 mutation have more severe disease (by eGFR and TKV; see figure) than patients with two PT-PKD1 mutations in cis, two NT-PKD1 mutations in trans, or PKD1 and PKD2 digenic mutations.

Conclusions: In this large cohort study from a single geographic region, we found that patients with genetic complexity in ~5% of families with a known PKD1 or PKD2 mutation. Delineating complex genetic by NGS has important implications for genetic counseling and may improve clinical prognostication in ADPKD.

Funding: Government Support - Non-U.S.

SA-PO773

ADPKD and Collagen Genes (COL4A3, COL4A4, COL4A5)

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Background: The familial hematuria diseases are a heterogeneous group of monogenic conditions caused by mutations in one of the collagen IV genes: COL4A3/A4/A5 that are expressed in the glomerular basement membranes (GBM) and are responsible for the most frequent forms of microscopic hematuria (MH), Alport syndrome, and thin basement membrane nephropathy (TBMN). Data suggest that about 1% of the world population may have MH and TBM, a frequency leads to occasional superimposition of TBMN with other glomerulopathies. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a major genetic disorder affecting up to 12.5 million individuals worldwide and it is the fourth most common global cause for renal replacement therapy. Two are the principle causative genes: PKD1 and PKD2. The aim of the study was to describe a cohort of clinically ADPKD patients (pts) studying collagen IV genes COL4A3/A4/A5.

Methods: We performed NGS with Sophia Genetic “Nephropathies Solution” Panel on clinically ADPKD pts. This panel includes 44 genes (target region 105.8kb) in different types of nephropathies. We considered variants that are categorized as VOUS, likely pathogenic or pathogenic (Class 3, 4 or 5 of ACMG) in COL4A3, COL4A4 and COL4A5 genes.

Results: We found 13 (6.3%) clinically potentially interesting (Class 3, 4 or 5 of ACMG) variants in collagen genes in 250 consecutive clinically ADPKD pts. We found 2 pts PKD1, PKD2, PKHD1 negative: 1pt variations carrier COL4A4 NM_000092.5: c.200G>T (p.Glu67fs+1G) and e.2756A>G (p.Glu919fs). 1 pt carrier COL4A3 NM_000915.1: c.609+3_609+6del and COL4A5 NM_000495: c.169G>A (p.Gly57Arg).

Conclusion: The study outlines the importance to consider also collagen genes even if we have a clear clinical manifestation of ADPKD. Analysis of genes involved in these 2 pathologies could lead to better understand the phenotype-genotype correlation at least in patients with both conditions.

Funding: Government Support - Non-U.S.
SA-PO775

Monoleaonic IFT140 Pathogenic Variants in Adult Polycystic Kidney Disease Patients Without Family History
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Background: IFT140 encodes a subunit of intracellular transport complex A, which is involved in retrograde ciliary transport. IFT140 is known as a causative gene of Meiner-Sardinio syndrome, an autosomal recessive ciliopathy that presents with short-costothoracic dysplasia. Recently, heterozygous variants in IFT140 were reported to cause autosomal dominant polycystic kidney disease (ADPKD). We investigated the presence of IFT140 pathogenic variants in patients with polycystic kidney disease without family history.

Methods: We performed a comprehensive genetic analysis in 151 adult polycystic kidney disease patients without family history. Targeted genes were 69-92 genes including IFT140 responsible for 6 hereditary cystic kidney diseases (ADPKD, autosomal recessive polycystic kidney disease, nephronophthisis, nephronophthisis-related ciliopathies, autosomal dominant tubular interstitial kidney disease, and autosomal dominant polycystic liver disease).

Results: Through this analysis, 50 patients (33%) had pathogenic variants in PKD1 or PKD2 genes. Additionally, 4 patients had pathogenic variants in other genes (HNF1B, n = 2; OFD1, n = 1; PKHD1, n = 1). In 6 of 97 patients (6%) who did not have any apparent pathogenic variant in known causative genes, heterozygous pathogenic variants were detected in IFT140 gene (frameshift variant, n = 3; nonsense variant, n = 2; splicing variant, n = 1). None of the patients with heterozygous pathogenic variants in IFT140 had liver cysts. Additionally, although total kidney volume were large (median, 1357 ml), renal cysts were asymmetric and atypical. Furthermore, the patients with IFT140 pathogenic variants were older (median, 59.5 years old) and had better renal function (median eGFR, 57.2 ml/min/1.73m^2) at the time of genetic analysis.

Conclusions: IFT140 should be considered as the responsible gene for polycystic kidney disease, even in the patients had no family history.

Funding: Government Support - Non-U.S.

SA-PO776

Identification of Transcripts Critical to Tuberous Sclerosis Complex (TSC)-mTOR Axis Dysregulation in Tuberous Sclerosis Complex Renal Cystic Disease
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Background: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutations in TSC1 or TSC2 genes, and affects over two million individuals worldwide. In the kidney, TSC is associated with the development of cysts and angiomylipomata, leading to renal failure. The cyst epithelia in various models of Tsc knockout mice (e.g., principal cell specific KO of Tsc1 or Tsc2, pericyte specific KO of Tsc1, and heterozygote Tsc2−/−), as well humans with TSC is overwhelmingly comprised of A-intercalated cells (ICs). Deletion of Foxi1, the transcription factor critical to the acid secretion and IC viability, completely abrogated the cystogenesis in Tsc1 KO mice.

Methods: RNA-seq analyses comparing the renal transcriptome of Wildtype (WT), Tsc1 KO, Tsc1/Foxi1 dKO, and Foxi1 KO mice were used to identify the differentially expressed transcripts (DET) that were activated in Tsc1 KO (exhibiting many cysts) and downregulated in Tsc1/Foxi1 dKO (that had no cysts) mice. The expression levels of mRNAs and proteins of interest were confirmed by northern and western blot analysis, Kit immunofluorescence displayed abundant labeling of both proteins on the basolateral membrane of ICs in the cysts in Tsc1 KO mice. KEGG enrichment analysis and expression studies showed the activation labeling of both proteins on the basolateral membrane of ICs in the cysts in Tsc1 KO mice. KEGG enrichment analysis and expression studies showed the activation of MAPK and PI3K/AKT pathways, which are critical in AVPR1 and c-KIT signal transduction. Further, Tsc2 in ICs lining the cysts was shown to be phospo-inactivated on multiple ERK, AKT and RSK1 target sites.

Conclusions: The activation of AVPR1a and c-KIT oncogene, in association with enhanced ERK1/2 signaling and TSC inactivation, point to a novel pathway that disrupts the TSC/mTORC1 axis in ICs and leads to unregulated cell growth in TSC cystogenesis.

Funding: Other NIH Support - NIH/NHLBI/T32HL007736, Veterans Affairs Support, Private Foundation Support

SA-PO777

Tuberculosis Sclerosis Complex (TSC) Renal Cyst Extracellular Vesicles (EVs) Have Unique miRNA and Protein Profile
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Background: Over one million people worldwide have tuberous sclerosis complex (TSC), and half exhibit renal cyst disease. There is an unmet clinical need as there are no approved therapies. We identified that TSC renal cystogenesis is a cell non-autonomous process. To address this, we investigated the role of extracellular vesicles (EVs) as a novel mechanism of renal cyst disease to find new therapeutic options. Understanding the mechanism(s) for TSC-associated renal cystogenesis has significant ramifications. Similar to the renal cyst disease-associated renal cell carcinoma seen in von Hippel Lindau disease, TSC-associated renal cyst disease also is associated with renal cell carcinoma in 4-5% of the patient. An in-depth understanding of renal cystogenesis and the abnormal proliferation that leads to renal cell carcinoma will lead to better prevention strategies and therapies.

Methods: After Institutional Review Board approval, we isolated TSC patient derived EVs and performed tunable resistive pulse sensing, electron microscopy, dynamic light scattering and western blot analysis to characterize the EVs. We also performed mass spectrometry for protein analysis, and RNASeq to better understand the miRNA and lncRNA associated with this disease state. For comparison, we used TSC serum derived EVs. For the analysis we used unsupervised clustering with hierarchical clustering and Pearson’s correlation coefficients as well as a principal component analysis.

Results: The EVs from the human cyst fluid showed the expected cup shape morphology. Western blot analyses revealed a signature for small EVs, which also contained aquaporin 2, supporting their origin from principal cells. Sizing by TRPS and DLS revealed the EVs were approximately 140 nm in diameter at a concentration of 10^5 EVs per ml. There was strong agreement among DLS, TRPS, and TEM sizing methods. The protein analysis revealed a significant number of proteins that clearly distinguished the EVs isolated from the cyst from the EVs isolated from plasma. These experiments clearly reveal the the cyst EVs are unique when compared to EVs derived from patients with TSC. Furthermore, there were unique miRNA and lncRNA signatures for the EVs isolated from the cysts.

Conclusions: EVs in TSC patient cyst fluid contain unique protein and RNA signatures that may offer new avenues into the biology of the disease, and more importantly, into possible therapeutic approaches.

Funding: Private Foundation Support

SA-PO778

Characterization of Exosomes Isolated from the Kidneys of Wild-Type (WT) and Tsc1 Knockout (Tsc1 KO) Mice
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Background: TSC is caused by mutations in TSC1 or TSC2 genes. Cysts are a major renal manifestation of TSC and can lead to end stage kidney disease. In human and mouse models of TSC the cyst epithelium is overwhelmingly comprised of genotypically normal A-intercalated cells (AIC). This suggests the presence of signals that alter the phenotype of AIC. EXO: ciliated extracellular vesicles generated by cells and mediate cellular communication, function, and growth. We posit that EXO are important mediators of dysregulated proliferation of AIC lining the cysts in TSC. To this end, we isolated, characterized, and identified the differences in the RNA content of EXO from WT and Tsc1 KO mice.

Methods: EXO from kidney explants were isolated by size exclusion chromatography. The isolated EXO were characterized by western blot analysis, transmission electron microscopy (TEM), and fluorescent nanoparticle tracking analysis (fNTA). EXO RNA was isolated and run through cDNA library preparation methodology for Nanopore sequencing and mapped to the mouse transcriptome.

Results: TEM studies showed that EXO sizes range from 50 to 300nm. The fNTA studies revealed that greater than 70-75% of isolated particles were EXO with size range of 50 to 300nm. The EXO were of similar size and distribution; however, the number of EXO was significantly higher in the preparations from the kidneys of Tsc1 KO mice. Isolated EXO were highly enriched for CD63 and RAB27A markers. RNASeq analysis reveal that 145 transcripts were differentially represented (p<0.05) in the EXO isolated from the kidneys of Tsc1/KO vs. WT mice. These included 24 lncRNAs (4 previously identified), 1 viRNA, 107 mRNAs, and 8 pseudogenes. Enrichment analysis revealed numerous pathways that differed between Tsc1 KO and WT exosomes, with significant fold enrichment found in the mTOR and phospholipase D signaling pathway and those of glycerophospholipid metabolism. The mRNA for LSEC254, a mitochondrial protein that functions in S-adenosylmethionine (SAM) S-adenosylhomocysteine (SAH) exchange, and Lpin2 were substantially enriched in Tsc1 KO mice. 

Conclusions: LPIN2 and SLC25A26 may affect mTOR activation via SAH levels and Lpin2 signaling, respectively, pointing to a potentially novel mechanism in TSC cystogenesis.

Funding: Other NIH Support - NIH/NHLBI/T32HL007736; NIHUL1TR001449, Veterans Affairs Support, Private Foundation Support
Cystic fibrosis (CF) is an autosomal recessive genetic disorder arising from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and leads to impaired ion transport across epithelial cell membranes. While the most affected organs in people with CF (PwCF) are the lungs and digestive system, advancements in clinical care and novel high efficiency CFTR modulator therapy have increased life expectancy for most PwCF, unveiling impacts on other organs, including the kidneys. Adult PwCF have up to 20-fold higher risk of end stage kidney disease. In vitro models suggest that CFTR may regulate renal metabolic pathways and protect from fibrosis, but nothing is known about such role in vivo. We performed single-nuclei (sn) multiomic analysis to elucidate the molecular mechanisms underlying CFTR role in the kidney.

Methods: Kidneys from 7–9 week old male C57BL/6J mice expressing wild-type (WT) CFTR or G542X CFTR (CFTR KO; N=2/group/sex) were formalin-fixed and paraffin-embedded. We performed morphometric analysis of glomerular and tubular structures using PAS staining. Glomerular density was assessed by counting the number of glomeruli using light microscopy (m3/kidney). Cortical area of the kidney was measured using Amira software. Glomerular density was expressed as the number of glomeruli per unit area (glomerul/min3). Lotus tetragonolobus lectin staining of proximal tubules was performed to evaluate presence of the functional glomerulo-tubular junctions (GTJ). Absence of Lotus positive cells in Bowman’s capsule defined the loss of GTJ.

Results: The mean renal cortical area was 31% smaller in KO male, compared to WT male. The corresponding kidney weight was 25% lower in KO male. The mean cortical area was 8% bigger despite 20% lower kidney weight in KO female, compared to WT female. Glomerular density was 40% and 33% higher in KO male and female, compared to WT male and female, respectively. The loss of GTJ connections was higher in the KO groups (49% and 65% in KO males and females, compared to 27% and 40% in the WT counterparts).

Conclusions: Decreased kidney weight, smaller mean cortical area, higher glomerular density, and loss of GTJ connections in KO groups support the critical role of CFTR in the kidney and suggest that CFTR dysfunction may predispose PwCF to CKD. Increased mean cortical volume despite a lower kidney weight and loss of GTJ connections in KO females emphasize that the impact of CFTR absence is modulated by sex-specific factors.

Funding: Other NIH Support - NIH R01HL144539, Private Foundation Support
SA-PO783
Differential Regulation of MYC Expression by PKHD1/Pkd1 in Human and Mouse Kidney: Phenotypic Implications for Recessive Polycystic Kidney Disease
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Background: ARPKD (MIM 263200) is caused by mutations in PKHD1, which encodes FPC. We previously showed that: 1) MYC/Myc is overexpressed in human ARPKD and mouse and contains cyli (cylin) kidneys, but not in several Pkd1 mutants; 2) the FPC C-terminal domain (FPC-CTD) upregulates, while cystin downregulates, the MYC/P-Mp1 promoter; 3) mouse and human FPC-CTD differ in subcellular localization (Yang, 2021). Here we present new data from informatic analyses and FPC-CTD overexpression in human and mouse epithelia.

Methods: Evo-devo mammalian organ database was queried for developmental expression patterns of cystogens. ClustalOmega and WebLogO3 were used to analyze the vertebrate FPC conservation. Immunoblotting and qRT-PCR were used to quantify proteins and mRNA.

Results: PKHD1 mRNA expression peaked before CTSI mRNA in fetal human kidney; in contrast, Ctsi mRNA expression peaked before Pkd1 mRNA in the developing mouse kidney. Developmental expression patterns of MYC/Myc mRNA were similar in human and mouse kidneys, peaking in early fetal development and gradually decreased thereafter. Sequence alignments of 102 vertebrate FPCs revealed higher conservation score of the extracellular (1.9) than the intracellular (1.5) domain. Ctsi mRNA and cystin protein were downregulated by 80% and 70%, respectively, in mIMCD-3 cells stably overexpressing mFPC-CTD. Stable FHC-CTD overexpression in TERT immortalized human renal epithelial (HTERT-IRE) cells overexpressing Pkd1 and eGFP did not alter cystin expression.

Conclusions: Higher expression of Ctsi vs. Pkd1 in the developing mouse kidney and the suppression of MYC expression by cystin could contribute to the low renal MYC expression in Pkd1 mutant mice. In contrast, the relatively lower levels of Ctsi vs. PKHD1 in developing human kidney may preclude a cystin-driven protective effect for renal cystogenesis. In addition, the low cross-species conservation of the FPC-CTD suggests functional differences that may contribute to differing susceptibilities to PKHD1/Pkd1 mutations and the disparate renal phenotypes.

Funding: NIDDK Support, Private Foundation Support

SA-PO784
Spontaneously Occurring Pkd1 Mutation (Pkd1(cyli/cyli)) with Altered Renal mRNA Processing and Hormonally Sensitive Hepato-Biliary Disease
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1Children’s National Hospital, Washington, DC; 2The George Washington University School of Medicine and Health Sciences, Washington, DC; 3The University of Alabama at Birmingham Heersink School of Medicine, Birmingham, AL; 4Children’s Hospital of Philadelphia, Philadelphia, PA.

Background: ARPKD (MIM 263200) is a hereditary hepato-renal fibrocystic disease characterized by renal and biliary epithelial cyst formation. We recently identified a spontaneous Pkd1 mutation that causes liver and kidney cyst formation in the cpk mouse. Further analysis will be performed to understand the mechanism of this mutation.

Funding: NIDDK Support, Private Foundation Support

SA-PO785
Functional TRPV4 Status Sets the Rate of Cytogenesis in Autosomal Recessive Polycystic Kidney Disease (ARPKD) During Variations in Dietary Potassium
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Background: Autosomal Recessive Polycystic Kidney Disease (ARPKD) manifests as cysts in the fluid-filled cysts in the collecting duct. Cystic cells are characterized by the impaired intracellular Ca2+ signaling ([Ca2+]i), elevated rAMP levels to drive augmented proliferation. Mechanosensitive TRPV4 channel plays a dominant role in maintaining [Ca2+]i, homeostasis and flow-sensitive [Ca2+]i signaling in the collecting duct. Systemic TRPV4 stimulation with GSK1016790A impedes cytogenesis in ARPKD models. Previously, we demonstrated that high dietary K+ regimen elevates both activity and expression of renal TRPV4.

Methods: Here, using fluorescence microscopy and systemic measurements, we tested how regulation of renal TRPV4 function by dietary K+ intake modulates the rate of cytogenesis and mechanosensitive [Ca2+]i signaling in cystic cells of PCK453 ARPKD rats.

Results: One month treatment with both high KCI (5% K+) and KB/C (5% K+ with bicarbonate/citrate) diets significantly augmented renal TRPV4 expression in PCK453 rats in comparison to that on the regular diet (0.9% K+). We next explored [Ca2+]i levels in freshly isolated renal cysts upon application of TRPV4 agonist GSK1016790A and high flow. Treatment of ARPKD cysts with KCI significantly increased [Ca2+]i signaling in cystic cells of ARPKD rats. At the systemic level, high KCI diet significantly decreased kidney-to-bodyweight ratio and reduced the cystic area in kidneys of PCK453 rats. High KB/C diet accelerated ARPKD progression and renal injury leading to a marked increase in the cystic area and particularly the number of cystic dilatations in the renal cortex. Of note, application of TRPV4 antagonist GSK2193874 reversed beneficial effects of high KCI diet.

Conclusions: Overall, we demonstrate that TRPV4 channel activity negatively regulates rAMP levels in cystic cells thus attenuating (high activity) or accelerating (low activity) ARPKD progression. Augmenting TRPV4 activity by increased dietary K+ intake may have therapeutic potential in PKD.

Funding: NIDDK Support, Private Foundation Support

SA-PO786
Ultrasound and 3D Imaging Characterisation of a Rat Model of Polycystic Kidney Disease
Maria K. Ougaard, Trine Porsgaard, Frederikke E. Sembach, Louise Thisted, Jacob L. Skytte, Johanna Perens, Michael Christensen, Gubra, Hoersholm, Denmark.

Background: Polycystic kidney disease (PKD) is a congenital fibrosed disorder for which there is no curative treatment. Consequently, PKD is classified as a medical condition with high unmet therapeutic need. Animal models with improved clinical translation potential optimally increases potential efficacy of novel drug candidates for PKD. The polycystic kidney (PKC) rat is an established genetic model of PKD with natural history and renal histologic abnormalities that resemble the human disease. Gubra has established a PKC rat breeding program to enable fast turnaround time of preclinical drug development. We have characterised disease progression in the PKC rat to aid in designing future pharmacological intervention studies.

Methods: Male PCK (PCK/Crl/Pkd1/pck/Crl) and control (CRL:CD(SD)) rats were randomised into study groups based on body weight (10 weeks). At the age of 17 and 25 weeks, rats underwent ultrasound assessment of kidney volume, urine collection for quantification of albuminuria, and plasma sampling for urea and creatinine analysis. At termination, kidneys were collected and total kidney volume, cyst number and volume were analysed using quantitative 3D imaging.

Results: Compared to age-matched control rats, PCK rats displayed marked albuminuria at 25 weeks of age. Plasma urea was progressively increased at both 17 and 25 weeks, while plasma creatinine was only increased at week 25. In vivo ultrasound measurements revealed that total kidney volume progressively increased (25 wks.: 4909 ± 371 mm³) compared to control rats (1784 ± 151 mm³). 3D light sheet imaging enabled whole-kidney counting of cysts and quantification of cyst volume (control: 10.9 ± 3.5 mm³ vs 25 wks.: 413.5 ± 57 mm³) as well as the total kidney volume that correlated to kidney ultrasound results.

Conclusions: The PCK rat displays hallmarks of PKD, characterized by age-dependent progressive increase in biomarkers of kidney injury, kidney hypertrophy and cyst formation. In vivo ultrasound and ex vivo quantitative whole-kidney 3D light sheet imaging is highly instrumental for detailed assessment of progressive kidney disease in the PCK rat. Accordingly, these imaging modalities are instrumental as key endpoints for development of potential therapeutic effects of preclinical drug candidates in the PCK rat model.

Funding: Commercial Support - Gubra
SA-PO787

Prevalence of APOL1 Variants in Persons with Proteinuric CKD

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**Background:** APOL1 variants (G1 or G2) are the genetic cause of progressive, proteinuric nephropathies referred to as APOL1-mediated kidney disease (AMKD). The prevalence of APOL1 variants, which are common in persons of recent African ancestry, is not well known as APOL1 genotyping is not routine in kidney disease care. We report data from a new interim analysis on the prevalence of APOL1 genotypes in proteinuric chronic kidney disease (CKD).

**Methods:** This ongoing global study is enrolling up to 2500 participants of recent African ancestry with FSGS or proteinuric (UPCR >0.5 g/g) nondiabetic kidney disease (NDDK) to determine the percent of participants who carry APOL1 variants, including by genotype category, and identify potential participants for trials evaluating APOL1 therapies. During a single visit, a blood sample is collected to determine the APOL1 genotype (validated PCR assay); genetic counseling is available.

**Results:** Interim analysis included 1463 participants. Among 392 participants with NDDK, 184 (46.9%) and 248 (23.2%) have 2 APOL1 variants, respectively (Table). Most participants with 2 APOL1 variants and proteinuric CKD are ≥50 to ≤60 years old (n=321/432; 74.3%).

**Conclusions:** The high prevalence of 2 APOL1 variants in participants with recent African ancestry and proteinuric CKD emphasizes the importance of APOL1 genotyping in kidney disease care to inform disease management and enable referral for clinical trials of APOL1-targeted therapies.

**Funding:** Commercial Support - Vertex Pharmaceuticals Incorporated

### Table: Baseline Demographics and APOL1 Genotyping Results

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**SA-PO788**

Small Molecule Inhibition of APOL1 Reverses Albuminuria in a Chronic Mouse Model of APOL1-Mediated Kidney Disease

Victoria Assimon, Sarah Bronner, Cecile Yu, Helen Chan, Sheela Crasta, Patrick S. Lee, Baiwei Lin, Yunqi Luo, Angela Octaviani, Adam Reid, Laura Sanman, Licheng Shi, Eva Situ, Sam Tep, Birong Zhang, David T. Beattie, Christopher Sinz, Maarten Hoek, Harold S. Bernstein, David J. Morgans, Eric Green. Maze Therapeutics Inc, South San Francisco, CA.

**Background:** Two coding variants in the APOL1 gene (G1 and G2) confer a greater risk for progressive, proteinuric kidney disease in individuals of African ancestry. Available therapies do not address the causal genetic driver of disease, highlighting the need for novel efficacious APOL1-targeted treatments. We have previously shown that pharmacologic inhibition of APOL1 pore function ameliorates albuminuria in an acute mouse model of APOL1-mediated kidney disease (AMKD). Here we describe the development of a chronic mouse model of AMKD with robust albuminuria and glomerulosclerosis and demonstrate that inhibition of APOL1 with a small molecule attenuates features of AMKD.

**Methods:** A novel model, heterogeneous for the APOL1 G1/G2 variants, was developed for these studies in addition to the homozygous APOL1 G2 mouse model previously described. Continuous increased APOL1 expression was achieved by infecting mice with an adeno-associated virus (AAV) engineered to express interferon-γ (IFN-γ). These mouse models were used to assess the effect of APOL1 small molecule inhibition on glomerular injury and urinary albumin-to-creatinine ratios (UACR).

**Results:** Administration of AAV-IFN-γ in APOL1 transgenic mice increased interferon levels and signaling after virus injection and led to sustained APOL1 induction, elevated UACR, and glomerulosclerosis on both genetic backgrounds. Oral administration of an APOL1 inhibitor robustly attenuated chronic IFN-γ-induced albuminuria in APOL1 transgenic mice.

**Conclusions:** Small molecule inhibition of APOL1 attenuates albuminuria in a chronic mouse model of AMKD. These findings support continued development of precision medicines for patients with AMKD.

**Funding:** Commercial Support - Maze Therapeutics

SA-PO789

Small Molecule Inhibition of APOL1 Reverses Albuminuria in a Chronic Mouse Model of APOL1-Mediated Kidney Disease

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**Background:** APOL1 protein (L1) (APOL1) high-risk genotypes cause CKD in the presence of interferon gamma (IFN-γ). To elucidate mechanisms, patient-derived induced pluripotent stem cells (iPSCs) were used to generate a kidney organoid model of APOL1 nephropathy.

**Methods:** iPSCs were generated from fibroblasts of two patients with APOL1 nephropathy homozygous for G1G1 and G2G2 risk variants (RV). Isogenic control iPSCs were generated using G1G1, G2G2 and isogenic control iPSCs. Organoids were treated with IFN-γ and analyzed by single cell transcriptomics, immunofluorescence imaging and mitochondrial respiratory assay.

**Results:** APOL1 gene expression was upregulated in all genotypes following IFN-γ. Single cell transcriptomics of organoids 3 days post IFN-γ treatment showed APOL1 induction was mainly in podocytes, confirmed with colocalized immunolabeling of APOL1 and podocalyxin. RV podocytes showed significantly decreased expression of nuclear DNA-encoded OXPHOS related genes, while mitochondrial DNA-encoded gene expressions were increased. Further, a novel subpopulation in RV podocytes was identified, characterized by a metabolic switch to glycolysis. Next, glomeruli were isolated from RV and isogenic control organoids to assess oxygen consumption rate and reactive oxygen species (ROS). In RV glomeruli, maximal respiration rate upon IFN-γ treatment did not increase, unlike in the isogenic control, and ROS levels were 30% higher.

**Conclusions:** We generated a kidney organoid model of APOL1 nephropathy using patient-derived RV and isogenic control iPSCs. Exposure of APOL1 RV organoids to IFN-γ induced podocyte mitochondrial dysfunction and may provide a mechanism for development of CKD. This model supports further research in mechanisms and potential therapeutics for APOL1 nephropathy.

**Funding:** Commercial Support - Maze Therapeutics
SA-PO790
APOL1-Inflammation and Hypoxia Axis in Ischemic Donor Kidneys

Background: The presence of two APOL1 renal risk variants (RRVs) in donor kidneys negatively impacts kidney allograft survival. We examined the effects of APOL1 RRVs on APOL1 expression and compared the differences in cytokine and APOL1 expression patterns between preservation methods cold storage (CS) and normothermic machine perfusion (NMP).

Methods: Discarded deceased donor kidney pairs underwent 6-hour NMP (n=6) and CS (n=6). Perfusion, biochemical, and histologic parameters were recorded. Paired donor kidneys with different APOL1 genotypes were compared with regard to the aforementioned parameters and gene expression under NMP and CS. DNA is extracted and genotyping for APOL1 RRVs on APOL1 expression and compared the differences in cytokine and APOL1 expression patterns between preservation methods cold storage (CS) and normothermic machine perfusion (NMP).

Results: Donor genotyping showed 5 kidney pairs with G0/G0 and a kidney pair with heterozygous G0/G1 RRV. Kidneys were successfully perfused, with improved renal blood flows and resistance over the course of perfusion, and evidence of urine output (Table 1). Transcriptomic analyses showed different expression patterns between APOL1 G0/G0 kidneys and G0/G1 kidney, particularly under NMP (Fig. 1). The kidney with APOL1 G0/G1 showed higher fold increase in expression of APOL1, TGF-β and IFN-γ compared to kidneys with G0/G0 under 6 hrs of NMP. Overall, APOL1 expression was significantly correlated with KIM1 (r=0.87, p<0.001), TGF-β (r=0.83, p<0.001), IFN-γ (r=0.77, p<0.001) and HIF-1α (r=0.81, p<0.001) in all kidney pairs.

Conclusions: Donor kidney with APOL1 G0/G1 RRV demonstrated different transcriptomic response to alternative preservation methods. Further studies needed to clarify the interplay between APOL1, inflammation and kidney injury in the setting of allograft ischemia and reperfusion.

Funding: Private Foundation Support

SA-PO791
Single-Nucleus RNA Sequencing Analysis of Interferon-Exposed APOL1 High-Risk Transgenic Mouse Reveals Distinct Injury Patterns in Podocytes and Endothelial Cells
Khun Zaw Latt,1 Teruhiko Yoshida,1 Shashi Shrivastav,1 Jurgen Heymann,1 Yongmei Zhao,1 Avi Z. Rosenberg,2 Jeffrey B. Kopp,1 National Institutes of Health, Bethesda, MD; 1Johns Hopkins University, Baltimore, MD.

Background: APOL1 high-risk genetic variants, termed G1 and G2, are associated with common variants G0, causing focal segmental glomerulosclerosis (FSGS), collapsing glomerulopathy, and arteriomegaloaneurysms in individuals with sub-Saharan African ancestry. Gene expression profiles of glomerular cells in APOL1-mediated cell injury have not been studied at the single cell level. We performed single-nucleus RNA sequencing (snRNA-seq) of glomeruli from wild-type (WT) and bacterial artificial chromosome (BAC)/APOL1-G0 and -G1 transgenic mice following interferon-g administration.

Methods: BAC/APOL1 transgenic mice received a single dose of interferon-g, administered retro-orbitally, and were euthanized 24 hours later. Glomeruli were isolated and nuclei were captured for snRNA-seq. The snRNA-seq data from BAC/APOL1-G0, BAC/APOL1-G1 and wild-type mice were integrated and analyzed using Seurat4. Podocytes and glomerular endothelial cell clusters were identified by expression of known marker genes. Subclustering and pseudotime analysis were performed to identify cell subpopulations and their characteristic gene signatures.

Results: The combined analysis of snRNA-seq datasets identified podocyte clusters expressing Nephi1 and glomerular endothelial cell (GEC) cluster expressing Ehd3 and Hec2. APOL1 was expressed by podocytes and endothelial cells. Expression levels were similar between APOL1-G0 and APOL1-G1 expressing cells within each cluster. Podocytes and GECs showed similar gene expression patterns of early injury but distinct patterns with more severe injury. Genes specific to the podocyte severe injury cluster in BAC/APOL1 mice were compared to APOL1-low-risk podocytes.

Conclusions: Following interferon administration to BAC/APOL1 mice, we observed a unique gene expression profile in a APOL1-G1 risk allele mouse compared to a APOL1-G0 mouse. APOL1 was expressed in podocytes and GECs. However, the gene expression patterns of injury in these two cell types were different and may reflect different roles by which these cells contribute to glomerular pathology in APOL1 glomerular disease.

Funding: NIDDK Support

SA-PO792
HIV-1 Protein Nef Acts in Synergy with APOL1-G1 to Impair Nephrocyte Function by Inhibiting Autophagy and Endocytosis Pathway
Junyi Zhu. University of Maryland Baltimore, Baltimore, MD.

Background: Individuals carrying APOL1 risk alleles G1 and G2 have higher chances of developing HIV-associated nephropathy (HIVAN). The role of APOL1 in HIVAN is mostly derived from studies done in cultured renal cells or clinical genetic
Atypical Hemolytic Uremic Syndrome (aHUS) Clinical Characteristics Associated with Renal Replacement Therapy (RRT) Initiation During Index Hospitalization and RRT Requirement After Discharge

SA-PO793

Atypical Hemolytic Uremic Syndrome (aHUS) Clinical Characteristics and Outcomes During Index Hospitalization Diagnosis in the Era of C5 Inhibitor Therapy (C5i)

Stephen W. Olson,1 Briana C. Ndife,1 Jennifer Nguyen,1 Elizabeth Nagelhout,2 Andrea Gabriela B. Barthel,2 Yingjie Ding.2 Novartis Pharmaceuticals Corporation, East Hanover, NJ; 1Genesis Research LLC, Hoboken, NJ.

Background: C5i therapy has significantly improved clinical outcomes for aHUS. Due to its rarity, there are few previous large aHUS retrospective cohort studies and these are limited to patients from outside the US, children, and/or prevalent patients from before the era of C5i. This study sought to describe the clinical characteristics and outcomes in one of the largest and most diverse incident adult US aHUS cohorts treated with C5i to date.

Methods: This was a retrospective cohort study of adult aHUS patients in the US diagnosed during hospitalization, derived from the US Premier Healthcare Database, which contains ~25% of all US hospitalizations (1/2011–6/2021). aHUS was defined as presence of a diagnostic code for thrombotic microangiopathy (TMA) or HUS and a treatment code for C5i in the absence of a diagnostic code for secondary causes of TMA or HUS. Prespecified clinical and outcome data were collected and analyzed using descriptive statistics.

Results: The cohort comprised 634 patients with a median age of 51 years (interquartile range [IQR] 32–64). The majority were female (67.2%), White (61.5%), and non-Hispanic (76.3%). Baseline co-morbidities included hypertension (70.5%), chronic kidney disease (30.4%), and diabetes (18%). Median intensive care unit (ICU) and hospital stays (IQR) were 6 (3–11) and 20 days (14–32), respectively. The median time from admission to C5i was 9 days (5–15). For patients receiving corticosteroids (C5i 78.5%) and therapeutic plasmapheresis (TPE) (69.1%), the median time from admission to treatment was 3 days (2–5). Median treatment durations for CS and TPE were 17 days (8–28) and 5 days (3–12). Renal replacement therapy (RRT) was initiated in 77.3% of patients and discontinued prior to discharge in 51% of these patients. In-hospital mortality was 12.3%, and 22.7% of patients required follow-up in skilled care facilities.

Conclusions: Despite the substantial clinical benefits from C5i, aHUS remains a morbid disease, as shown by hospital and ICU stay duration, RRT incidence, discharge care requirements, and mortality described in this US cohort. Future efforts should focus on improved time to diagnosis and developing novel therapies.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO794

Atypical Hemolytic Uremic Syndrome (aHUS) Clinical Characteristics and Treatment Patterns Associated with Mortality During Index Hospitalization

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Background: aHUS is caused by dysregulation of the alternative complement pathway and is associated with significant renal morbidity. This study described the clinical characteristics and treatment patterns associated with mortality using evidence from one of the largest and most diverse incident aHUS cohorts in the US during the C5i era.

Methods: This was a retrospective cohort study of 634 incident hospitalized adult aHUS patients derived from the Premier Healthcare Database, which contains ~25% of all US hospitalizations (1/2011–6/2021). aHUS was defined as presence of a diagnostic code for TMA/HUS and a treatment code for a C5i in the absence of a diagnostic code for secondary causes of TMA/HUS. Demographic and clinical characteristics were analyzed using t-test, Wilcoxon rank test, Fisher’s exact test or Chi-squared test as appropriate.

Results: Overall, 78 patients (12.3%) died during hospitalization. Of 285 patients with mortality data post-discharge, 30- and 365-day mortality rates were 4% and 9%, respectively. In-hospital aHUS mortality was associated with older median age (65 vs 49 years, p=0.01) and longer median delay between admission and therapeutic plasmapheresis (TPE) (15 vs 8 days, p=0.001) and C5i (15 vs 8 days, p=0.001). Although not associated with exposure or time until corticosteroids (CS), mortality was associated with duration of CS use (27 vs 16 days, p=0.001) and time from C5i initiation to discontinuation (14 vs 6 days, p=0.02). Mortality was associated with increased median time to renal replacement therapy (RRT) (4 vs 3 days, p<0.001) but not RRT requirement.

Conclusions: Delayed TPE, RRT, and C5i treatment and prolonged CS exposure are associated with increased mortality in aHUS. Future efforts should be made to reduce any treatment delays and develop more targeted, steroid-sparing treatments.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO796

Rapid Nephrogenomics in Intensive Care for Early Intervention in Adult Thrombotic Microangiopathies

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Background: Nephrogenomics, represents the study of genetic factors influencing kidney function and diseases. The field has rapidly advanced in recent years due to the development of high-throughput sequencing technologies such as next-generation sequencing (NGS). Thrombotic microangiopathy (TMA) encompasses various genetically driven diseases with some of them could benefit from early intervention (C5 blocking, ViiH2 therapy). Structural variants (SV) in the CFI/CFHR gene region leading to the formation of gene fusions constitute a specific molecular diagnostic bottleneck associated with C5 complement dependent TMA (cTMA) cases. However, the highly repetitive character of sequences in this region, makes it difficult to detect these SVs when using standard short-read sequencing. Our current turn-around time for the diagnosis of TMA (3 weeks) is too long in some clinical context. Ultra-fast sequencing techniques using long reads Nanopore technologies can provide efficient and versatile cost-effective analysis in a matter of hours.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Methods: Here we report diagnostic results of Nanopore sequencing with adaptive sampling using TMA, which is a method to enrich sequences or genes of interest. We lowered our TAT to 5 days with long reads sequencing and adaptive sampling. We established a rapid molecular diagnosis that allows time-decision making on the use of anti-C5 treatment for complement-mediated TMA (c-TMA), as averting unnecessary costly and potentially harmful therapy in patients who will in any case not respond to the anti-C5 treatment.

Results: With rapid and long reads sequencing, we were able to diagnose a case of independent complement-TMA with a variant in MMACHC. We also retrospectively validated the detection of known SVs in four samples on which MLPA (Gold standard method to identify SV) analysis was performed. We were able to detect all the SVs in these samples such as CFHR1-CFHR1 hybrid, CFHR1-CFHY hybrids of different sizes and a deletion of CFHR1-CFHR3.

Conclusions: Thus, rapid genomics using nanopore technologies can provide valuable insights into disease detection and treatment efficacy improving patient diagnosis and prognostic, enabling optimal and early therapeutic intervention.

Funding: Government Support - Non-U.S.

SA-PO797

Unusual Case of Thrombotic Microangiopathy (TMA) in the Setting of Severe Hypertension
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Introduction: 22-year-old female with a past medical history of hypertension since age 3, left ventricular hypertrophy since childhood, and hypokalemia and metabolic alkalosis who was referred for severe active on chronic thrombotic microangiopathy in the setting of difficult to control blood pressure. Her blood pressure had been previously well controlled but developed refractory hypertension starting in 12/2020. She had been on Nifedipine and Losartan but developed bilateral lower extremity edema in 2021 and was switched to Verapamil and Enalapril. She was on Amiloride and due to uncontrolled blood pressure, was switched from Hydralazine to Labetolol with better blood pressure control. Despite the combination of enalapril and amlodipine, she remained with low levels of potassium.

Case Description: Previous work-up for secondary hypertension had been negative and patient had no family history of HTN. Renal biopsy in 2021 showed chronic-active thrombotic microangiopathy, largely affecting blood vessels, focal segmental and diffuse global sclerosing glomerulopathy, severe tubular atrophy and interstitial fibrosis, severe and diffuse chronic changes, and advanced IFTA and global glomerulosclerosis. TMA secondary to TTP, anti-cardiolipin syndrome, scleroderma, drugs, and infection were ruled out. Patient had a positive ANA but negative ENA and no clinical or laboratory signs of lupus. Genetic testing for complement regulatory proteins that are associated aHUS were unremarkable.

Discussion: At time of referral, we performed genetic testing and patient was found to have compound heterozygous mutations in HSD11B2 gene, which results in apparent mineralocorticoid excess (AME) an autosomal recessive disorder. Patient progressed to end stage renal disease. She received a deceased donor kidney transplant after a short course of peritoneal dialysis. Post-transplant course was complicated with prolonged hypotension secondary to chronic adrenal suppression, and responded well to Florinef. This case highlights the heterogeneity of TMA presentation and inform providers on management of hypotension after kidney transplantation in patients with AME.

SA-PO798

Primary Atypical Hemolytic Uremic Syndrome Presenting with Raynaud Phenomenon Triggered by COVID-19
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Introduction: COVID-19 has been linked to atypical hemolytic uremic syndrome (aHUS), although skin manifestations are rarely reported.

Case Description: A 48-year-old female with Mixed connective tissue disease (MCTD) presented after COVID-19 with Raynaud’s phenomenon. Blood film showed schistocytes, ADAMTS13 level was 45%, before PLEX therapy. Labs (Coombs, antiphospholipid, CH50, hepatitis, HIV) were unremarkable but she had a positive RNP antibody and ANA with a titer of 1:320. Renal biopsy showed thrombotic microangiopathy, largely affecting blood vessels, focal segmental and diffuse global sclerosing glomerulopathy, severe tubular atrophy and interstitial fibrosis, severe and diffuse chronic changes, and advanced IFTA and global glomerulosclerosis. TMA secondary to TTP, anti-cardiolipin syndrome, scleroderma, drugs, and infection were ruled out. Patient had a positive ANA but negative ENA and no clinical or laboratory signs of lupus. Genetic testing for complement regulatory proteins that are associated aHUS were unremarkable.

Discussion: At time of referral, we performed genetic testing and patient was found to have compound heterozygous mutations in HSD11B2 gene, which results in apparent mineralocorticoid excess (AME) an autosomal recessive disorder. Patient progressed to end stage renal disease. She received a deceased donor kidney transplant after a short course of peritoneal dialysis. Post-transplant course was complicated with prolonged hypotension secondary to chronic adrenal suppression, and responded well to Florinef. This case highlights the heterogeneity of TMA presentation and inform providers on management of hypotension after kidney transplantation in patients with AME.
for Shiga toxin. We suspected this was a case of atypical HUS (aHUS) in the setting of recent viral infection (COVID-19). Genetic panel for aHUS was ordered, and patient was started on Eculizumab (human anti-C5 monoclonal antibody).

**Discussion:** Patient’s clinical status significantly improved after the first dose of Eculizumab. Platelet count and BUN normalized. Hemoglobin and plasma creatinine improved significantly (8.1 g/dL and 0.8 mg/dL, respectively). LDIH was down trending by the time of discharge (1238 U/L). Genetic panel revealed an extremely rare heterozygous nonsense variant in exon 5 of the CD46 (c.486T>A, p.Cys162Stop) confirming our working diagnosis. This case demonstrates the importance of prompt recognition of aHUS, genetic testing for complement-mediated aHUS and early initiation of Eculizumab to reduce the risk of permanent kidney damage. It also shows that COVID-19 infection may act as trigger for complement-mediated aHUS.

**SA-PO800**

**Partial Rescue of Complement-Induced Organ Injuries in a Factor H Mutant Mouse by MASP3 Deficiency**

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**Background:** Complement is activated through three canonical pathways: classical pathway (CP), lectin pathway (LP) and alternative pathway (AP). MASP3 was known as a component of LP, but according to recent reports, MASPs was also participate AP. MASP3 gene knock-out mice (MASP3/-/-) showed no AP activity and furthermore, MASP3 was clarified that it will be responsible for the AP activation through the interaction of factor H with MASP3. We generated MASP3 knockout mice (MASP3-/-) and crossed with factor H mutant mice (FH R/R) which showed thrombotic microangiopathy and systemic thrombophelia as we previously reported. We then compared F'H-/- MASP3-/- with littermates, F'H+/- MASP3 wild type(F'H+/-) in survival, hemoglobin or platelet level, and histologic change in different organs including kidney. **Results:** We found that MASP3 deficiency rescued FH deficient mice from the effects of thrombocytopenia, anemia and renal failure. They were also prevented from large vein thrombosis in liver and kidney. However, about 30% of F'H-/- MASP3-/- died of extra-renal organ injuries such as intra-abdominal, pulmonary hemorrhage and cerebral ischemia. We measured LPS based AP activity with 20% serum from mice and found that a complement AP activity in FH deficient mice was higher and remained at a higher level even with MASP3 deficiency. This difference in AP activity was due to the absence of MASP3. **Conclusions:** These findings demonstrated that MASP3 could be therapeutic target for complement AP mediated diseases, but it is important to assess whether residual AP activity by pro-F'D cause tissue injury in each setting.

**Funding:** Other NIH Support - NIAID

**SA-PO801**

**An Unusual Case of Lupus-Associated Atypical Hemolytic Uremic Syndrome Presenting with Diffuse Alveolar Hemorrhage and Acute Renal Failure**

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**Introduction:** Atypical hemolytic uremic syndrome (aHUS) is a rare genetic disease characterized by acute renal injury (AKI), thrombotic microangiopathy (TMA), and other organ involvement. The disease occurs when genetic mutations alter complement regulatory proteins, most commonly complement factor H. As a diagnosis of exclusion, it presents a unique diagnostic challenge. Eculizumab, a monoclonal antibody against complement C5, is the treatment of choice for primary aHUS.

**Case Information:** A 43 year old male with past medical history of systemic lupus erythematosus, Grave’s disease, and hypertension presented to our institution with respiratory distress, hemoptysis, and subjective fevers. He had recently been treated with intravenous antibodies after sustaining a cat bite. On presentation, he was profoundly hypoxic with elevated D-dimers and LDH, and diffuse bilateral alveolar infiltrates. Patient was subsequently intubated, and serial broncholar lavage was consistent with diffuse alveolar hemorrhage (DAH). Renal function rapidly declined and lupus pneumonitis and nephritis were suspected; renal biopsy showed class III lupus nephritis. Pulse dose steroids and rituximab were initiated. Despite this, patient developed recurrent hemoptysis, worsening renal failure, and purpuric rash, which did not improve with plasmapheresis. In setting of markedly elevated D-dimers and LDH, thrombocytopenia, low haptoglobin, and peripheral smear revealing schistocytes, thrombotic microangiopathy was suspected. Furthermore, markedly depressed complement levels pointed towards complement activation, likely triggered by his previous infection, in adult onset atypical hemolytic uremic syndrome. Eculizumab was initiated and patient was eventually discharged to rehabilitation unit. Genetic testing revealed he was positive for all HUS genes except thrombomodulin gene mutation.

**Discussion:** This is an unusual case of lupus associated aHUS, likely triggered by infection caused by cat bite which triggered alternate complement pathway causing DAH. Atypical HUS presenting as DAH is extremely rare, and this case pointed towards limited TMA. It is imperative that aHUS remains on the differential for patients with AKI and suspected TMA, as recognition of this disorder drastically alters management. Timely management lowers morbidity and mortality of aHUS.

**SA-PO802**

**Diagnostic Utility of Whole Exome Sequencing in Adults with CKD and Biological Markers of Thrombotic Microangiopathy**

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**Background:** Chronic kidney disease (CKD) in adults may be associated with biological markers of thrombotic microangiopathy (TMA), defined as a mechanical hemolytic anemia with a decreased platelet count. In a number of cases, even after an extensive investigation including the search for variants in genes regulating the complement pathway, a definitive diagnosis cannot be achieved. Whole Exome Sequencing (WES), which examines the entire coding regions of the genome, could be of interest in these clinical forms.

**Methods:** We included all consecutive adult patients who underwent WES for CKD of unknown origin between 10/10/17 and 31/12/22 in the Nephrology Department of Sorbonne University (Tenon and Pitié-Salpêtrière hospitals). The collection of clinical characteristics, including the presence of biological markers of TMA, is prospectively done by the prescribing physician. We retrospectively assessed whether patients had been accurately classified (Figure 1). All diagnoses were made according to the guidelines of the American College of Medical Genetics and Genomics.

**Results:** During the study period, 1410 patients underwent WES, and 193/1410 (14%) exhibited biological markers of TMA. Among them, WES identified a variant consistent with the renal phenotype in 31/193 (16%) cases. 22/31 (71%) did not involve genes regulating the alternative complement pathway: type 4 collagen (COL4A3, COL4A4, COL4A5) (n=7), nephropathia epidemicogenes-associated genes (ITC21B, NPH3, NPH3p4) (n=5), PIF1 (n=2), TRPC6, PA2X, SOX18, IFN1A, MAMHC, SPTB and MTFL1 (1-1 each). Complement-related disorders involved CFI (n=4), CFI (n=3), CD46 and C2 (n=1 each).

**Conclusions:** Whole Exome Sequencing of 193 patients with CKD associated with TMA resulted in a diagnosis in 31/193 (16%) of the cases, and 22/31 (71%) diagnoses did not involve the alternative complement pathway.

**SA-PO803**

**The Value of Advanced Cardiac Magnetic Resonance Imaging Technologies in Detecting the Characteristics of Cardiac Involvement in Anderson-Fabry Disease**

**Junlan Yang,** Bin Wang. Southeast University, Nanjing, China.

**Background:** Anderson-Fabry disease (AFD) is a genetic disorder associated with cardiac involvement. Advanced cardiac magnetic resonance (CMR) technologies, including T1 mapping and gadolinium-enhanced CMR, have been used to detect and evaluate cardiac involvement in AFD patients. However, there is limited information on the characteristic CMR manifestations in Chinese AFD patients.

**Methods:** In this cross-sectional study, data were collected from patients with AFD diagnosed at this center from January 2022 to March 2023. Compared with echocardiography, CMR was used to evaluate cardiac function, the degree of cardiac structural lesions, and to analyze characteristic CMR findings in AFD.

**Results:** 20 patients with AFD from nine families were included. This study showed that left ventricular hypertrophy (LVH) was detected in 85% of patients (18.41 ± 4.56 mm), suggesting that echocardiography may underestimate the severity of LVH in AFD patients (P<0.001). Moreover, all patients exhibited characteristic CMR findings of cardiac involvement in AFD (Fig.1, Fig.2), including decreased T1 values (95% of patients) and late gadolinium enhancement (LGE) associated with myocardial fibrosis (55% of patients).

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

**Underline represents presenting author.**
Conclusions: This study demonstrated that CMR is a valuable tool for detecting and assessing cardiac involvement in AFD patients, providing characteristic CMR findings, including LVH, decreased T1 values, and LGE associated with myocardial fibrosis. Moreover, this study highlighted the diagnostic superiority of CMR over echocardiography in assessing LVH in AFD patients.

doubling of serum creatinine level from the start of analysis [two consecutive values]; 94.4% of patients did not experience a renal Fabry-associated clinical event (FACE: eGFR ≤ 60 mL/min/1.73 m²). When analyzed by eGFR category at enrollment annualized rate of change was 1.0 (3.9) in patients with eGFR ≥ 120 (33.6), −0.4 (4.9) in patients with eGFR ≥ 70 (33.6), and −0.4 (3.5) in patients with eGFR ≥ 50 (12.8%). Overall, 94.4% of patients did not experience a renal Fabry-associated clinical event (FACE: doubling of serum creatinine level from the start of analysis [two consecutive values]; end-stage renal disease requiring long term dialysis or transplantation). Seven patients each experienced one renal FACE for an incidence of 14.2/1000 patient-years. When excluding patients with the mostly cardiac variant p.2.N15S (69.6%, n=87) mean eGFR rate of change was −1.4 (4.6) mL/min/1.73 m²/year, n=81 and renal FACEs incidence was 20.9/1000 patient-years.

Conclusions: These data support sustained effectiveness with migalastat, regardless of kidney function at enrollment, in an amenable real-world cohort of patients with Fabry disease.

Funding: Commercial Support - Amicus Therapeutics

SA-PO805
Evaluation of Long-Term Renal Outcomes in Fabry Disease: A Single-Centre Prospective Cohort Study in North-West England

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Background: Fabry disease (FD) is a rare X-linked lysosomal storage disorder whereby deficiency of α-galactosidase-A results in progressive renal impairment and end-stage renal failure (ESRF). International recommendations suggest enzyme replacement therapy (ERT) in those with early signs of renal dysfunction, yet limited data exist on long-term outcomes.

Methods: 395 patients were included from a national FD database from conception to 1 February 2022. Baseline data include FD mutation, diagnosis and ERT initiation dates, renal biochemical values, co-morbidities and medications. Those on renal replacement therapy (ERT) were excluded. Rapidly progressive renal dysfunction was defined as eGFR decline of >1 mL/min/year. Primary outcomes include ESRF requiring RRT, all-cause mortality, and non-fatal cardiovascular events (NFCVE).

Results: 395 patients (M=172,F=223) with median follow-up of 6.4 years were analysed. Males received more treatment (147 v 92, p<0.001), had RRT (12 v 1, p<0.001), experienced NFCVE (75 v 42, p<0.001) and all-cause mortality (21 v 8, p<0.001). Sub-cohort analysis (n=260) showed faster eGFR decline was not predictive of RRT, but associated with higher rates of NFCVE (52 v 50, p>0.01) and all-cause mortality (17 v 8, p<0.004;fig.1). Multivariate regression demonstrated only advancing age associated with faster renal disease progression (OR:1.05; 95% CI: 1.02-1.07; p<0.001). 33 developed ESRF during median follow-up of 10.9 years. Genetic analysis showed highest prevalence of the commonest late-onset variant c.644A>G:p.N215S. 18(55%) started ERT, and 6 discontinued due to gastrointestinal intolerance or tiredness. 15(45%) experienced NFCVE, with stroke/TIA being commonest (n=6).

Conclusions: Our study supports early initiation of ERT, prior to onset of any renal decline, and advanced age a predictor of adverse outcomes.

SA-PO804
FollowME Fabry Pathfinders Registry: Renal Effectiveness in a Cohort of Patients on Migalastat Treatment for at Least Three Years

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FollowME: The followME Fabry Pathfinders registry (EUPAS20599) is evaluating the real-world safety, effectiveness and patient-reported outcomes for patients with Fabry disease who were enrolled into one of three groups: migalastat-amenable GLA variants receiving migalastat, any GLA variant receiving enzyme replacement therapy and migalastat-amenable GLA variants not receiving Fabry disease-specific therapy (untreated).

Methods: We present effectiveness data across categories of kidney function at enrollment in a cohort of patients who had received ≥3 years of migalastat treatment. Enrolled patients were ≥12 years old with an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m².

Results: As of August 2022, 125 patients (60.0% males; median age, 58.0 years) with amenable GLA variants had a mean migalastat exposure of 3.9 years. At enrollment, meanSD eGFR was 83.7 ± 22.5 mL/min/1.73 m², and overall, 17 (14.7%) patients had an eGFR ≥ 120 (33.6%), 32 (25.6%) had eGFR ≥ 70 (33.6%) and overall, 147 (117) patients had an eGFR ≥ 50 (33.6%). MeanSD eGFR annualized rate of change (mL/min/1.73 m²/year) in the overall cohort was −0.9 (4.9). When analyzed by eGFR category at enrollment annualized change was −1.0 (3.9) in patients with eGFR ≥ 90 (33.6%), −1.0 (5.9) in patients with eGFR ≥ 70 (33.6%), and −0.4 (3.5) in patients with eGFR ≥ 50 (12.8%). Overall, 94.4% of patients did not experience a renal Fabry-associated clinical event (FACE: doubling of serum creatinine level from the start of analysis [two consecutive values];
Results: Diagnostic median age was 10.9 year in males and 9.8 year in females, 26.4% in males and 31.8% in females were diagnosed by family screening. 11.8% in males were diagnosed by genetic test for other genetic disorders. At enrollment (median age 12.0 year), 29 (85.3%) of males and 5 (45.0%) of females reported symptoms (Fig1, 2). The median age of symptom onset was 6.7 year in males and 8.0 year in females. The most frequent symptom, neuropathic pain, was reported by 79.4% of males (median age 8 year) and 45.0% of females (median age 9 year). Anhidrosis or hypohidrosis were reported by 48.9%. 50% of males underwent lung function evaluation indicated obstructive respiratory diseases. 4 Of the 6 males developed Low bone mineral density. A few patients had serious manifestations, stage 5 chronic kidney disease (n=1), arrhythmia (n=4), and left ventricular hypertrophy (n=3). 22 had received agalsidase (start at median age 13.7 year in males and 13.5 year in females).

Conclusions: We provide an overview of the multicenter network of MDT for children with FD in China.

Figure 1. Biomarker levels in Fabry patients, patient controls and healthy controls

HC: Healthy control; PC: Patient control; ** MCP-1 p=0.0025 ***KIM-1 p=0.001 **YKL-40 p=0.0013 ***CysC p=0.0013

SA-PO807

New Biomarkers to Quantify Fabry Disease Activity

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Background: Fabry disease (FD) is a rare, genetic lysosomal storage disease. Kidney and cardiac involvement are the leading causes of morbidity and mortality. Slow progression, genotypic and phenotypic heterogeneity prevents accurate prediction of the disease progression. We aimed to investigate the association of different biomarkers with FD activity for this unmet need.

Methods: In this case-control study, we examined 87 Fabry patients (FP), 46 CKD patients and 41 healthy controls (HC). Study subjects were recruited according to inclusion and exclusion criteria. We studied KIM-1, MCP-1, YKL-40, TNFR-1, TNFR-2, CysC with ELISA and eGFR was calculated based on cr and cr-Cys-C in all subjects. Statistical analysis was carried out using log transformed values of biomarker levels adjusted for age, sex and BMI.

Results: Box plots of biomarker levels are shown in Figure 1. While there was no difference between FP and HC regarding eGFR(cr); eGFR(cr-CysC) was significantly lower in FP compared to HC. KIM-1 was significantly lower in FP compared to CKD patients, and it was significantly higher in FP with cardiac involvement than in those without cardiac involvement as in renal involvement. YKL-40 was significantly lower in FP without kidney involvement compared to both control groups, probably reflecting the effect of enzyme replacement therapy (ERT). KIM-1 and YKL-40 were correlated with Lyso Gb3 while MCP-1 was not.

Conclusions: MCP-1, KIM-1, YKL-40 and CysC seem to be useful markers for the management of FP, each associated with a different aspect of the disease. While KIM-1 symptom, neuropathic pain, was reported by 79.4% of males (median age 8 year) and 45.0% of females (median age 9 year). Anhidrosis or hypohidrosis were reported by 48.9%. 50% of males underwent lung function evaluation indicated obstructive respiratory diseases. 4 Of the 6 males developed Low bone mineral density. A few patients had serious manifestations, stage 5 chronic kidney disease (n=1), arrhythmia (n=4), and left ventricular hypertrophy (n=3). 22 had received agalsidase (start at median age 13.7 year in males and 13.5 year in females).

Conclusions: We provide an overview of the multicenter network of MDT for children with FD in China.
SA-PO810
Exome Sequencing in Individuals with CAKUT Identifies De Novo Variants in Novel Candidate Genes in 15.5% of the Population

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Background: Congenital anomalies of the kidney and urinary tract (CAKUT) represents the most frequent birth defect and encompasses a large variety of malformations arising from defective nephrogenesis. To date, mutations in 50 monogenic genes are known to cause CAKUT. However, in only 15-20% of CAKUT cases a causative mutation in a known monogenic CAKUT gene can be identified. Recent studies show the impact of de novo variants in FOXP1 and ZMYM2 in individuals with CAKUT, suggesting that de novo variants contribute to the genetic disease etiology.

Methods: In this study, we performed exome sequencing (ES) in 731 families out of which 264 were trio families in order to detect novel CAKUT candidate genes.

Results: i) Through proband-parent based evaluation, a variant in a single candidate gene was detected in 79 of 264 families (29.9%). ii) In 41 of 264 trio families (15.5%), we identified strong de novo variants in 43 potential novel CAKUT candidate genes. a) Of these 43 de novo variants, truncating or splice site de novo variants were found in nine genes (ASPHD1, COPSTA, DUSP23, FBXW7, GRHL1, MTHFD1, PLXG4, SLTM, SOX13). b) Four de novo variants were detected in murine CAKUT genes (AGRN, COPSTA, PDE1A, PDS5A). c) Interestingly, a relatively high percentage of de novo variants (25.6%, 11 out of 43) occurred in genes that are involved in transcription (BRPF1, BIX, COPSTA, DLX5, FBXW7, GRHL1, IRX6, PRX1, SLTM, SOX13, TLK2). d) Four de novo variants were found in genes that are paralogs of known disease causing CAKUT genes (AGRN, HSP90AB1, PTPRZ1, SOX13). Scoring variants in identified genes based on these categories (a-d), identified COPSTA and SOX13 as the most promising new candidate genes for CAKUT.

Conclusions: Our findings suggest that de novo variants in novel candidate genes may contribute to the CAKUT pathogenesis. Here, we propose two novel candidate genes for CAKUT.

SA-PO811
GEN1 Is a Likely Candidate Gene for Human Congenital Anomalies of the Kidney and Urinary Tract
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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are among the most prevalent birth defects. Although many pathogenic genes of CAKUT have been discovered, they are far from enough to reveal the causes of all CAKUT patients. Previous studies suggest that Gen1 is a mouse CAKUT gene.

Methods: There are three main parts, population data collection, in vitro function verification, and point mutation mouse construction and phenotypic observation (Fig1).

Results: DNA from 910 individuals with CAKUT were collected, among which 26 GEN1 variants were identified, and two GEN1 (missense) variants in a non-CAKUT group were found. In vitro, 10 variants (eight in the CAKUT group and two in the non-CAKUT group) were selected to verify mutant protein stability and protein stability changed in six variants in the CAKUT group. Using an electrophoretic mobility shift assay on eight variants (six in the CAKUT group and two in the non-CAKUT group), the enzymatic hydrolysis and DNA-binding abilities of mutant proteins were found to be impaired to varying degrees in CAKUT group, among which the most serious functional damage was observed in the Gen1 variant that produced a truncated protein. Moreover, a mini-gene splicing assay showed that the c.1071+3A>G variant in CAKUT group significantly affected splicing function. Three point mutant mouse strains were constructed and CAKUT phenotypes were replicated (Fig2).

Conclusions: Our findings promoted that de novo variants in novel candidate genes may contribute to the CAKUT pathogenesis. Here, we propose two novel candidate genes for CAKUT.
SA-PO813
Large-Scale Exome Sequencing Analysis Implies FOXQ1, FOXI2, EXOSC2, and MMP15 as Candidate Genes for Human Congenital Uroflow Obstructive Uropathy
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Background: Congenital obstructive uropathy (COU) is the most frequent urinary tract anomaly occurring in up to 2% of pregnancies, constituting a leading cause of pediatric chronic kidney disease. The genetic causes of COU are not well understood and remain to be described.

Methods: We conducted an exome sequencing (ES) study on 880 COU cases, encompassing three main classes of congenital urinary obstructions: a) Ureteropelvic Junction Obstruction (UPJO; N=331), b) Ureterovesical Junction Obstruction / megoureter (UVR; N=188), and c) COU not otherwise specified (COU-NOS; N=361). To investigate the excess burden of rare coding variants on COU, we performed exome-wide collapsing analysis comparing the above 880 cases and 16,135 population controls with ES data using 4 main genetic models (3 dominant and one recessive). Analyses were conducted on the entire dataset and then again after removal of cases harboring diagnostic/pathogenic Mendelian mutations and structural variants. Study-wide exome-wide significant threshold was set at 1.25 x 10^-6.

Results: In the analysis on the entire cohort of 880 COU cases, the top signal was for an ES discovery in the dominant ultra-rare model from European population (P= 8.49 x 10^-9; OR= infinite). The signal improved after removal of solved cases, excluding exome-wide significance (P= 7.64 x 10^-9; OR= infinite), and supporting candidacy for this gene. Moreover, Foxq1 is specially expressed in the mouse developing ureteric buds, ureteric epithelium cells of collecting duct and human urinary tracts. From the subtype analysis, we found the following suggestive signals: EXOSC2 (P=2.96 x 10^-10; OR= infinite); and FOX2 (P= 5.52 x 10^-10; OR= 82.63) for UPJO; MMP15 (P=2.56 x 10^-10; OR= 21.93) for UVRJO.

Conclusions: These findings expand and deepen our understanding of the genetic underpinnings of COU, identify novel candidate genes, and highlight the high genetic heterogeneity of disease. We are currently pursuing these findings using human and mouse derived urinary tract enriched organoids.

Funding: Other NIH Support - R01 DK103184, R01 DK115574 and P20 DK116191

SA-PO814
Unraveling the Role of TET2 Gene Variants in Kidney Disease Development: A Multi-omics Approach

Background: In the quest to understand the genetic causes of kidney disease, Genome-wide association studies (GWAS) have recognized hundreds of sites, yet the predicted genes, variants, and pathways remain ambiguous.

Methods: To pinpoint the genes linked to kidney disease, we combined kidney function GWAS, human kidney expression quantitative trait analysis (eQTL), and methylation quantitative trait analysis (meQTL). To discover the variants that modify gene expression, we used a kidney-specific single cell RNA-sequencing dataset and (Crispr-based) genome editing. We created kidney-specific TET2 knockout mice and manipulated gene expression in human kidney cells using CRISPR to study its role in kidney disease progression. We performed single-nucleus multomics studies in knock-out mice to delve into the role of TET2.

Results: We identified the ten–eleven translocation (Tet) DNA demethylase TET2, and the variants that change its expression in kidney tubule cells as a novel kidney disease risk gene, risk loci and target cell type. Experiments with kidney-specific TET2 knockout mouse models confirmed its protective role in cisplatin-induced acute kidney disease and UUO/adeno-induced chronic kidney disease and kidney fibrosis development. Single-nucleus profiling of TET2 knock-out mice indicated changed expression in genes related to cellular differentiation in the absence of TET2. Further cellular studies suggested that TET2 might be vital for tubule cell differentiation and could instigate kidney disease development by altering the cytosine hydroxymethylation level of associated differentiation genes.

Conclusions: Our findings underscore the crucial role of TET2-mediated active cytosine hydroxymethylation on genes associated with differentiation in tubule cells in the onset of kidney disease.

Funding: NIDDK Support

SA-PO815
Genetic Contributions to Lower Urinary Tract Dysfunction
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Background: Proper bladder function requires coordinated interactions between the urothelium, detrusor smooth muscle, ureteral sphincter, and neuronal circuitry. Historically, severe voiding dysfunction, or the so-called non-neurogenic neurogenic bladder, was attributed to urinary withholding and behavioral maladaptation. However, several monogenic causes of lower urinary tract dysfunction have been identified, leading to a paradigm shift in our understanding of this disease. The aim of this study is to better understand the genetic landscape of voiding dysfunction in children.

Methods: We performed exome sequencing (ES) in 16 individuals with non-neurogenic congenital bladder dysfunction. Individuals with obstructive uropathy, spinal cord lesions, or a known neurological cause for their disease were excluded. In addition, we reviewed ES results from 24 individuals with non-neurogenic neurogenic bladder who have been described in our prior studies (van der Ven JASN 2018 158:1560-1569; Van Genen Med Genet 2022) and analyzed data for variants in 76 candidate genes purported to play a role in urothelial signaling, detrusor function, or neuronal innervation of the bladder.

Results: We identified a pathogenic variant in 3/16 (18%) individuals with lower urinary tract dysfunction. Two individuals had homozgyous variants in HPSE2 (c.1099-2A>G, essential splice; exon9 deletion) and one individual had a homozgyous variant in a phosphoglycerate kinase 4 (PGK1) gene, and a renal-renal ciliopathy. Of the 24 individuals described in our prior publications, four had known pathogenic variants, of which three were homozgyous pathogenic variants in HPSE2 (c.490G>T, essential splice; exon7 deletion) and one was a frameshift variant in the downstream transcription factor HNF1B. The PHSE2 cohort of our research is composed of four cases harboring a monogenic cause for their disease. Notably, two individuals in this cohort had homozgyous deletions in exon 9 in HPSE2, which were identified only through manual inspection of ES data.

Conclusions: Variants in HPSE2 are a common cause of non-neurogenic neurogenic bladder in our consanguineous cohort. Structural variants in HPSE2 were identified in our cohort and have been described previously (Beaman Front Genet 13:896125, 2022), underscoring the importance of incorporating CNV analyses into genetic testing for individuals with lower urinary tract dysfunction or voiding dysfunction.

Funding: NIDDK Support

SA-PO816
Phenotypic Quantification of an Hnf1b Knockout Mouse Model Selina Holzel, Caroline M. Kolvenbach, Florian Buerger, Katharina Lembreg, Ken Saída, Seyyoung Yu, Daanya Salmanullah, Bshara Mansour, Izsedel Elmunbarak, Nils D. Mertens, Shirlee Shril, Friedhelm Hildebrandt. Boston Children’s Hospital, Boston, MA.

Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) constitute the most frequent birth defect and are the leading cause of chronic kidney disease in the first three decades of life. Approximately 50 monogenic genes, if mutated, are known to cause CAKUT, explaining 5-20% of disease origin. Mutations in the transcription factor HNF1B represent the most common monogenic cause of CAKUT in 5% up to 30% of affected patients. To date, prevention and treatment options for patients with CAKUT are limited. To enable gene replacement therapy (GRT) for CAKUT, we recently characterized a published conditional Hnf1b knockout mouse model (Gresh EMBO J 7:1657-68, 2004) and developed an additional quantifiable phenotyping method to enable reproducible reference for evaluation of future GRT effects.

Methods: Kidney specific Hnf1b inactivation is achieved by usage of the Cre-LoxP technology under a kidney specific promoter (KspCre). We utilized a colony of heterozygous breeder pairs (Hnf1b+/-, KspCre-, C57BL/6J) and phenotypically screened mutant animals (Hnf1b-/-, KspCre+), compared to heterozygous littermate controls starting at P0. For quantitative analyses we focused on the following independent parameters, adapted to Gresh et al. Kaplan-Meier survival, weight gain over time, macroscopic and light microscopic examination of kidney and urinary tract.

Results: 83.3% (n=6) of mutant mice died before weaning with survival rates ranging from 1-12 days (median 9 days). Mutant mice living past P5 (n=2) showed growth retardation and an average weight reduction of 41% compared to controls. Macroscopically, we observed ureteral dilation in 100% and hydronephrosis in 33.3% of mutant animals (n=3). Upon light microscopy we detected and quantified renal tubular cysts in equatorial kidney sections with an average of 129 cysts in mutant animals (n=3) and 0 cysts in controls (n=3).

Conclusions: We performed quantitative phenotype evaluation of a kidney specific Hnf1b knockout mouse model (Gresh et al.) providing reference for future in vivo mouse studies aiming for treatment of CAKUT.

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

SA-PO817
A Causal Relationship Between Body Mass Index and AKI Is Mediated by the Metabolome
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Background: Obesity is a known risk factor for chronic kidney disease, but its association with acute kidney injury is unclear. We investigated the causal relationship between body mass index (BMI), the metabolome, and acute kidney injury (AKI) using a Mendelian randomization (MR) experiment.

Methods: We performed MR using genome-wide association summary statistics of BMI as the exposure (GIANT Consortium, n = 681,275), the metabolome as a mediator (MuTHER Consortium, n = 7,822), and AKI as the outcome (FinnGen Consortium, n = 2,383 cases, n = 212,841 controls). First, a two-sample MR tested the association of AKI with each of the inverse variance weighted (IVW) meta-analytic point estimates from the weighted median, weighted mode, and MR-Egger regression sensitivity analyses. We then applied

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO818

Decreased Kidney Volume Is Associated with AKI

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Background: Decreased kidney volume may increase glomerular filtration and nephron workload, potentially increasing the risk of acute kidney injury (AKI). However, the mechanisms of this relationship are unclear. In this study, we investigated the relationship between kidney volume, as measured by MRI, and AKI using Mendelian randomization (MR).

Methods: We performed a two-sample MR experiment using genome-wide summary statistics for kidney volume as the exposure from the UK Biobank (n = 32,860) and AKI as the outcome from the FinnGen Consortium (n = 2,383 cases, n = 212,841 controls). The inverse variance weighted (IVW) analysis was the primary outcome, and the results were evaluated with sensitivity analyses.

Results: An association between kidney volume and acute kidney injury was observed in the IVW analysis (β = −0.56, SE = 0.097, p = 5.85E−09), weighted median (β = 0.55, SE = 0.17, p = 1.17E−03), weighted mode (β = 0.58, SE = 0.28, p = 0.03), and MR-Egger regression analyses (β = 0.617, SE = 0.26, p = 0.01). There were 14 significant BMI-metabolite relationships (p < 1.11E−04), of which 8 were identified as causal using the MR method (β = 0.55, SE = 0.17, p < 1.17E−03), weighted mode (β = 0.56, SE = 0.17, p = 0.01), weighted median (β = 0.56, SE = 0.17, p = 0.01), and MR-Egger regression (β = 0.56, SE = 0.17, p < 5.85E−09). These results suggest that BMI is a causal risk factor for AKI and may protect against acute kidney injury. Some of the involved genes relate to anthropomorphic features, such as body mass index, and kidney outcomes deserve further investigation.

Funding: Veterans Affairs Support

SA-PO819

Identifying Somatic Mosaicism for Tuberous Sclerosis Complex by Targeted Next-Generation Sequencing

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Background: Tuberous sclerosis complex (TSC) is a rare disease typically manifested with hamartomas affecting the skin, heart, brain, liver, and kidney. However, 15-20% of patients display mild clinical features suggestive but not diagnostic of TSC, and often they have no pathogenic TSC1 and TSC2 mutation detected (NMD). Here, we report our study of a cohort of patients with mild clinical features suggestive of TSC somatic mosaicism (SM) using Next Generation Sequencing (NGS).

Methods: We performed targeted gene panel screen by NGS using DNA samples from blood, buccal mucosa, and urinary epithelial cells (when available) and a minor allele frequency of 1% cut-off to detect mosaicism. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF ≤1%) deleterious variants of high and moderate impact as predicted by multiple predictive algorithms. All potential pathogenic mosaic TSC1 and TSC2 variants were validated by a novel in-house assay (Mosaic Detection by Enrichment of Mutant Allele; MODEMA) or droplet digital PCR.

Results: From a clinical review of 80 pts with confirmed or possible TSC, 18 patients with mild disease suspicious of TSC SM were sequenced. We found germline missense TSC1/TSC2 mutations in 5 patients, mosaic TSC1/TSC2 mutations in 9 patients in whom 7 were validated by MODEMA and/or digital PCR, and 4 with NMD. Patients with confirmed TSC SM were predominantly young female; all had multiple renal angiomyolipomas and few extra-renal clinical features.

Conclusions: Patients with mild clinical features suggestive but not diagnostic of TSC can be caused by missense or mosaic TSC1/TSC2 mutations. The diagnosis of TSC SM has important implications for genetic counselling and clinical prognostication, and can be improved by NGS.

SA-PO820

Renal Transplantation in a Recipient with Birt-Hogg-Dube Syndrome

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Introduction: Birt-Hogg-Dube Syndrome (BHDS) is a rare autosomal dominant disorder caused by folliculin (FLCN) germline mutations. Renal cell carcinoma (RCC) is the most serious manifestation of this condition occurring at a rate of 30%. Unlike other inherited renal cancers, BHDS is associated with a wide range of histologies. Although preserving renal function remains the central goal of management, the risk of end stage renal disease remains high. Patients with other inherited renal carcinomas (e.g. Von Hippel Lindau) have been successfully transplanted in the past. Herein, we demonstrate how renal transplant can also be a viable treatment course for some patients with BHDS related RCC.

Case Description: A 48-year-old male presented to our facility for evaluation of recurrent pneumothorax. CT chest revealed bilateral pulmonary cysts and multiple bilateral renal masses. Given the coexisting pulmonary cysts and renal masses, he was evaluated and diagnosed with BHDS. After discussion with the patient, bilateral radical nephrectomy was performed due to the presence of multifocal tumors measuring up to 5 cm. Tumor pathology was consistent with oncocytoma and chromophobe RCC, pT1N0M0. After two years of hemodialysis and surveillance, the patient was deemed a candidate for kidney transplant. Induction therapy consisted of thymoglobulin and solumedrol and the patient was discharged with mycophenolate mofetil, prednisone, and tacrolimus as maintenance.

Discussion: Tumor aggressiveness, metastasis risk, and time in remission are important factors when evaluating a patient with history of BHDS associated RCC for renal transplant. BHDS associated chromophobe and hybrid chromophobe/oncocytic tumors are less aggressive and it has been observed that the metastasis associated with these cancers tends to be more indolent in nature. Therefore, these patients are suitable candidates for transplant after a minimum waiting period. Post-transplant, immunosuppression with mTOR inhibitors can be considered since mutation of tumor suppressor FLCN in the mTOR pathway is central to BHDS pathogenesis.
SA-PO821
The Progressive Decline of Kidney Function: Can We Have an Answer?
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Introduction: With the field of nephrology moving towards personalized medicine, genetics is taking its lead in providing patient care. Tuberous sclerosis complex (TSC) is an inherited disorder with lesions involving multiple organs, including the kidneys. While TSC is often diagnosed during childhood, some cases might not be recognized until adulthood.

Case Description: Here we present a 58 y.o. female with a history of breast cancer, seizures, parathyroid adenoma, strictures of the esophagus, dental pitting, oral fibromas, and hyperpigmented macules in the mouth, who was referred due to abnormal results. Creatinine 1.6 mg/dL, eGFR 33 mL/min/1.73. Her family history was positive for cancer in her father of unknown origin. Her kidney ultrasound showed multiple fat-density tumors within both kidneys and a left renal cortical cyst. CT abdomen demonstrated bilaterally enlarged kidneys with innumerable fat-containing lesions consistent with angiomylipomatosis. CT head revealed intracranial calcifications with MRI positive for cortical and subcortical glioneuronal tumors and giant cell glcicyctoma. On CT lungs, there were numerous scattered thin-walled cysts throughout both lungs with numerous scattered nodules. Recently, the patient underwent surgery to remove a 4.4 cm invasive adenocarcinoma of the rectum with negative margins and lymph nodes for malignancy on biopsy. Genetic testing was performed that showed heterozygous pathogenic missense mutation in the TSC2 gene with AD inheritance mode: c.1832G>A (p. Arg611Gln), NM_000548.5 supporting the diagnosis of TSC. Multiple laboratories in the Clinical Database predict this variant as pathogenic and absent in the gnomAD dataset, which tells about the rarity of this mutation. Silico’s analysis supports the idea that this missense variant disrupts protein structure/function. Inactivation of the tuberin-hamartin complex mechanism of our patient’s phenotype.

Discussion: Currently, the patients continue to have progressive worsening of kidney function with a creatinine of 3.5-3.7 mg/dL. However, knowing the exact diagnosis helps with the appropriate management, prognosis and offered potential screening and diagnosing opportunities for family members.

SA-PO822
Investigation of T Cells Contributing to the Production of IgA-Type Autoantibodies Against Mesangial Cells in IgA Nephropathy
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Background: In IgA nephropathy (IgAN), the mechanism by which IgA antibodies (Abs) are selectively deposited in the glomerular mesangial region has not been elucidated. However, we have recently uncovered its mechanism by identifying IgA type auto-Ab against mesangial antigens, B220-, in gddY mice, a spontaneous IgAN animal model and IgAN patients (Y. Nihei, H. Iwasaki and Y. Suzuki et al., Sci. Adv 2023). We also found that a significant number of IgA+ plasmablasts (PBs) accumulated in the kidneys of gddY mice and these PBs produced IgA auto-Abs that bind to B220- and the surface of mesangial cells. We cloned cDNAs encoding IgA heavy and light chains from gddY PBs isolated from the kidney of gddY mice and found that most of the heavy and light-chain V region genes of these PBs contained significant numbers of somatic mutations, indicating that they were generated in a T-cell-dependent manner through the germinal center. However, the detailed mechanisms of IgA auto-Abs production, such as which types of T cells are responsible for the induction of auto-Abs, are not clear. In the present study, we analyzed CD4+ T cells in the kidney of gddY.

Methods: GddY mice were generated through selectively mating individuals within an early-disease onset group of gddY mice for more than 20 generations. All individual gddY mice exhibit proteinuria and glomerular IgA deposition by 8 weeks of age, followed by obvious renal failure and the pathology being similar to human IgAN. Isolated leukocytes from kidney of gddY or BALB/c mice at age of 8 weeks were analyzed by flow cytometry.

Results: We found that a significant number of CD4+ T cells accumulated in the kidneys of gddY mice compared to BALB/c. In details, Th1 (CD4+ IFN-γ+), Th17 (CD4+ IL-17+) and Treg (CD4+ Foxp3+) cells were significantly accumulated in the kidney of gddY compared to BALB/c. No significant differences were seen in the number of Th2 (CD4+ IL-4+), Th17 and Treg cells in the kidney of gddY or BALB/c.

Conclusions: Current findings revealed that a significant number of CD4+ T cells, especially Th1, Th17 and Treg, but not Th2 cells accumulated in kidney of gddY. We will clarify the role of these CD4+ T cells in the induction of auto-Abs in IgAN.

SA-PO823
Molecular Classification of Lupus Nephritis Based on Immune Pathway Profiling: Correlations with Histological Class and Clinical Manifestations
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Background: LN (lupus nephritis) is an autoimmune disease, involves tissue inflammation of multiple organs, including the kidney. Lupus nephritis is an autoimmune complex glomerulonephritis that develops as a complication of SLE. Dysregulation of intrarenal immune tolerance to nuclear autoantigens produces autoantibody and immune disorders. Sirt6 is the NAD+–dependent deacetylase and mono-ADP ribosyltransferase and is involved in genome maintenance and metabolism. This study investigates the effect of proximal tubule-specific Sirt6 knockdown on murine lupus nephritis.

Methods: To investigate the role of Sirt6 specifically in proximal renal tubules, we crossed gGal-cre mice and Sirt6flox/flox mice to generate Sirt6 conditional knock-out mice. The back area’s skin was shaved and treated topically three times per week, with 100 μg of resiquimod in 100 μL of acetone for eight weeks. After murine kidney sample collection, we evaluated renal histology and immunofluorescent study for inflammatory cells and lymphatic vessels. We also assessed inflammatory cytokines and chemokines, lymphangiogenic factors by qRT-PCR.

Results: The loss of Sirt6 in proximal tubules aggravates glomerular mesangial cell proliferation and tubulointerstitial inflammation, and there also increases inflammatory cytokines and chemokines such as ICAM-1, VCAM-1, MCP-1, BAFF, IL-17, and CCL13 mRNA levels to increased compared with wild-type mice.

Conclusions: Our data suggest that proximal tubule Sirt6 is important in resiquimod-induced lupus nephritis, especially in regulating tubulointerstitial inflammation.

Funding: Government Support - Non-U.S.
SA-P0825
Analysis of Galnt14-Null Mice Links O-Glycosylation Defects to Elevated Circulating IgA Levels and Altered IgA+ B Cell Tissue Distribution
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Background: Defects in O-glycosylation of IgA are a characteristic finding in IgA nephropathy. It is not known if aberrant O-glycosylation can impact IgA homeostasis, such as B-cell residence, homing, and migration. At least 17 distinct N-acetylgalactosaminyltransferases (GalNAc-T1-17) can initiate O-glycosylation of proteins.

Methods: We studied the circulating IgA, and the mucosal and non-mucosal tissue resident IgA+ B-cells in Galnt14-/- mice compared to WT mice using ELISA and flow cytometry.

Results: Galnt14 is expressed in human and murine lymphoid tissue, specifically within germinal centers which is the major site for B-cell maturation, antibody class switching and proliferation. Serum IgA levels were significantly elevated in the Galnt14-/- mice compared to the WT mice (1.31±0.4 mg/ml and 0.75±0.1 mg/ml, respectively, P < 0.01). IgA+ B-cells in mucosal and non-mucosal tissues were examined to determine if there was an abnormal distribution of IgA+ B-cells. An increase in the percentage of IgA+ B-cells was observed in the non-mucosal tissues of Galnt14-/- mice compared to WT mice (2.0±0.5% and 0.6±0.1%, respectively, P < 0.01; and peritoneal cavity: 6.1±2.3% and 3.8±0.9%, respectively, P < 0.01). Finally, reciprocal adoptive transfer experiments demonstrated that splenic derived B-cells isolated from Galnt14-/- reduced IgA+ B-cells in the Peyer’s patches (P < 0.01). Our results implicate Galnt14 in the regulation of IgA homeostasis, specifically within germinal centers, which is the major site for B-cell maturation, antibody class switching and proliferation. Serum IgA levels were significantly elevated in the Galnt14-/- mice compared to the WT mice (1.31±0.4 mg/ml and 0.75±0.1 mg/ml, respectively, P < 0.01).}

SA-P0826
Spatial Transcriptomic Profiling to Understand Organ Cross-Talk: Insight into Environment-Linked Pulmonary-Renal Disease
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Background: Environmental inhalational exposures are implicated in etiopathogenesis of autoimmune pulmonary-renal diseases and CKDUs. Underlying mechanisms of disrupted immune control and cross-organ injury are poorly understood. To gain insight into this under-studied field, we leveraged a tractable preclinical model dependent on mouse lung exposure to crystalline silica (CsI) dust. Inhalation of CsI is linked to SLE and ANCA vasculitis in humans and exposure to CsI generated from burned crops is suspected in pathogenesis of CKDUs. In mice CsI exposure induces lung inflammation and lymphoid aggregates and promotes autoimmunity. To gain insight into molecular pathways dysregulated by inhaled CsI, we used spatial gene expression (GE) profiling.

Methods: Transcriptome analysis was performed using a 10X Genomics Visium platform with CytoAssist at the Molecular Genomics Core of the Duke Molecular Physiology Institute. An FFPE section of lung harvested 3 months after CsI exposure was used for FFPE tissue sections from cSI-exposed autoAb+ Tg mice, whereas only a few scattered CsI+ cells were identified in V-exposed lung.

Results: CsI+ nuclei were identified within TLS in lung tissue of all cSI-exposed mice. In one of three BXXBS mice, a single TLS had an exceptionally high Fosprotein+ cell count, highlighting the potential for microne molecule heterogeneity. Exclusion of this outlier revealed significantly fewer Fosprotein+ cells/TLS in BXXBS vs B6 mice: 4.6±0.2 in BXXBS vs 8.1±0.6 in B6 (means±SD, p<0.05). Immunofluorescence and RNASe imaging showed that Fosprotein+ cells also localized to TLS regions in cSI-exposed autoAb Tg mice, whereas on it. However the role of S1P signaling in podocytes and the kidney is largely unknown. S1P signaling has a wide range of effects depending on the receptor and the cell type. The heterotrimer collagen 4a345 is disrupted. Alport syndrome results in glomerular filtration rate (GFR) decreases. Alport syndrome manifests as a wide range of renal dysfunctions depending on the receptor (e.g. podocytes) and the cell type. S1P signaling plays a large role in the immune system as lymphocyte migration is dependent on it. However the role of S1P signaling in podocytes and the kidney is largely unknown.

Methods: S1P was measured through liquid-chromatography mass spectrometry. Col4a3+/- mice were treated with either vehicle or 25mg/kg CYM50358 (S1PR4 antagonist) every other day starting at 4 weeks of age until sacrifice at 8 weeks of age. Albumin to creatinine ratio was determined through ELISA. Mesangial expansion was determined by PAS staining. Lipid accumulation was determined by oil red o staining. Fibrosis was determined by picro-sirus red staining.

Results: Col4a3+/- mice have elevated S1P in the kidneys compared to control mice. We see higher kidney cortex expression of S1PR1 in Col4a3+/- mice compared to control mice. We see that treatment with a S1PR4 antagonist is sufficient to lower proteinuria, We see higher kidney cortex expression of S1PR1 in Col4a3+/- mice compared to control mice. We see that treatment with a S1PR4 antagonist is sufficient to lower proteinuria, beneficial as well for slowing the progression of renal failure. Targeting other S1PR may be beneficial as well for slowing the progression of renal failure.

Funding: NIDDK Support, Other U.S. Government Support

SA-P0827
A Role for Lung Foxp3+ T-Regulatory (Treg) Cells in Modulating Lupus Autoantibody Production Exacerbated by Silica Dust Exposure
Mary H. Foster,1 Adhika Kumar,1 Koki Abe,1 Tomokazu Souma,1 Robert M. Tighe,1 Lanette Fee.1 Duke University, Durham, NC;1 Durham VA Health Care System, Durham, NC.

Background: Gene-environment (GxE) interactions promote systemic autoimmunity and induction of autoantibodies (autoAb) that destroy kidneys in SLE and ANCA vasculitis. Inhalation of crystalline silica (CsI) dust, an exposure compellingly linked to human autoimmune diseases, induces local tertiary lymphoid structures (TLS) enriched in T and B cells. In lupus and other autoimmune-prone strains, CsI inhalation increases local and systemic autoAb and accelerates nephritis. To test the hypothesis that immune control is defective in GxE-associated tissue microenvironments in lupus, we measured cells expressing transcription factor forkhead box protein 3 (Foxp3), a key marker of regulatory T cells (Treg), in cSI-exposed lupus BXXBS and non-autoimmune C57BL/6j (B6) mice.

Methods: Lungs harvested from female mice 7-9 weeks after CsI exposure were sectioned and stained with anti-Foxp3 and anti-B220 (B cell) antibodies and visualized using a Zeiss Axios Imager. TLS-associated Foxp3+ nuclei were enumerated in n=16 TLS per mouse using Zeiss Zen software, with TLS identified as loci of densely packed nuclei overlapping B220+ clusters.

Conclusions: Foxp3+ Treg are recruited to lungs after CsI inhalation and localize to lymphocyte-rich TLS, suggesting a role in regulation of local autoimmune responses. Next, we examined Foxp3 expression in TLS of cSI-exposed lupus Tg mice in this lupus-prone strain. Understanding the composition and contribution of local tissue immune niches in GxE-influenced pulmonary-renal diseases such as lupus may identify novel approaches to therapy.

Funding: Other NIH Support - National Institute of Environmental Health Sciences (NIEHS)

SA-P0828
Targeting Sphingosine-1-Phosphate Receptor 4 in a Mouse Model of Alport Syndrome
Matthew Toleroico, Judith T. Molina David, Sandra M. Merscher, Alessia Fornoni. University of Miami School of Medicine, Miami, FL.

Background: Alport syndrome is a genetic condition in which the ability to produce the heterotrimer collagen 4a345 is disrupted. Alport syndrome results in glomerular disease and eventually renal failure. Sphingosine-1-phosphate (SIP) is a bioactive sphingolipid that exerts its effects by interacting with one of its five receptors (S1PR1-5). S1PR2 signaling has a wide range of effects depending on the receptor and the cell type. S1P signaling plays a large role in the immune system as lymphocyte migration is dependent on it. However the role of S1P signaling in podocytes and the kidney is largely unknown.

Methods: S1P was measured through liquid-chromatography mass spectrometry. Col4a3+/- mice were treated with either vehicle or 25mg/kg CYM50358 (S1PR4 antagonist) every other day starting at 4 weeks of age until sacrifice at 8 weeks of age. Albumin to creatinine ratio was determined through ELISA. Mesangial expansion was determined by PAS staining. Lipid accumulation was determined by oil red o staining. Fibrosis was determined by picro-sirus red staining.

Results: Col4a3+/- mice have elevated S1P in the kidneys compared to control mice. We see higher kidney cortex expression of S1PR1 in Col4a3+/- mice compared to control mice. We see that treatment with a S1PR4 antagonist is sufficient to lower proteinuria, beneficial as well for slowing the progression of renal failure. Targeting other S1PR may be beneficial as well for slowing the progression of renal failure. Funding: NIDDK Support, Other U.S. Government Support

SA-P0829
The High-Throughput Approach Identifies Compounds that Block PLA2R and Anti-PLA2R Antibody Interactions. A. Kusheret.1, 2,3 Peng University First Hospital Department of Nephrology Renal Division, Beijing, China;1 Peking University College of Chemistry and Molecular Engineering, Beijing, China;2 Peking University Synthetic and Functional Biomolecules Center, Beijing, China.

Background: The pathogenicity of anti-phospholipase A2 receptor (PLA2R) antibodies has been elucidated in primary membranous nephropathy (MN).

Methods: Small-molecule compounds were screened for their inhibition effects to the binding between PLA2R and its antibodies by ELISA. The affinity of anti-PLA2R

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Underline represents presenting author.

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antibodies from MN patients to the full-length extracellular PL2AR was determined by surface plasmon resonance (SPR). The blocking ability of each compound was tested by SPR competition study. The affinity of each compound was determined by SPR.

**Results:** 15 candidate compounds were selected from a library of over 4,000 small-molecule compounds for their inhibition rates > 20% to the binding between PL2AR and its antibodies. The affinity of anti-PL2AR antibodies and PL2AR antigens was similar among patients as approximately 1.0 nM. The inhibitory potential of the 15 candidates was assessed by SPR and three compounds, Macrocarpel B, Doramectin, and Hypocrellin exhibit reproducible inhibitory ability, with Macrocarpel B being the most significant one. Macrocarpel B could eliminate nearly 30% of the antigen-antibody interaction in a dose-dependent manner, which was similar to the performance of the 31-mer peptide in SPR competitive inhibition assay. The competing Macrocarpel B bound to the immobilized PL2AR with an affinity of approximately 1.1 nMm, whereas no interaction was detected between it and anti-PL2AR antibody/ lgG.

**Conclusions:** We found a small molecular compound, Macrocarpel B, which could efficiently abrogate the binding between PL2AR and anti-PL2AR antibodies. These findings may have potential clinical value.

**SA-PO830**

**Potency Assessment of a Recombinant IgA Protease: Toward the Treatment of IgA Nephropathy**

Chutian Shu,1 Jing Jin,2 Yuan Zhu,1 Chencai Liang,1 Andrew Mareczko,1

1Alebund Biotech, Inc., Shanghai, China; 2Northwestern University Feinberg School of Medicine, Chicago, IL.

**Background:** Microbial IgA proteases represent a structurally heterogenous group of proteins. Despite their structural diversity, IgA proteases are highly specific to cleave the hinge region of human IgA1 heavy chain. Here we explore the potential use of an IgA protease derived from Streptococcus strain TIGR4 for the treatment of IgA nephropathy by the clearance of IgA deposits in the glomerular mesangial area.

**Methods:** We designed a TIGR4 with a truncation at its N-terminus in a fusion configuration with Fc for extending its plasma half-life. We then expressed this TIGR4-Fc fusion in E. coli strain BL21 under a Tac promoter, purified through MabSelect PrismA columns, and assessed its purity, stability, and potency.

**Results:** Recombinant TIGR4-Fc was expressed as a ~350 kDa dimer attributable to dimeric Fc in its native fold. The purity is estimated to be ~90% on an SDS PAGE. At 10 mg/mL, it remains stable in PBS at 20°C for over a week without visible precipitation. When subjecting TIGR4-Fc to PBS of human IgA1, enzymatic cleavage of the heavy chain occurs. With TIGR4-Fc at 2 and 20 µg/mL, and the substrate at 1,000 µg/mL, all IgA was cleaved by the enzyme. When TIGR4-Fc is at 0.2 µg/mL, a partial cleavage of IgA was observed with an incremental of cleavage over a period of 24 hours.

**Conclusions:** These results demonstrated the feasibility of constructing a recombinant IgA protease in fusion with Fc. The resulting biologic exhibited stability in solution and was observed with an incremental of cleavage over a period of 24 hours.

**Figure:** TIGR4-Fc@0.2µg/mL (not visible on gel)

<table>
<thead>
<tr>
<th>MW</th>
<th>1 hr</th>
<th>2 hr</th>
<th>4 hr</th>
<th>24 hr</th>
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</thead>
<tbody>
<tr>
<td>IgA1 @1,000µg/mL (heavy chain cleaved)</td>
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</table>

| IgA1, intact |
| IgA1, Fab |
| IgA1, Fc |

Fab and Fc of IgA1 are cleavage fragments.

**SA-PO831**

**Type 2 Innate Lymphoid Cells Are Activated in Steroid-Resistant Nephrotic Syndrome**

Liangjian Lu,1 Chang-Yien Chan,2 Yaqooh Chan,1 Sharon Teo,1 Yi Yang Lim,1 Mya Than,1 Kar Hui Ng,2 Hui Kim Yap,1,2 Kho Tek Puat-National University Children’s Medical Institute, National University Health System, Singapore, Singapore; 1National University of Singapore; Yong Loo Lin School of Medicine, Singapore, Singapore.

**Background:** 15% of children with nephrotic syndrome (NS) have steroid-resistant disease, which portends a poor renal prognosis. Approximately half of these patients are able to achieve remission, but only with intensive immunosuppression including calcineurin inhibitors and/or Rituximab. Given the demonstrated role of Type 2 innate lymphoid cells (ILC2) in steroid-resistant allergic asthma, and the association between INS and atopic disease, this study aimed to examine ILC2 populations in steroid-resistant (SRNS) compared to steroid-dependent INS (SDNS).

**Methods:** We recruited 18 patients (age: 15.7±1.9 years) with SDNS or SRNS, of whom were in partial/complete remission (urine protein:creatinine ratio<0.1 g/mmol). ILCs were identified as CD45+Lin-CD127+ cells. Of these, ILC1 were CRTH2+ and inflammatory ILC2 were CRTH2+CD127+ cells. Among patients with SRNS, ILC2 increased in remission compared to SDNS (p=0.01). Conversely, ILC2 increased in relapse for SRNS patients (p=0.01) but not SDNS patients (p=0.09). Correspondingly, IL22 increased in relapse for SRNS patients (p=0.01) but not SDNS patients (p=0.99) (Figure).

**Conclusions:** ILC2s are activated in SRNS during relapse, but not in SDNS. If validated, ILC2s can be a potential target for therapy in SRNS.

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

**SA-PO832**

**Neutrophil Reactive Oxygen Species Generation and Association with Clinical Disease Markers in Lupus Nephritis**

Rebecca Lubinmag,1 Makayla Brady,1 Nicholas A. Short,1 Shweta Tandon,1 Michelle T. Barati, Madhavi J. Rane,2 David W. Powell,1 Dawn J. Caster.

1University of Louisville School of Medicine, Louisville, KY.

**Background:** 15% of children with nephrotic syndrome (INS) have steroid-resistant disease, which portends a poor renal prognosis. Approximately half of these patients are able to achieve remission, but only with intensive immunosuppression including calcineurin inhibitors and/or Rituximab. Given the demonstrated role of Type 2 innate lymphoid cells (ILC2) in steroid-resistant allergic asthma, and the association between INS and atopic disease, this study aimed to examine ILC2 populations in steroid-resistant (SRNS) compared to steroid-dependent INS (SDNS).

**Methods:** We recruited 18 patients (age: 15.7±1.9 years) with SDNS or SRNS, of whom were in partial/complete remission (urine protein:creatinine ratio<0.1 g/mmol). ILCs were identified as CD45+Lin-CD127+ cells. Of these, ILC1 were CRTH2+ and inflammatory ILC2 were CRTH2+CD127+ cells. Among patients with SRNS, ILC2 increased in remission compared to SDNS (p=0.01). Correspondingly, IL22 increased in relapse for SRNS patients (p=0.01) but not SDNS patients (p=0.09) (Figure).

**Conclusions:** ILC2s are activated in SRNS during relapse, but not in SDNS. If validated, ILC2s can be a potential target for therapy in SRNS.

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

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

Underline represents presenting author.

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from untreated to iMLF plus TNF-α was greater in controls (p=0.0041). Multiple linear regression was used to test if clinical data in LN patients is associated with ROS generation in LN. For untreated, anti-dsDNA (p=0.0439) and eGFR (p=0.0318) were associated. For iMLF, C4 (p=0.0286) was associated. For iMLF plus TNF-α, UPCR (p=0.0210), C3 (p=0.0199), C4 (p=0.0025), creatinine (p=0.0325), and eGFR (p=0.0130) were associated. Finally, anti-dsDNA was associated with fold change in ROS for untreated to iMLF (p=0.0136) and untreated to iMLF plus TNF-α (p=0.0152).

Conclusions: LN neutrophils had a greater response to iMLF than controls. This suggests the possibility of endogenous primers in LN serum, which may play a role in LN pathogenesis. Further studies beyond ROS generation in LN are ongoing regarding the utility of clinical markers in LN as well as potential new markers. Using clinical data to predict underlying disease may improve future treatments.

Funding: NIDDK Support

SA-PO833

Dapagliflozin vs. Ramipril Therapy in Mice with Alport Syndrome

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[1] Saint Louis University School of Medicine, Saint Louis, MO; [2] Cedars-Sinai Medical Center Department of Pathology & Laboratory Medicine, Los Angeles, CA; [3] Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada; [4] Washington University in St Louis School of Medicine, St Louis, MO.

Background: Angiotensin-converting enzyme inhibitors (ACEi) have been the best studied treatment for Alport syndrome with established benefits for renal function and survival in animals and humans. Recent clinical trials have shown that sodium glucose co-transporter 2 inhibitors (SGLT2i) are a key disease-modifying therapy to prevent the progression of chronic kidney disease when used on a background of renin-angiotensin-aldosterone system (RAAS) blockade. The objective of this study is to investigate whether SGLT2i exerts renoprotection as much as ACEi in Alport syndrome.

Methods: We studied male Col4a3 knockout mice, an Alport syndrome model, on a 129S1/SvImJ background. Dapagliflozin (1.5 mg/kg/day) or Ramipril (10 mg/kg/day) were orally administered via drinking water, starting at 4 weeks of age to 10 weeks of age (N=6-8/group). Wild-type (WT) and Alport littermates received vehicle for the same duration and served as controls. Glomerular filtration rate (GFR) was measured byulin-labeled inulin clearance in conscious mice, and kidneys were processed for histology (PAS, Sirius Red staining).

Results: Alport mice treated with Dapagliflozin had enhanced glucose excretion in urine, but blood glucose level was not changed. At 10 weeks of age, Alport mice developed a significant body mass loss, decreased renal weight, and elevated blood pressure. These were attenuated by Ramipril, but not by Dapagliflozin. Histological analysis of Alport mouse kidneys showed global and segmental glomerulosclerosis, tubular casts and tubulointerstitial fibrosis, which were more consistently improved by Ramipril than by Dapagliflozin.

Conclusions: Ramipril had more favorable effects on preservation of renal function and renal architecture in Col4a3 knockout Alport mice than Dapagliflozin. Our head-to-head comparison indicates that SGLT2i may not be an alternative option for ACEi in glomerular diseases. Further studies are currently in progress to investigate the effects of a higher dose of Dapagliflozin and of combined treatment of SGLT2i with RAASI.

Funding: Private Foundation Support

SA-PO834

Plasma TET2 as Potential Noninvasive Biomarker for Type IV Lupus Nephritis

Hua Zhou,1 Jeffrey B. Kopp,2 Jiayue Liu,1 Hongyu Yang,1 Congcong Yang,1 Junjun Luan.1 Shengjing Hospital of China Medical University, Shenyang, China; 2National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.

Background: Therapeutic regimen of lupus nephritis (LN) should be based on the pathological classification by renal biopsy. The class IV is most common type and has the worst prognosis in LN patients. However, some patients are contraindicated to be treated by renal biopsy. A non-invasive biomarker that can mirror to renal classification will help clinical decision-making. Ten-eleven translocation methylcytosine dioxygenase 2 (TET2) has been reported to involve in the pathogenesis of systemic lupus erythematosus and kidney diseases. We aim to verify whether plasma TET2 can reflect renal classification in LN patients.

Methods: Plasma samples were collected from 49 patients diagnosed as LN approved by renal biopsy in our department from January 2019 to January 2023 and 27 age- and sex-matched healthy volunteers (NC). Class IV (n=14) and class III + IV/V/V were included in LN patients. Plasma levels of TET2 were analyzed by enzyme-linked immunosorbent assay. Student’s t test or one way ANOVA test and receiver operating characteristic curve (ROC) were used for the data analysis.

Results: Plasma TET2 levels were increased in LN patients compared to NC. Plasma TET2 differentiated LN from NC with a high diagnostic accuracy with area under the curve (AUC=0.77, p<0.001, n=76). The sensitivity for diagnosing LN was 65.30%, and the specificity was 85.20%. Further more, plasma TET2 levels in class IV were decreased compared to that in class III + IV/V/V inside LN patients. Plasma TET2 also differentiated class IV from class III + IV/V/V (AUC=0.73, p<0.001, n=45) with the sensitivity 85.7%, and the specificity 80.6% with TET2 cutoff as 350 pg/ml.

Conclusions: Plasma TET2 level differentiated LN class IV from class III+V/IV+V/V. Combination with sAlb increased the differentiation efficiency. A panel of blood TET2 and sAlb might help in diagnosing LN class IV for those patients with contraindication of renal biopsy and benefiting to therapeutic decision. This study needs to be validated in large cohort of LN patients.

Funding: Government Support - Non-U.S.

SA-PO835

Identification of Anti-Peroxidasin Antibodies in Human and Experimental Glomerulonephritis

Imperial College London, London, London, United Kingdom.

Background: Peroxidasin (Pxdn) is an extracellular matrix (ECM) haem peroxidase critical for forming sulphuric bonds which crosslink type IV collagen. Sulphuric bonds contribute to structural integrity and stability of the ECM and act to sequester the Goodpasture antigen giving it immune privilege. Autoantibodies to peroxidase have previously been identified in patients with anti-glomerular basement (GBM) disease and MPO-ANCA associated vasculitis (MPO-AAV).

Methods: Circulating anti-Pxdn IgG was measured by ELISA in serum from patients (anti-GBM disease, AAV, and healthy volunteers) and rats with experimental autoimmune glomerulonephritis (EAG), an autoimmune model of anti-GBM disease. For coating, recombinant rat Pxdn was expressed in HEK293 cells and purified; human Pxdn was from a commercial source (OriGene). Antibody specificity was confirmed using immunoblotting. Expression of Pxdn, digested IgG, and smooth muscle actin (SMA) in kidney tissue was assessed by indirect immunofluorescence (IF).

Results: Circulating anti-Pxdn IgG antibodies were detected in 29.4% of (15/51) patients with anti-GBM disease, 14.2% (2/14) of patients with active MPO-AAV, and 0% (0/6) patients with active PR3-AAV (Fig 1A). Circulating anti-Pxdn IgG antibodies were detectable at day 28 after induction of EAG (peak glomerular injury) in 86.7% (13/15) of rats (Fig 1B). Anti-PXDN antibodies were detectable at low titre from day 18 suggesting they may arise later than anti-c3IV/NC1 antibodies which are detected from day 7. IF staining of kidney tissue in EAG identified Pxdn at areas of glomerular injury and crescent formation. Pxdn co-localised with SMA but not with digested rat IgG (Fig 1C).

Conclusions: We confirm the presence of anti-Pxdn antibodies in patients with glomerulonephritis. In EAG, anti-Pxdn antibodies were evident after the development of antibodies against c3IV/NC1 and glomerular Pxdn expression was only detected after disease onset: thus we suggest anti-Pxdn antibodies may arise by a process of intermolecular epitope spreading in the diseased glomerulus.

SA-PO836

Glomerular Parietal Epithelial Cell Expression of Cathepsin C Increases G1072

Michelle T. Barati, Jon B. Klein, Michael Merchant. University of Louisville, Louisville, KY.

Background: Collapsing glomerulopathy (CG) is a feature of human immunodeficiency virus-associated nephropathy (HIVN). Previous studies in kidney biopsies of patients with primary, collapsing variant of focal segmental glomerulosclerosis (cFSGS) demonstrated activated glomerular parietal epithelial cells (PECs) expressing cathepsin C protease, migrating into glomerular tufts. Similar results were found with preliminary lab studies in biopsies of HIVN patients. Cathepsin C is normally absent in the glomerular tuft, suggesting the PECs introduction of this protease may contribute to extracellular matrix (ECM) deposition in cFSGS. For this study, we addressed the hypothesis that cathepsin C expression increases in PECs lining Bowman’s capsule and PECs migrating onto glomerular tufts in TG26 mouse model of HIVN.

Methods: Kidneys from 8 week old male and female TG26 transgenic and FVB wt mice used for this study were provided by Dr. Klottman lab, baylor college of medicine. Formalin-fixed paraffin-embedded kidney sections were subject to co-immunofluorescence staining for claudin-1, a marker of PECs, and cathepsin C. Images were acquired by confocal microscopy.

Results: claudin-1 and cathepsin C were localized to glomerular parietal epithelial cells lining Bowman’s capsule in wt mice. In glomeruli of TG26 mice, PECs lining Bowman’s capsule showed increased expression of cathepsin C and had hypertrophied morphology, suggesting PEC activation. Glomeruli of TG26 mice also showed migration of Claudin-1-positive PECs onto the glomerular tuft and these cells also expressed cathepsin C.
Conclusions: Glomerular PECs exhibit increased expression of cathepsin C in Tg26 mouse model of HIVAN CG. These findings are similar to our findings in human primary cFSFG and HIVAN, demonstrating utility of this mouse model to define the role of PEC induction of cathepsin C in the pathogenesis of CG. Defining the cellular and molecular basis for abnormal ECM remodeling in cFSFG offers the potential of interrupting disease progression.

SA-PO837
Interstitial Fibrosis in ANCA-Associated Vasculitis: Myeloperoxidase (MPO) vs. PR3
Helena Jordi,1 Jordi Vilardell,1,2 Irene Silva,1 Beatrice Bardaji de Quixano,1 Monica M. Diaz Encarnacion,1* Group of Renal Inflammatory Diseases (GERI).1,2 Fundacio Puigvert, Barcelona, Spain; 3Universitat Autonoma de Barcelona, Barcelona, Spain.

Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis characterized by inflammation of small blood vessels, being the kidney one of the most frequently affected organs. AAV has a high morbidity and mortality rate, leading to rapidly progressive renal failure that may lead to end-stage kidney disease. Its pathogenesis is a complex and multifactorial process involving inflammation and fibrosis. PR3-ANCA and MPO-ANCA have clinical-demographic differences and different renal phenotypes observed in kidney biopsy. The histopathological subgrouping into four classes (focal, crescentic, mixed, and sclerotic) is useful for predicting long-term renal survival, the worst being sclerotic class. Our aim is to determine whether interstitial fibrosis in AAV is at least as important as glomerular sclerosis in prognosis.

Methods: Retrospective single-center study of 95 AAV patients (78 MPO-ANCA and 17 PR3-ANCA) diagnosed by renal biopsy, with at least 1-year follow-up. Type of immunosuppressive therapy and renal/patient survival were evaluated. Histomorphometric quantification using MetaMorph® software on trichrome-stained biopsies slides to measure the degree of fibrosis. Data analysis performed under standard conditions.

Results: PR3-ANCA population was predominantly male (70%, mean age=62, mean follow-up=54 months), while MPO-ANCA population was mainly female (65.8%, mean age=66, follow-up=65 months). There were no statistically significant differences in renal function between MPO and PR3-ANCA at diagnosis. Albeit renal function improved throughout follow-up in PR3-ANCA (p=0.02) and MPO-ANCA (p=0.05), MPO-ANCA showed worse renal function than PR3-ANCA (p=0.01) at the end of follow-up. MPO-ANCA showed more interstitial fibrosis at diagnosis than PR3-ANCA (p=0.01). However, there were no significant differences in the incidence of glomerulosclerosis (p=0.26). PR3-ANCA showed more crescentic proliferation (p=0.03) but less fibrotic crescents than MPO-ANCA at diagnosis.

Conclusions: The method we used allows a quantitative assessment of renal fibrosis. Our data confirm that renal prognosis is better in PR3-ANCA than in MPO-ANCA. This could be explained by a greater interstitial fibrosis, as well as more fibrotic crescents in MPO-ANCA at diagnosis.

SA-PO838
The Protein/Creatinine Ratio Is a Reliable Indictor of 24-Hour Urine Protein, Regardless of the Level of Renal Function in Patients with Glomerulopathies
Gabriel Brayan Gutierrez Peredo,1,2 Iris Montaño-Castellon,1,2 Andrea Jimena Gutierrez-Peredo,1,2 Antonio A. Lopes,1,2 TUNARI Study.1
1Professor Edgard Santos University Hospital, Federal University of Bahia, Salvador, Brazil; 2Postgraduate Program in Medicine and Health, Federal University of Bahia, Salvador, Brazil.

Background: We aimed to determine the accuracy of the urine isolated protein/creatinine ratio (PCR) test, against the gold standard 24-hour urine protein (24hUP) measurement in patients with glomerulopathies, and according to the levels of renal function.

Methods: This prospective study of patients with glomerulopathies was developed by Professor Edgard Santos University Hospital in Salvador, Bahia-Brazil. The PCR and 24hUP measurements were performed using conventional methods within a maximum interval of 24 hours between the measurements. The patients were classified into three groups according to their renal function, group 1 = < 30 ml/min/1.73m2, group 2 = 30-60 ml/min/1.73m2 and group 3 = >60 ml/min/1.73m2. Spearman correlation coefficient (r) and ROC curves were employed to compare PCR with 24hUP.

Results: The total was 167 urinary samples from 134 patients. The mean age was 42 ± 16 yrs, 68% were female and 91% non-white. A good correlation was observed between PCR and 24hUP total sample (r= 0.7, p = 0.0000), as well as in comparison with the different levels of renal function (r= 0.8 for group 1, r = 0.9 for group 2 and r = 0.8 for group 3). The ROC between PCR and 24hUP total sample yield an AUC of 0.94 (CI= 0.89, 0.97), high sensitivity of 91% and specificity of 83%, at the optimal cut-off point was 0.7. The groups representing three levels of renal function showed high sensitivity and specificity in comparisons of both methods (group 1= 82%, 100%, group 2= 97%, 89% and group 3 = 88%, 92%) with an AUC of 0.99, 0.96 and 0.96, respectively.

Conclusions: PCR shows high sensitivity and specificity for monitoring patients with glomerulopathies compared to 24hUP. Our findings suggest that PCR is a useful parameter to evaluate and monitor patients with different glomerulopathies regardless of the level of renal function.

Results in the total sample and by degree of renal function comparing protein/creatinine ratio with 24-hour urine protein

<table>
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SA-PO839
Association of Neuroblastoma Suppressor of Tumorigenicity 1 (NBL1) with Interstitial Fibrosis Severity and Kidney Function Decline in IgA Nephropathy
Eiji Kobayashi,1,2 Eiichiro Satake,1 Masanori Abe,1 Nihon University School of Medicine, Tokyo, Japan; 1Joslin Diabetes Center, Boston, MA.

Background: We recently showed that the presence of neuroblastoma suppressor of tumorigenicity 1 (NBL1) in circulation is closely linked to the progression of kidney disease and histological abnormalities in individuals with diabetic kidney disease. This research aimed to investigate the potential association between serum NBL1 levels and kidney function, as well as renal histological lesions, in patients with IgA nephropathy (IgAN).

Methods: In this study, we assessed the NBL1 levels in 109 individuals with IgAN by using serum samples collected immediately before renal biopsy. We also evaluated the significance of serum NBL1 in relation to kidney function and renal histological findings based on the Oxford Classification (MEST score). Moreover, we examined the correlation between serum NBL1 and the long-term decline in kidney function among IgAN patients who had follow-up data on their estimated glomerular filtration rate (eGFR) (n=76).

Results: In early-stage IgAN patients, serum NBL1 levels were found to be higher compared to healthy individuals (p=0.01). Logistic regression analysis revealed a significant and independent association between serum NBL1 levels and tubular atrophy/interstitial fibrosis. Through immunohistochemical staining, NBL1 was highly expressed in the tubulointerstitium during the early stages of IgAN. Additionally, a significant correlation between serum NBL1 levels and the eGFR slope was identified on Spearman’s rank correlation.

Conclusions: The serum NBL1 level was significantly associated with the severity of renal interstitial fibrosis and future kidney disease progression in patients with IgAN. Thus, circulating NBL1 may serve as a good biomarker for evaluating renal interstitial fibrosis and the risk of kidney disease progression.

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

SA-PO840
Longitudinal Changes in IgA1 O- and N-glycoforms in IgA Nephropathy
Masaya Hirayama, Yukako Ohyyama, Yudai Tsuji, Naotake Tsuibo, Kazuo Takahashi. Fujita Health University School of Medicine, Toyoake, Japan.

Background: An increased level of circulating aberrantly glycosylated IgA1 has been considered a significant initial step in the pathogenesis of IgAN. Recently, the molecular features of IgA1 O- and N-glycoforms in patients with IgAN have been reported using high-resolution mass spectrometry (HRMS). While specific glycopeptides have been reported to be a possible predictor of IgAN and glomerular function, it is still largely unclear how the glycosylation of IgA1 changes according to treatment. In this study, we aimed to determine the difference in IgA1 O- and N-glycoforms changes between different treatment groups at two time points: at diagnosis and post-treatment, using a prospective cohort enrolled at Fujita Health University Hospital.

Methods: We registered patients diagnosed with primary IgAN by renal biopsy during 2017-2019. Ten patients who received tocilizumab and corticosteroid therapy (T-CST group), eight patients who received conservative therapy (CO group), and five patients with other renal diseases who were treated with corticosteroid therapy (ORD group) were enrolled. IgA was purified from the serum of patients at two time points (diagnosis and post-treatment). After neuraminidase treatment, O-glycoforms of the IgA1 hinge region (HR) and N-glycoforms of the Fc region were analyzed using online liquid chromatography-HRMS.

Results: The mass spectrometry analysis of O-glycoforms of IgA1 HR showed that the ratio of N-acetylgalactosamine in the IgA1 HR was significantly increased only in the T-CST group from diagnosis to post-treatment (P = 0.0235), while the number of galactose in the IgA1 HR remained unchanged in all groups. The mass spectrometry analysis of N-glycoforms also showed several changes only in the T-CST group. In asparagine (Asn)54, at post-treatment, there was a significant increase in the relative abundance of the oligomannose-type (P = 0.0020) and a significant decrease in the galactosylation of the tri-antennary-type (P = 0.0098); whereas in Asn58, there was a significant decrease in the relative abundance of fucosylated glycan (P = 0.0195).

Conclusions: This study found that some glycoforms previously reported to be characteristics of IgAN were altered only in the T-CST group of IgAN but not in the CO group of IgAN or the ORD group. The detection of O- and N-glycoform alterations may be IgAN-specific biomarkers of disease activity.

Funding: Government Support - Non-U.S.
Integrin β1 Mediates Interactions of IgA1-Containing Circulating Immune Complexes from IgA Nephropathy Patients with Cultured Primary Human Mesangial Cells

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Background: Biopsies from patients with IgA nephropathy include proliferation of mesangial cells and glomerular IgA1 that probably originates from deposition of circulating immune complexes (CIC) with variable amounts of IgA1, IgG, complement C3, and other proteins, e.g., fibronectin (FN). C-terminal segment of FN may bind IgA, and serum levels of IgA-FN complexes may have diagnostic value for IgA nephropathy. The mechanism by which CIC induce proliferation of the mesangial cells is not well understood. We explored interactions between CIC, mesangial cells, FN, and FN’s receptors (integrin α1β1 and α5β1).

Methods: Cultured quiescent human mesangial cells were incubated for 15 min at 37°C with CIC from sera of IgA nephropathy, without or with integrin α1β1 inhibitor obtustatin or integrin α5β1 inhibitor RGD. The integrins were immunoprecipitated (IP) from cell lysates using specific antibodies. Cell lysates and IP products were analyzed by SDS-PAGE/immunoblotting with antibodies specific for IgA, IgG, IgM, FN, and selected phosphorysproteins. To assess effects of FN on CIC association with mesangial cells, CIC were incubated 15 min at 37°C with the cells and purified FN, with or without obtustatin.

Results: Variable amounts of IgA and IgG were detected in the lysates of cells incubated with CIC. CIC induced phosphorylation of several proteins, including PDGFR-β, Axl, ERK, and integrin β1. Obtustatin reduced the amounts of IgA and IgG in the lysates and decreased CIC-induced phosphorylation of ERK, Axl, integrin β1, and PDGFR-β. IgA, IgG, and FN were detected in the IP with antibodies specific for integrin α1β1 and α5β1. Obtustatin reduced amounts of IgA and IgG in the IP in the presence of FN in the cells with CIC enhanced the amounts of IgA, IgG, and IgM in lysates about 1.2-4.7-fold. Obtustatin decreased the FN-enhanced amounts of IgA, IgG, and IgM in lysates by about 10-25%.

Conclusions: CIC from patients with IgA nephropathy added to cultured mesangial cells induced cellular signaling and variable association of IgA1/FnG1m in the cell lysates. Addition of FN enhanced the association of IgA1/GfG1m with the cells. Future studies are needed to define mechanisms of integrin β1 and CIC interactions and a possible role of FN in these processes.

Funding: NIH/NIDDK Support

Characterization of IgA1-Containing Circulating Immune Complexes in Patients with IgA Nephropathy with Progressive vs. Nonprogressive Disease

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Background: IgA nephropathy (IgAN) is an autoimmune disease wherein circulating immune complexes (CIC) deposit in the glomeruli and induce mesangiolipophagocytic injury and proliferation of mesangial cells. The origin of IgA1 in IgAN is unknown. We previously reported that mesangial cells incubated with some CIC from IgAN patients showed an increase in Gd-IgA1 production which is dependent on Gd-IgA1 bound by IgA1 antibodies (Ab) specific for Gd-IgA1. Serum levels of Gd-IgA1 and IgA1/Nab predict disease progression, but little is known about characteristics of the CIC. Here, we analyzed the mesangiolipophagocytic activity and composition of CIC from patients with progressive vs. non-progressive IgAN.

Methods: CIC from sera of IgAN patients with progressive (IgAN-P; n=3) or non-progressive IgAN (IgAN-Np; n=2) disease were isolated by size-exclusion chromatography (SEC) and further electrophoretically separated under reducing conditions. CIC of molecular mass (Mr) ≥700 kDa stimulated proliferation of MC. Jacalin affinity chromatography was used to deplete total serum IgA1 before SEC. Serum levels of IgA, IgG, IgM, C3, C4, and C3d were determined by ELISA and CIC composition was assessed by SEC fractions were devoid of IgA, IgG, and C3. Conclusions: IgAN CIC with Mr >700 kDa that stimulate cellular proliferation of MC contained IgA1 with IgG and covalently attached C3. Jacalin affinity chromatography confirmed association of IgA1 with C3 and IgG. Moreover, IgA1-Np had more active CIC compared to IgAN-Np CIC. Future studies will determine similarities and differences in the composition and amounts of these CIC associated with disease severity and/or progression.

Funding: NIDDK Support, Private Foundation Support

Therapeutic Effect of Nanoparticle-Mediated shRNA Delivery in Lupus Nephritis Mice

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Background: Lupus nephritis (LN) is the most common and severe manifestation of systemic lupus erythematosus (SLE). LN pathogenesis is complex and incomplete understood. Therapy approach are predominantly nonspecific immunosuppressive medications. More effective drugs with favorable safety profiles are urgently needed. MRL/lpr mouse develop lupus nephritis that mostly assemble disease manifestation in lupus patients. WD repeats and FYVE-domain-containing protein 1 (WDFY1) is an adaptor protein involved in inflammatory pathways in LN.

Methods: Protein levels of WDFY1 were analyzed by Western blot and immunofluorescent staining in the kidney of nephritic MRL/lpr mouse and lupus nephritis patients. Lupus-like disease was first induced in C57BL/6 mice by ip administration with 1 X 10^9 splenocytes from bm12 mice. Serum autoantibody levels were measured by nephritogenic test. Mesangial cell proliferation in vitro was assessed. Twelve-week-old MRL/lpr mice were treated with nanoparticle encapsulated WDFY1-shRNA for 5 weeks. Renal pathology, immune complex deposition, and complement activation were examined.

Results: Significantly enhanced WDFY1 expression was detected in the kidney of MRL/lpr mouse compared to the age/sex-matched MRL/MpJ mouse. The expression levels also correlated with the nephritis disease activity. Kidney sections from LN patients also showed increased WDFY1 expression compared to kidney samples from healthy controls. B6.WT mice developed increased levels of anti-dsDNA and anti-choromat autoAbs after receiving bm12 splenocytes. AutoAbs production was significantly diminished in B6.WDFY1KO mice receiving the same dose of bm12 splenocytes. Most importantly, MRL/lpr mice treated with nanoparticle encapsulated WDFY1-shRNA showed improved kidney function with significantly decreased BUN and proteinuria.

Conclusions: Observations made here support the usefulness of WDFY1 for the treatment of lupus and lupus nephritis. Results may lead to more effective and safer molecular-species approaches.

Funding: NIDDK Support

Humoral Immune Responses Primed by the Alteration of Gut Microbiota Were Associated with Galactose-Deficient IgA1 Production in IgA Nephropathy

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Background: Galactose-deficient IgA1 (GdIgA1) is critical in the formation of immunoglobulin deposits (IgG) in IgA nephropathy (IgAN), whereas the origin of GdIgA1 is unknown. We focused on the immune response to fucal microbiota in IgAN patients.

Methods: By running 16s rRNA gene sequencing, we compared IgAN samples to the control samples from household-matched or nonrelated individuals. Levels of plasma IgA and polyclonal IgA complexes were assessed, and candidate microbes that can either incite IgA1-directed antibody response or degrade IgA through specific IgA protease activities were identified.

Results: The IgAN group showed distinct formation of fucal microbiota as compared to a healthy control. Particularly, high abundance of Escherichia-Shigella was associated with the disease group based on analyses using Receiver-operating Characteristic (AUC 0.837, 95% CI 0.738-0.914), Principle Coordinates, and the LEfSe algorithm (LDA score: 4.56, p<0.001). Accordingly, the bacterial levels directly correlated with high titers of plasma GdIgA1 (r=0.36, p<0.001), and patients had higher IgA1 against stx2C2.88αα4.61 IU/ml vs. 1.34αα5.35 IU/ml, p=0.03), the main antigen of Escherichia-Shigella. Conversely, the healthy controls showed relatively higher abundance of the commensal bacteria that produce IgA-degrading proteases. Particularly, the abundance of some intestinal bacteria expressing IgA proteases showed an inverse correlation with the levels of plasma GdIgA1 in IgAN.

Conclusions: Our data suggest that mucosal IgA production, including those of GdIgA1, is potentially linked to the immune reactivities against gut Escherichia-Shigella, and conversely, the IgA protease-producing microbiota in the gut are suppressed in IgAN patients.

Funding: SA-PO845

Neutrophil Degranulation in Lupus Nephritis

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Background: There is accumulating evidence for neutrophil involvement in lupus nephritis (LN). Neutrophils are recruited into glomeruli following immune complex deposition, where they release toxic antimicrobial agents and immune regulatory molecules from preformed granules. Our previous reports with mice and cultured

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cells show that neutrophil granule proteins contribute to immune complex-mediated glomerular injury and drive the development of podocyte damage. The aim of this study is to investigate the contribution of neutrophil degranulation in human LN.

**Methods:** Levels of twelve neutrophil granule proteins were measured in urine and serum from 10 LN patients with active disease and 8 healthy controls (HC) using an antibody-based array and ELISA validation, with use of controls in serum from HC patients, and neutrophil elastase was the only protein higher in LN serum. Degranulation of all granule subsets were significantly enhanced in untreated neutrophils from LN patients compared to HC. Serum from active LN patients, but not HC serum, significantly activated granule release in HC neutrophils.

**Conclusions:** Our findings suggest that enhanced neutrophil degranulation could play a role in LN pathology and that urine measurement of neutrophil granule proteins could serve as markers of kidney inflammation.

**Funding:** FNIHD Support

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**SA-PO846**

**The C-Terminal Region of HTRA1 Is the Predominant Target for Autoimmunity in HTRA1-Associated Membranous Nephropathy (MN)**

**Laith Al-Rahabi,** 1 Linda Reinhard, 1 Michael Ehrmann, 2 Elion Hoxha, 3 Laurentine H. Beck, 2 Alex R. López, 2 Patricia M. Moreno, 2 Maribel Díaz-Ricart, 2 Marta Palomo, 2 Josep Miquel Blasco Pelicano, 2

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**Background:** We previously identified HTRA1 as a novel antigen in 4.2% of uncharacterized MN patients. This secreted serine protease is expressed in various tissues with high homology across human and rodent species (~92%). The trypsin-like serine protease domain in HTRA1 is responsible for its proteolytic activity whereas its PDZ domain facilitates protein-protein interactions by tethering HTRA1 to specific sites in the extracellular matrix.

**Methods:** Immunoblotting/cyclic constrained epitope mapping of patient serum from two independent cohorts with various truncated recombinant HTRA1 proteins. WT and HTRA1 KO mice were immunized with full-length human HTRA1.

**Results:** Sera from patients with HTRA1-associated MN is known to recognize native and recombinant human HTRA1 even under reducing conditions, which are expected to disrupt the conformation of the highly disulfide bonded N-terminal region of HTRA1. According to antibody binding, both cycling and glucerosylated antibodies from patients with HTRA1-associated MN recognize the HTRA1 C-terminus, which encompasses its PDZ and protease domains. Immunoization of WT or HTRA1 KO mice with human HTRA1 generates mouse Ab against HTRA1. Importantly, these mouse autoantibodies recognized the HTRA1 C-terminus (similar to what is seen with patient-derived autoantibodies).

To further approximate the location of the targeted epitopes of HTRA1 autoantibodies, immunoblotting of reactive sera with various truncated recombinant HTRA1 proteins showed that HTRA1 autoantibody-containing human sera recognized full length HTRA1 and HTRA1 C-terminus.

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

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**SA-PO847**

**Oxford Kidney Pathology Atlas: Single Cellular Profiling of Renal Biopsy Tissue**

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**Background:** Glomerular damage is central to many kidney diseases, thus a better understanding of glomerular cell pathology is essential for developing more targeted therapies. Through transproteomic and proteomic profiling of human renal tissue may address this challenge. Many studies utilize nephrectomy sections, with limited samples, technical glomerular dissociation bias, and non-standardized methodology restricting the research application of biopsies. As part of the Oxford Kidney Pathology Atlas study, we developed experimental protocols for processing standard human renal biopsy samples for single nuclei RNA sequencing (snRNA-seq) and glomerular proteomics and generated pilot data from healthy donors and an early primary idiopathic nephrotic syndrome (nS) case.

**Methods:** Biopsy cores from deceased patients and pre-transplantation protocols were processed for clinical histology, snRNA-Seq and targeted glomerular proteomics. SnRNA-Seq libraries were sequenced using the TruSeq stranded mRNA library prep kit and the Illumina NextSeq 500. Exons were annotated with Ensembl and RNA-Seq data were analyzed using the Bioconductor package Seurat. Glomerular regions from formalin-fixed paraffin-embedded (FFPE) renal biopsy sections were isolated via targeted laser capture microdissection coupled with mass spectrometry (MS). MS results were analyzed using DI-ANN and Perseus software to assess relative protein abundance.

**Results:** We conducted a targeted proteomics titration experiment with varying numbers of isolated glomeruli from healthy donors to establish the minimum material required for proteomics. We isolated glomerular proteins from FFPE-embedded renal section, quantifying over 4.5k unique proteins from a single glomerulus and over 5k proteins from 6-10 human glomeruli. By snRNA-Seq, libraries were generated per single biopsy core, with glomerular and tubular populations represented. Despite normal histology, nS patient-derived nuclei enriched in select proximal tubule and glomerular cell clusters, with altered gene signatures including increased cellular transport function and extracellular matrix accumulation, and reduced podocyte function.

**Conclusions:** From this work, we demonstrate that glomerular proteomic markers can be captured from 6 glomeruli from a human FFPE biopsy section. Key renal cell types are detectable by snRNA-Seq from standard clinical biopsy core, sufficient to detect differential cell composition and gene expression in disease tissue. This platform will be applied to identify new therapeutic targets in kidney disease.

**Funding:** Commercial Support - Novo Nordisk
Late Renal Recovery in a Patient with Solitary Kidney and ANCA-Positive Glomerulonephritis (GN) Treated with Rituximab
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Introduction: ANCA vasculitis is the most common form of new-onset GN in adults >50. It is often associated with high rate of morbidity and mortality, especially when it causes significant renal injury requiring RRT. These patients often do not come off RRT primarily when they have known CKD.

Case Description: 82yoF with CKD stage IIIa baseline SCr >0.9-1.1 with solitary right kidney due to renal cell cancer s/p left nephrectomy was found to have rapidly progressive AKI with SCr rising from 2.2 to 3.7 in a span of 2 weeks with associated dyspnea, leg edema, and fatigue. She was found to have focal necrotizing and crescentic-immune GN with vascular findings consistent with vasculitis on her kidney biopsy. The crescents were limited to 4 of 46 glomeruli but had 13 globally sclerosed glomeruli with moderate interstitial fibrosis and 40-50% tubular atrophy. Along with positive c-ANCA and anti-MPO antibodies, she was confirmed to have ANCA vasculitis. Although she remained non-oliguric, her SCr continued to rise at 4.6 requiring hemodialysis (HD), which was continued even after hospital discharge. She was pulsed with steroids and was started on rituximab infusion after discharge. She was continued on rituximab and was able to come off HD after 8 months due to improvement in her SCr to 2.0-2.2 range. She remains off HD with last SCr of 2.1 from earlier this month.

Discussion: ANCA vasculitis remains a rare yet lethal disease that is yet to be fully understood. It is still unknown how ANCA antibodies develop. One study has shown that only 43% of patients who required RRT at the time of diagnosis were able to come off at 1 year. The prognosis is even poorer when they have known CKD with much lower rates of meaningful kidney recovery after initiating RRT at around 5%. Xu et al. emphasize how pathologic severity may determine renal recovery for ANCA vasculitis requiring RRT at disease onset with high proportion of fibrous crescent and global glomerulosclerosis being a predictor of dialysis dependence. Our patient’s renal recovery indicates that even with advanced age, baseline CKD, and moderate tubulointerstitial involvement, it is possible to remove vasculitis in the form of crescentic glomerular lesions with rituximab. We also make a case for biopsy of a solitary kidney when absolutely indicated despite the risks involved.

Paraneoplastic IgA Nephropathy Associated with Renal Cell Carcinoma
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Introduction: Malignancy is a rare and underrecognized cause of secondary IgA nephropathy, particularly in elderly patients. We present a case of IgA nephropathy likely paraneoplastic to renal cell carcinoma (RCC) that resolved after tumor resection.

Case Description: A 71-year-old previously healthy woman presented to the nephrology clinic with an elevated serum creatinine. Although asymptomatic, the patient noted her son had IgA nephropathy requiring kidney transplant. On examination, she was hypertensive to 158/88 mmHg but had a normal cardiologypulmonary examination with no peripheral edema. Laboratory studies showed a serum creatinine elevated to 2.7 mg/dL from normal baseline. Urinalysis showed 100 mg/dL protein, large blood, 68 WBC, HPF, and 83 RBC/HPF. Serologic workup was unremarkable. A kidney ultrasound showed a solid mass occupying a large portion of the right kidney. Studies revealed no local or distant metastases.

Discussion: IgA nephropathy can be associated with infection, autoimmune conditions, liver disease, and malignancies—such as lung cancers, lymphomas, IgA myeloma, and RCC. This case represents a paraneoplastic IgA nephropathy associated with clear cell RCC that resolved post-nephrectomy. Although fewer than ten cases related to RCC are reported in the literature, multiple studies have identified pathologic evidence of IgA nephropathy in RCC nephropathy specimens. This suggests that IgA nephropathy may result from tumor-induced antigen-antibody response. The primary goal of treatment is to address the underlying malignancy to minimize the risk of further kidney injury. Rituximab is a reasonable addition to the immunosuppressive therapy armamentarium. In this case, removing the tumor led to significant improvement possibly due to elimination of tumor-induced immune interactions.

Peripheral Neuropathy Leading to Diagnosis of ANCA-Associated Glomerulonephritis
Matthew F. Baker, Laura Malone, Maura A. Watson, Amy J. Frankston. Walter Reed National Military Medical Center, Bethesda, MD.

Introduction: ANCA-associated glomerulonephritis (GN) rarely presents with concomitant neurologic symptoms.

Case Description: A man in his seventies with type 2 diabetes mellitus and hypertension was admitted with 6-months of worsening extremity weakness and gait instability leading to a fall. Electromyogram demonstrated diffuse demyelinating polyneuropathy. On admission, he had acute kidney injury (AKI) with serum creatinine 1.86 mg/dL (0.9-2.4 mg/dL at baseline). Urine microscopy showed acanthocytosis, red blood cell casts, and dense granular casts. Renal biopsy demonstrated crescentic GN, acute interstitial nephritis with tubular necrosis, and a medium-sized artery occluded by thrombus. Direct immunofluorescence was positive for C3 and negative for IgA, IgG, IgA, C1q, fibrinogen, albumin, or kappa/lambda light chains. Perinuclear ANCA titer was elevated at 1:320. Anti-MPO antibodies were >8 units; anti-PR3 antibodies were elevated at 2.7 units. Diagnoses of ANCA-associated GN and microscopic polyangitis (MPA) were made. He was treated with induction methylprednisolone and rituximab followed by prednisone taper. After treatment, renal function and extremity neuropathy symptoms improved. Serum creatinine improved from 2.42 mg/dL pre-treatment to 2.0 mg/dL at hospital discharge.

Discussion: The initial presentation of weakness and polyneuropathy is an unusual dominant symptom for MPA, which may have delayed recognition of renal involvement. He lacked other symptoms, including rash or sinusitis, that are often associated with systemic small-vessel vasculitis. C3 positivity on direct immunofluorescence does not rule out ANCA-associated GN despite its classic “pauic-immune” appearance. Plasminapheresis was considered due to concurrent AKI and autoimmune-mediated demyelinating polyneuropathy but was deferred due to lack of rapid renal failure or pulmonary hemorrhage. Immunosuppressive therapy directed at preserving kidney function also improved the neuropathy suggesting that these were both due to MPA. Recognition of unusual features of MPA-associated GN as demonstrated in this case aided diagnosis and should be considered in AKI cases with neurologic derangements. The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.
Glomerular Diseases: From Inflammation to Fibrosis - III

Case Description: 55-year-old woman with a history of metastatic vulvar squamous cell carcinoma, presented with lower extremity pain, right groin abscess and acute kidney injury (AKI). Baseline creatinine was 0.46 mg/dL and peaked at 6.9. No nephrotoxins were reported on history or review of medical records. Urinalysis was significant for WBC 21-50/hpf, RBC 0-2/hpf, protein 300 mg/dL, small blood and Urobilinogen to creatinine ratio was 9mg/g. Hcp C was positive with VDRL-657,000. Complements were normal. Serological and paraproteinemia workup was negative. Kidney biopsy showed MPGN pattern with lesions suggestive of thrombotic microangiopathy (TMA) in 80% of capillary loops on light microscopy (LM) and electron microscopy (EM). Immunofluorescence (IF) was negative for IgG, IgA, IgM, C1q, kappa, lambda or fibrin. Based on LM and IF findings, diagnosis of C3GN and TMA was made, although TMA itself is very uncommon. It was presumed that activation of alternate complement pathway played a role in TMA. It was complicated by endocapillary proliferation of both TMA and C3GN with such high serum creatinine level. Electron microscopy (EM) eventually cleared the final diagnosis. EM revealed thin delicate randomly arrayed fibrils within the mesangial matrix and Congo Red and Thioflavin-T staining was positive in the mesangium and capillary loops. What was read as TMA were actually amyloid deposits. Mass spectrometry revealed AA Amyloidosis and AA amyloidosis presented as C3 glomerulopathy (C3G) with renal-limited TMA associated with MPGN.

Discussion: This patient presented with multiple challenges in terms of diagnosis. Hepatitis C related MPGN, Infection related glomerulonephritis and paracrine related TMA were all considerations. Light microscopy and IF were suggestive of C3GN with TMA which fit clinical picture (and all can present in a similar fashion). Eventually EM clinched the diagnosis. It proved to be a case of mistaken identity. EM is invaluable in making management decisions especially when LM and IF are not corroborating with clinical and pathological findings. Patient deterioration was rapid and did not pursue active treatment and chose hospice care.

SA-PO856

Collapsing Focal Segmental Glomerulosclerosis (FSGS) with APOL1 Gene Mutation in Adult-Onset Still Disease (AOSD)

Zain AlShanabaleh, Syeda B. Ahmad. UPMC, Pittsburgh, PA.

Introduction: Collapsing FSGS is a distinct variant characterized by hypertrophy and hypercellularity of the glomerular tuft. Collapsing FSGS is generally idiopathic but may be seen with HIV or COVID-19 and cases not attributed to HIV are often idiopathic. Amongst the other secondary causes are autoimmune diseases such as AOSD. We present a case of collapsing FSGS attributed to AOSD in a high risk patient with APOL1 gene mutation.

Case Description: Our patient is a 24-year-old incarcerated African-American male with history of left nephrectomy who presented with orbital and facial swelling. He reported subjective fevers for 4 to 5 months, 40 pound weight loss; pain, stiffness, and swelling in bilateral hands. On exam, patient was febrile to 101 Fahrenheit, tachycardic to 110 beats/minute with peripheral edema, swelling and an injection of bilateral second-fourth proximal interphalangeal joints. Skin examination revealed a rash over his right eyelid and bilateral knuckles. Lab investigations revealed WBCs 13.1 with 82% neutrophils, creatinine 4.3 mg/dL, albumin 2.1 g/dL, AST 206 IU/L, ALT 292 IU/L, Alk phos 110 IU/L, total bilirubin 0.5, 5.5 mg/dL, INR 1.37 mg/mL, ESR 104, CRP 71.3, urine protein/creatinine ratio (UPCR) 14,450. Other than ANA positivity 1:80, his additional work up, including hepatitis profile, TB, COVID, HIV, syphilis, CMV, EBV, C3/C4, and Anti-CCP, was negative. Renal biopsy was consistent with collapsing FSGS with mild-moderate chronic glomerulosclerosis. Malignancy screening was negative. Genetic testing for APOL1(G1 & G2) was positive.

Discussion: AOSD displays renal manifestations in 25% of cases including mesangiocapillary glomerulonephritis. Collapsing FSGS secondary to AOSD is extremely rare. To the best of our knowledge, our case represents the first reported case of collapsing FSGS attributed to AOSD. In our reported case, the renal biopsy provided a histological diagnosis of collapsing FSGS. Serologic and infectious workup were negative and a diagnosis of AOSD was established after fulfilling the Yamaguchi criteria. Our case is the first reported case to describe collapsing FSGS attributed to AOSD in a high risk patient with APOL1 gene mutation. Further studies are needed to determine treatment options. Our patient was treated with losartan and prednisone 60mg daily with symptom improvement and UPCR downtrended to 8,153 within 2 months.

SA-PO885

Carlfilzomib-Associated Thrombotic Microangiopathy with Kidney Infarction Treated with Eculizumab


Introduction: Thrombotic microangiopathy (TMA) results from endothelial cell injury that can lead to kidney injury. Drug-induced TMA (DTMA) is a rare but serious adverse effect of certain medications, including carfilzomib, a proteasome inhibitor used for multiple myeloma (MM). Parenchymal kidney injury is a rare and severe complication of TMA, which can lead to significant acute kidney injury (AKI). We report a case of kidney infarction with anuric AKI associated with carfilzomib use.

Case Description: A 66 yo White woman with refractory IgG lambda MM began carfilzomib-based therapy. Kidney function was stable until 6 months after carfilzomib, when she experienced rapid decline in urine output and AKI with a creatinine of 7.4 mg/dL (baseline 0.6 two weeks prior), with thrombocytopenia and anemia. In 2 days she was anuric and required hemodialysis (HD). Labs showed low haptoglobin and negative antistreptolysin titer, suggesting microangiopathic hemolytic anemia. ADAMTS-13, C3, C4, E. coli Shiga-like toxins were normal. A kidney biopsy confirmed TMA with fibrin thrombi affecting glomeruli and arteries, plus parenchymal kidney necrosis.

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

Underline represents presenting author.
SA-PO858
Monoclonal Gammapathy of Renal Significance Presenting as Cryoglobulinemic Glomerulonephritis
Shirley Bottes, Emmanuel A. Aydin-Ghormoz, Swati Mehta, Krishnakumar D. Hongalgi. Albany Medical College, Albany, NY.

Introduction: Monoclonal gammapathy of undetermined significance (MGUS) is a premalignant plasma cell disorder characterized by serum monoclonal protein <3g/dl, clonal plasma cells <10% on bone marrow biopsy, and absence of end-organ damage. Treatment is not recommended. When monoclonal immunoglobulin causes kidney damage, monoclonal gammapathy of renal significance (MGRS) is diagnosed and treatment involves chemotherapy. We describe a patient with known MGUS presenting with AKI and cryoglobulinemic glomerulonephritis (CG) secondary to development of MGRS.

Case Description: A 73 year-old-man with CKD stage 3, type 2 DM, chronic microscopic hematuria, and MGUS presented with AKI. Previous CKD workup showed 0.5g/day proteinuria, positive ANA, low C4, positive rheumatoid factor, and negative dsDNA and ANCA. He had elevated free kappa light chains on SLEP and bone marrow biopsy confirmed IgM MGUS. CKD and proteinuria were attributed to diabetic kidney disease. Work-up of chronic hematuria was unrevealing. He presented 8 months later with fatigue, dyspnea, epistaxis, lower extremity rash, and hematuria with Cr 2.2 mg/dL (baseline 1.7) and 24 hour urine protein 3.5g. Serology was positive for cryoglobulin and negative for Hepatitis B, C, and HIV. Kidney biopsy showed diffuse, focal crescentic mixed cryoglobuliminic glomerulonephritis, likely type II, with focal leukocyctlastic vasculitis, focal severe arteriosclerosis, and moderate to severe interstitial fibrosis and tubular atrophy. He underwent 5 sessions of plasmapheresis, IV rituximab, and induction with MMF therapy. Prompt nephrology referral and biopsy in MGUS patients with elevated proteinuria, negative for Hepatitis B, C, and HIV is important and guides treatment. Prompt nephropathy referral and biopsy in MGUS patients with elevated creatinine, proteinuria, and hematuria allows for diagnosis of MGRS and initiation of therapy to preserve kidney function, avoid long term dialysis, and reduce mortality.

Discussion: AA amyloidosis is caused by extracellular deposition of serum amyloid A protein—a hepatic acute phase reactant—in tissues, and can occur in many chronic inflammatory conditions. Proteinuria kidney disease is a common presentation of AA amyloidosis; amyloid goiter is an uncommon presentation and associated hyperthyroidism is rare. Our patient’s presentation with amyloid goiter, hyperthyroidism, and kidney failure has not previously been reported to our knowledge. Treatment of AA amyloidosis largely depends on identification of an inciting chronic inflammatory disease; however, extensive workup did not reveal a cause in our patient. She was initiated on hemodialysis for kidney failure and treated with beta blockade and methimazole for hyperthyroidism.

SA-PO860
Membranoproliferative Glomerulonephritis: A Rare Presentation in Systemic Sclerosis

Introduction: Systemic sclerosis (SSc) is a chronic autoimmune condition that can affect multiple organ systems. Renal involvement in SSc can range from asymptomatic reduction of GFR to life-threatening scleroderma renal crisis (SRC). Membranoproliferative glomerulonephritis (MPGN) is a rare and under-investigated renal manifestation of SSc. MPGN is a histological pattern of glomerular injury consisting of mesangial hypercellularity and proliferation of glomerular capillary walls with subsequent formation of new basement membrane. Although MPGN can be caused by a variety of primary and secondary conditions, descriptions of its association with SSc are limited. We present a unique case of MPGN as a manifestation of systemic sclerosis in an adult patient, highlighting the challenges of diagnosis and management of MPGN in the context of SSc.

Case Description: A 64-year-old woman with a history of SSC, controlled hypertension, Raynaud’s syndrome, and chronic kidney disease presented to our hospital with acute kidney injury and elevated blood pressure. Laboratory tests showed AKI, proteinuria, microscopic hematuria, and low complement levels. He did not meet the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group diagnostic criteria for SRC. Serologies were unremarkable for SLE and hepatitis B and C. No paraprotein was detected. A renal biopsy revealed immune complex-mediated glomerulonephritis (ICGN) with an MPGN pattern. The patient was started on mycophenolate mofetil (MMF) and showed improvement in renal function and complement levels.

Discussion: This case represents, to our knowledge, the second reported case of MPGN associated with SSc. It emphasizes the importance of understanding the various renal manifestations of SSc in patients with this condition and AKI, and the importance of considering diagnoses other than SSc. MPGN can be immune complex-mediated or complement-mediated, with specific complement levels indicating the pathway involved. Treatment depends on the underlying cause and may involve immunosuppressive agents for underlying autoimmune disease, chemotherapy for hematologic malignancies, or antimicrobials for systemic infection. In this case, the patient showed improvement with MMF therapy. Prompt evaluation and intervention are crucial to prevent permanent kidney damage in SSc patients with renal involvement.

SA-PO859
A Unique Presentation of AA Amyloidosis
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Introduction: While the overall prevalence of kidney amyloidosis in native kidney biopsies performed globally is 1.6%, in the United States, only 7% of these cases are due to AA amyloidosis. We describe a unique multisystem presentation of AA amyloidosis.

Case Description: A 64 year-old Pakistani woman with hypertension and goiter presented to the hospital for five days of abdominal pain and watery diarrhea, in addition to several weeks of worsening fatigue. She had goiter and tachycardia on exam, and laboratory studies demonstrated hyperthyroidism and non-oliguric kidney failure with 8.8 g protein in a 24 hour urine collection. Thyroid ultrasound showed diffuse fatty infiltration; kidney and urinary tract ultrasound was unrevealing. Kidney histology showed glomerular mesangial expansion with eosinophilic matrix and substantial fibrosis. Congo red stain revealed amyloid deposition in glomeruli, vessels, and the tubulointerstitium, identified as amyloid A with immunohistochemistry. Thyroid histology showed adipocytes with entrapped benign thyroid follicles (diffuse lipomatosis) and amyloid deposits in vessel walls by Congo red stain.

Discussion: AA amyloidosis is caused by extracellular deposition of serum amyloid A protein—a hepatic acute phase reactant—in tissues, and can occur in many chronic inflammatory conditions. Proteinuria kidney disease is a common presentation of AA amyloidosis; amyloid goiter is an uncommon presentation and associated hyperthyroidism is rare. Our patient’s presentation with amyloid goiter, hyperthyroidism, and kidney failure has not previously been reported to our knowledge. Treatment of AA amyloidosis largely depends on identification of an inciting chronic inflammatory disease; however, extensive workup did not reveal a cause in our patient. She was initiated on hemodialysis for kidney failure and treated with beta blockade and methimazole for hyperthyroidism.
hospitalization patient developed an AKI with Cr 1.65 mg/dL on presentation (recent baseline Cr 1.3-1.5 mg/dL) which rapidly peaked to Cr 3.6 mg/dL over the next 7 days. Initial concern was for acute interstitial nephritis from antibiotics vs infection-related GN. Notable labs include 24 hour UPCR 282 mg; UA: >50 RBCs, 0-5 WBCs. On urine microscopy, numerous isomorphic RBCs seen with few acanthocytes, no RBC/WBC or granular casts. Immunologic workup revealed normal complement levels (C3 94 mg/dL, C4 26 mg/dL), negative ANA, ANCA, Anti-GBM, cryoglobulin levels. Renal biopsy performed revealed pauci-immune focal crescentic glomerulonephritis. There was consideration to starting immunosuppression with corticosteroids; however, patient’s Cr spontaneously down trended on supportive management with IV antibiotics (cefaroline). On discharge patient’s creatinine was 1.6 and 1.2 on follow-up 3 months later.

Discussion: AN-PING is rare, poorly recognized clinical entity among crescentic glomerulonephritis. Primarily related to its negative serology, AN-PING is often diagnosed late on renal biopsy. This delayed diagnosis has resulted in AN-PING patients having a worse prognosis and higher mortality relative to ANCA-positive GN. Treatment of AN-PING is challenging due to its association with Infection and malignancy (20%), and must be approached on a case-by-case basis.

SA-PO863
Complex Clinical Interplay: A Case of Systemic Lupus Erythematosus Coexisting with Type II Cryoglobulinemia
Madison M. Ladines, Salem Vilayet, Waleed A. ELSheikhMohammed, Tibor Fulop. Medical University of South Carolina, Charleston, SC.

Introduction: The coexistence of Systemic Lupus Erythematosus (SLE) and cryoglobulinemia, characterized by the presence of cryoglobulins in the serum, represents a rare and challenging clinical scenario. This report highlights a case of a 32-year-old male with both conditions, presenting with acute kidney injury. Case Description: A 32-year-old African American female with SLE and Type II cryoglobulinemia presented with severe shortness of breath, kidney failure, and peripheral edema. Initial lab work revealed acute kidney injury (creatinine: 0.6 mg/dL to 2 mg/dL in 3 weeks). Treatment included azathioprine, prednisone, and intravenous metoxeturane. Her condition deteriorated with increased shortness of breath and hemoptysis. Lab findings: positive antinuclear antibodies, kappa-restricted IgM kappa and polyclonal IgG), negative hepatitis panel, and normal renal ultrasound. Kidney biopsy showed hyaline pseudo-thrombi and subendothelial/mesangial deposits on electron microscopy. Subsequently treated with therapeutic plasma exchange and cyclophosphamide infusions. Discharged with a stable creatinine level (0.9 mg/dL) on rituximab, hydroxychloroquine, and prednisone.

Discussion: The intersection of SLE and Type II Cryoglobulinemia presents a complex clinical picture with multiple implications. While studies suggest that cryoglobulinemia in SLE patients does not necessarily correlate with severe complications unless coupled with cryoglobulinemic vasculitis, our patient developed biopsy-proven lupus cryoglobulinemic glomerulonephritis, indicating systemic involvement. This case underscores the critical need for kidney biopsy in lupus management to target therapy for optimal outcomes.

SA-PO862
Secondary IgA Nephropathy as Red Herring in a Case of AKI
Emmanuel A. Aiydin-Ghormoz, Andrea R. Lightle, Mauricio Monroy. Albany Medical College, Albany, NY.

Introduction: Liver disease, and particularly alcoholic cirrhosis, is the most common cause of secondary IgA Nephropathy (IgAN), with 50-90% of cirrhotic patients exhibiting glomerular IgA deposition. Despite this, <10% of adult patients show clinical evidence of glomerular kidney disease. We report a case of ATN with underlying diabetic kidney disease and microscopic hematuria due to cirrhotic IgAN.

Case Description: A 65-year-old man with history of type-2 diabetes mellitus and hypertension presented to our hospital after outpatient lab work showed elevated creatinine. His diabetes was managed with insulin. He had been prescribed metformin 6 months earlier but discontinued it 3 weeks before presentation due to severe diarrhea, which had partially resolved after cessation. He denied any known history of kidney disease and did not use NSAIDs. He did report heavy alcohol use for many years. Serum creatinine level was 3.7mg/dL with unknown baseline. UA was active with 3+ protein, 50-100 RBCs/HFP, and 0-5 coarse granular casts/HFP. He had ascites with nodular contour of the liver and an atrophic left kidney on imaging. Paracentesis revealed SAAG >1.1 and ascites total protein 1.6g/dl. Creatinine remained stable. ANA, dsDNA, C3, C4, cryoglobulins, ANCA, and hepatitis panel were all negative. Serum immunofixation revealed no paraprotein. Right kidney biopsy was performed and showed ATN, significant mesangiproliferative IgA deposition, diabetic and hypertensive nephropathy with severe arteriosclerosis and arteriolar hyalinisation, and secondary FSGS. His rise in creatinine was attributed to ATN, hematuria and proteinuria were explained by glomerular accumulation of IgA, while FSGS was attributed to diabetic Kimmelstiel-Wilson nodule formation and segmental scarring due to immune complex deposition. Kidney function slowly worsened with development of uremic symptoms, requiring initiation of hemodialysis.

Discussion: Decreased hepatic clearance of IgA complexes is the suspected etiology of secondary IgAN in patient with liver cirrhosis. Despite its infrequent presentation, this diagnosis should be suspected in cirrhotic patients presenting with AKI and active UA with the decision to perform kidney biopsy based on the clinical presentation. Regrettably, our patient’s biopsy showed advanced chronic changes due to DM, HTN, and secondary FSGS, and progression to ESRD was inevitable.
SA-PO865
Human Immunodeficiency Virus-Associated Lupus-Like Nephritis: An Undetectable Viral Load and Negative Lupus Serologies
Muhammad Z. Khan, Jason M. Kiddy, Kennerly C. Patrick. Katz Family Division of Nephrology and Hypertension, Virginia Commonwealth University Health System, Richmond, VA.

Introduction: HIV is a common cause of a wide array of kidney abnormalities including both glomerular and tubular disorders. HIV associated immune complex kidney disease (HIV-ICK) is a unique entity which includes lupus like nephritis which presents without classic serologic findings of lupus. We describe the case of a 29-year old man with HIV who was diagnosed with lupus like nephritis without a diagnosis of lupus.

Case Description: A 29-year old man with a history of HIV on anti-retroviral therapy (ART) and chronic kidney disease stage 4 presented with dyspnea and acute kidney injury. Pertinent labs included serum creatinine of 3.7 mg/dl up from 2.7 mg/dl and dipstick positive for hematuria and proteinuria. Urine microscopy had acanthocytes. Spot urine protein creatinine ratio was 0.7 g/g. A broad serologic workup was performed which was unremarkable (Table). HIV viral load was undetectable. A kidney biopsy was performed. A kidney biopsy was performed. Mesangial expansion and hypercellularity was noted without crescents. There was patchy tubular atrophy and interstitial fibrosis. Immunofluorescence staining pattern was positive for Ig (Immunoglobulin) A, IgG, IgM, C (complement) Ig, and C3. Electron microscopy showed multiple subepithelial and mesangial electron dense deposits. A diagnosis of lupus like glomerulonephritis was made. Given the undetectable viral load kidney function was monitored closely without any active pharmacologic intervention.

Discussion: We present the case of HIV related immune complex glomerulonephritis. This case is unique because lupus like nephritis developed despite an undetectable HIV viral load and negative lupus serologies. The pharmacologic therapy in such cases is a subject for research. The optimal treatment remains unknown as yet.

Pertinent serologic markers

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Cytoplasmic</th>
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<tbody>
<tr>
<td>C5</td>
<td>1.5 mg/mL (0-20)</td>
</tr>
<tr>
<td>C4</td>
<td>20 mg/dL (18-40)</td>
</tr>
<tr>
<td>ANCA</td>
<td>1.2 (0.5-1.5)</td>
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SA-PO866
Efficacy of ANCA Autoantibody Clearance by High-Dose Immunoglobulins Prior to Plasma Exchange in Severe Pulmonary Renal Syndrome
Bioern Tampe, Universitatsmedizin Gottingen, Gottingen, Germany.

Introduction: Plasma exchange rapidly depletes pathogenic anti-neutrophil cytoplasmic autoantibodies (ANCAs) and is considered for induction therapy in severe ANCA-associated vasculitis. The aim of plasma exchange is to remove putative disease mediators from the circulation, such as toxic macromolecules and pathogenic ANCs.

Case Description: To our knowledge, we here provide the first report of applying high-dose IVIGs prior to plasma exchange and assessment of ANCA autoantibody elimination in a patient with severe pulmonary renal syndrome due to ANCA associated vasculitis. After high-dose application of intravenous immunoglobulins (IVIGs) prior to plasma exchange treatment, efficacy of myeloperoxidase (MPO)-ANCA autoantibody elimination was substantially increased, associated with rapid clearance of MPO-ANCA autoantibodies. High-dose IVIGs resulted in marked reduction of MPO-ANCA autoantibody levels and did not directly affect autoantibody clearance by plasma exchange itself, as also confirmed by comparable MPO-ANCAs in the exchange fluid relative to serum levels. Moreover, measurements of serum creatinine and albuminuria confirmed that high-dose IVIGs were well tolerated and did not exacerbate kidney injury.

Discussion: We are aware that our observations require validation in larger study populations, that kinetics may have also been affected by previous induction therapy, pretreatment time of IVIGs or ANCA autoantibody subtypes, and that the exact mechanisms contributing to our observations require further investigation. Furthermore, the immunosuppressant is not fully accurate due to values higher than the manufacturer’s reference range. Nevertheless, this ANCA level-driven approach might contribute to novel therapeutic strategies to increase efficacy of pathogenic ANCA autoantibody clearance in severe AAV.

SA-PO867
Extreme Fatigue as the Only Complaint in Double-Positive Anti-Glomerular Basement Membrane (GBM) and ANCA Disease: An Unusual Presentation
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Introduction: Acute glomerulonephritis (GN) due to anti-glomerular basement membrane (GBM) disease is extremely rare with reported incidence of one per million. Double positive disease with anti-GBM phenotype on kidney biopsy and ANCA positive titers on serology is reported to present in older population with high relapse rates compared to anti-GBM disease alone. Extreme fatigue as the only presenting complaint is uncommon, here we present one such case.

Case Description: 76 year old female who leads an active life-style presents to her PCP’s office with extreme fatigue of 3 weeks duration. Initial work-up revealed AKI with serum creatinine of 4.19 mg/dL. She was admitted for further evaluation. Urinalysis was +ve for large blood, >10 RBCHP, and protein. She received IV fluids, serology for GN work up was sent and discharged home. She was re-admitted later as myeloperoxidase (MPO)-ANCA titers were reported positive. Kidney biopsy revealed crescentic GN with 85% glomerular involvement. Treatment was initiated with pulse steroids, rituximab and plasma exchange for ANCA vasculitis till kidney biopsy findings confirmed anti GBM disease (Figure 1), anti-GBM titer results following a few days after kidney biopsy. Response to treatment is shown in Figure 2.

Discussion: Double-positive vasculitis with anti-GBM and ANCA is rare. Our patient did not have any lung involvement. While Rituximab alone for induction is not commonly reported in double positive disease, our patient was extremely frail and hence did not receive cyclophosphamide. A high degree of clinical suspicion for acute GN is needed when elderly patients present with AKI and an abnormal UA, extreme fatigue could be the only complaint.

Figure 1: Kidney biopsy findings
A. - Trichrome stain showing glomeruli with crescents; and fibrocellular (85% cellular crescents noted). B. - Diffuse linear IgG-GBM deposition by immunofluorescence.

Figure 2
SA-PO869
Non-Hepatitis C Virus (HCV)-Related Mixed Cryoglobulinemic Vasculitis with Biopsy-Proven Renal Involvement: The Effects of Rituximab
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Background: Remarkable results in severe HCV-related cryoglobulinemic vasculitis have been obtained with Rituximab. Details of the clinical characteristics and effective treatment of non-HCV-related cryoglobulinemic syndromes are presently lacking.
Methods: This paper reports on a prospective single-Center open study aimed at evaluating the clinical presentation and effects of Rituximab administered alone in patients with severe non-HCV-related cryoglobulinemic syndrome.
Results: The study group included 11 patients followed for at least 6 months. Three patients had type I cryoglobulinemia, 6 had type II and the remaining 2 patients had type III HCV-related mixed cryoglobulinemic vasculitis. All 11 patients presented with biopsy-proven renal involvement, 4 out of 11 with leukocytoclastic vasculitis, and 8 with involvement of the peripheral nervous system. Renal biopsy revealed diffuse membranoproliferative glomerulonephritis (MPGN) in 9 out of 11 patients. Extracapillary proliferation and necrosis of the glomerular tuft was observed in 1 of these 9 cases. Interstitial nephritis together with mesangial expansion and capillary immune deposits were observed in 1 patient. Prevalent interstitial fibrosis and glomerular sclerosis were detected in the remaining case. Patients underwent treatment with Rituximab alone. After 6 months we observed a remarkable improvement in the necrotizing skin ulcers and a substantial amelioration of the electrophysiologic parameters of motor and sensory peripheral neuropathy. Improvement in both renal function (from 2.8 to 1.4 mg/dL, p < 0.001) and proteinuria (from 4.2 to 0.2 g/dL, p < 0.001) was observed in 9 out of 11 patients while 1 could not be fully treated because of a severe infusion reaction and sudden development of anti-Rituximab antibodies. Good renal response was confirmed at the end of follow-up (38.4 months). Three patients had a relapse at 6, 12, and 48 months, respectively.
Conclusions: In our cohort the administration of 4 once-weekly infusions of Rituximab followed by 2 more infusions after 1 and 2 months proved to be effective in the management of these rare patients.
SA-PO870
Safety and Efficacy of Avacopan in Patients 65 Years and Older with ANCA-Associated Vasculitis
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Background: Older adults are at increased risk of glucocorticoid (GC)-related toxicity; minimization of GCs is a major focus for treatment of patients with ANCA-associated vasculitis (AAV). Although AAV especially affects older adults, many studies have excluded patients ≥75 years (y). In the Phase 3 ADVOCATE trial of avacopan, there was no exclusion criterion for maximum patient age.
Methods: This post hoc analysis reports safety and efficacy of avacopan compared to a prednisone taper in the subgroups of patients 65-74y (N=109) and ≥75y (N=51).
Results: In both studied age and treatment groups, a similar proportion of patients (69-73.1%) achieved remission at week 26 (Table 1). In the 65-74y age group, sustained remission rates at week 52 were 55.1% in the prednisone arm and 65.0% in the avacopan arm. Relapse rates were 18.8% in the prednisone arm and 12.3% in the avacopan arm. The total all-source median GC dose was 5.3x higher in the prednisone vs avacopan arm.
Conclusions: Safety and efficacy of avacopan in patients ≥65y demonstrated similar trends of efficacy and safety of avacopan as in the overall ADVOCATE trial, including reductions in GC-related toxicities, supporting a role for avacopan in the treatment of older patients with AAV.
SA-PO871
Efficacy and Safety Experience with Avacopan Beyond 52 Weeks in the Early Access Program (EAP)
Federico Alberici,1 Carlo Salvarani,2 Christine Chan,1 Achim Oebenberg,1 Tamara Popov,4 Università degli Studi di Brescia, Brescia, Italy;4Azienda Unità Sanitaria Locale - IRCCS Tecnologie Avanzate e Modelli Assistenziali in Oncologia di Reggio Emilia, Reggio Emilia, Italy;4CISL Vifor, Redwood, CA;4Vifor Pharma Management Ltd, Glattbrugg, Switzerland.
Background: Avacopan, a selective C5aR1 inhibitor, has demonstrated efficacy and safety over 52 weeks in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis responder, efficacy and safety data on avacopan beyond 52 weeks are currently limited. Here, we describe the experience with avacopan beyond 52 weeks from the EAP. Methods: Safety and efficacy in patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) were in the EAP were recorded in a global safety database (Ephesia DMS Software) from Feb 19 2019 – Aug 2023. Any events (AE) included a lack of effect and other events (i.e., relapse or worsening of disease).
Results: A total of 19 patients were treated with avacopan beyond 52 weeks within the EAP. Average age was 47 years, with 13 patients (68%) diagnosed with GPA and 6 (32%) with MPA. The median duration of therapy was 17 months (range 12–45). A total of 9 of AEs were recorded in 2 patients (10.6%) (Table 1). One vasculitis flare was recorded 6 months after avacopan initiation and coincided with an unintended dose reduction to 20 mg BID, due to a product supply issue during COVID. The event was well-managed with rituximab, with no additional use of glucocorticoids, and avacopan 30 mg BID was reinstated. No further cases of a lack of effect, worsening of disease, or disease relapse were reported. Data regarding concomitant medications did not indicate a decline in the patients’ status during treatment. No treatment discontinuations due to AEs were recorded. Other events (i.e., relapse or worsening of disease) were reported. Data regarding concomitant medications did not indicate a decline in the patients’ status during treatment. No treatment discontinuations due to AEs were recorded. No events of interest (i.e., new or changed AEs) were reported. Data regarding concomitant medications did not indicate a decline in the patients’ status during treatment. No treatment discontinuations due to AEs were recorded. Details of the clinical characteristics and effective treatment of patients ≥75y age group, sustained remission rates at week 52 were 56.0% in the prednisone arm and 65.4% in the avacopan arm. Relapse rates were 20.8% in the prednisone arm and 3.8% in the avacopan arm. Median GC dose was 4.8x higher in the prednisone vs avacopan arm. SAEs occurred in 14/25 patients (56%) in the prednisone arm and 17/26 patients (65%) in the avacopan arm.
Other results including renal and quality of life outcomes are in Table 1. Conclusions: A subgroup analysis of patients ≥65y demonstrated similar trends of efficacy and safety of avacopan as in the overall ADVOCATE trial, including reductions in GC-related toxicities, supporting a role for avacopan in the treatment of older patients with AAV.
SA-PO872
Avacopan in Combination with Rituximab and Low-Dose Cyclophosphamide for Treatment of Severe ANCA-Associated Glomerulonephritis
Amrita Dhutta,1,2 Maria Prendecchi,2 Fatima R. Shuaib,1 Marie B. Condon,1 Megan Griffith,3 Jeremy B. Levy,1 Nicholas R. Medjerall-Thomas,2 Lina Nikolopoulou,1 Tom Cairns,1 Stephen P. McArdle,3 Imperial College Healthcare NHS Trust, London, United Kingdom; Imperial College London, London, United Kingdom.

Background: Avacopan is approved in the USA and Europe as a novel treatment for ANCA-associated vasculitis. There are limited data regarding avacopan use in those with severe renal disease, and of ‘real-world’ experience using avacopan in combination remission-induction regimens.

Methods: Prospective cohort study of patients with ANCA-associated glomerulonephritis (ANCA-GN) treated at a single centre in London, UK from December 2022. Data presented as median (+/- IQR) unless otherwise stated.

Results: To date, 27 patients with ANCA-GN have received avacopan (median age 58 years [range 24-90]); 22 of 50 patients, 5 relapsing). Baseline parameters: BVAS 16 (IQR 12-19), CRP 61mg/dL (21-174), creatinine 258mol/L (149-391), eGFR 58 years [range 24-90]; 22 patients received combination induction treatment with rituximab (2g) and low-dose IV cyclophosphamide (median dose 2.2g [1.0-2.5]); 4 were treated with rituximab alone; 8 received adjunctive plasma exchange. Glucocorticoid (GC) use: The median dose of IV methylprednisolone was 0mg (0-500). 25/27 patients received oral prednisolone with median dose and duration of 270mg (210-420) and 8 days (7-16), respectively. Outcomes: The median duration of follow up is currently 2 months: 26/27 have achieved disease remission (BVAS <0.1 patients had progressive eGFR decline). Improvements in renal parameters were as follows: creatinine 152umol/L (125-257), eGFR 37ml/min/1.73m2 (23-48), uPCR 42mg/mmol (15-281). In those who presented with eGFR ≤20ml/min/1.73m2 ongoing analysis will examine long-term renal recovery in this subgroup.

Conclusions: This early series suggests that avacopan is well-tolerated and facilitates GC minimisation in patients with active ANCA-GN, in a non-trial setting, and in combination with rituximab and low-dose cyclophosphamide. Renal recovery was favourable in those presenting with eGFR ≤20ml/min/1.73m2. Ongoing analysis will examine long-term renal recovery in this subgroup.

SA-PO874
Pneumoecystis jirovecii Pneumonia Prophylaxis in Patients with ANCA Vasculitis on Rituximab Maintenance Therapy
Faten Agedel,1 Dustin Le,2 Duvuru Geetha.1 Johns Hopkins University, Baltimore, MD.

Background: Although an increased risk of Pneumocystis jirovecii pneumonia (PJP) has been reported in adults receiving rituximab, current evidence is lacking on the utility of PJP prophylaxis in ANCA patients on maintenance rituximab therapy.

Methods: We performed an observational, single-center, retrospective study examining outcomes of patients with ANCA on rituximab maintenance therapy with and without PJP prophylaxis. We included patients that were followed in our center from 6/1/2009-4/1/2023. Outcomes included PJP prophylaxis use, PJP infections, infections requiring hospitalization, death, and end-stage kidney disease (ESKD). Outcomes were analyzed using test, Fisher exact test, univariate, and multivariate logistic regression as appropriate.

Results: A total of 129 patients were included. The mean (SD) age was 62.5 (±16) years old and the mean (SD) follow-up was 7.2 (±4.5) years. 44% of patients received PJP prophylaxis, whereas 56% of patients did not. Trimethoprim-Sulfamethoxazole was used in 31% of patients, followed by Dapsone (7%), and Atovaquone (6%). In the PJP prophylaxis group, the mean (SD) duration of rituximab therapy was 3.6 (±2.5) years, and the mean (SD) prednisone dose was 0.06 mg (±1.87). In patients who did not receive PJP prophylaxis, the mean (SD) duration of rituximab therapy was 3.1 (±2.1) years, and the mean (SD) prednisone dose was 1.13 mg (±0.47). There were no PJP infections in the entire cohort. Lung infection was associated with increased odds of PJP prophylaxis prescription (OR 4.09 [95% CI 1.8-9.82]). CD4 count <200 cells/mm3 (n=5) and serum IgG level <500 mg/dL (n=32) were not associated with higher odds of PJP prophylaxis prescription (p=0.09 and p=0.08, respectively). PJP prophylaxis did not decrease infection rates requiring hospitalization, ESKD, or death. Corticosteroid use was associated with increased rates of infections requiring hospitalizations (OR 5.75 [95% CI 2.00-16.92]) and death (OR 4.49 [95% CI 1.26-15.82]) even after adjustment for age, gender, and PJP prophylaxis use.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: Regardless of use of PJP prophylaxis, PJP pneumonia was not observed in AAV patients receiving maintenance rituximab therapy. AAV patients with lung involvement were more likely to be on PJP prophylaxis. Additional studies are needed to confirm these findings to guide PJP prophylaxis use in AAV patients.

SA-PO875

EQUALISE Type B: Clinical Results of Itilizumab, a Novel Anti-C6D Therapy, in Subjects with Lupus Nephritis

Kenneth Kalunian,1 Srejith Parameswaran,2 Robert W. Levin,3 Nelson P. Kopyt,1 Stephen Connelly,1 Eugene Sun,1 Catherine Kim,1 Maple M. Fung,1 Manish Rath2
1University of California San Diego, La Jolla, CA; 2Jawaharlal Institute of Postgraduate Medical Education and Research, Pondicherry, India; 3University of South Florida, Tampa, FL; 4Leigh University, Bethlehem, PA; 5Equillium Inc, La Jolla, CA; 6Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Background: Itilizumab is a first-in-class, non-depleting, monoclonal antibody against the co-stimulator receptor C6D that blocks its interaction with ALCAM, to inhibit T<sub>reg</sub> cell activity and trafficking. It is being evaluated to treat immunoinflammatory diseases where T cells play a central role, including active proliferative lupus nephritis (apLN). We present results from EQUALISE (Type B; NCT01428579), a Phase 1b study of itilizumab in subjects with apLN.

Methods: 17 adult subjects with apLN (SIS/RPS class III or IV with or without class V) were enrolled. All were treated with open-label itilizumab 1.6 mg/kg SC Q2W for up to 13 IV treatments of MMF (2-3g/d) and corticosteroids (rapid taper to <prednisone 10mg/day by W10). Subjects had 12 weeks follow-up post dosing. Safety and efficacy were assessed.

Results: The median subject age was 34 years; 94% were female with 82% Asian; majority (66%) had class IV<sup>+</sup>V disease (47%). Mean duration of LN was 5.4 years with Baseline mean 24 hour urine protein of 4.9 g and eGFR of 104 ml/min/1.73 m<sup>2</sup>. Treatment was completed in 11 subjects with 4 discontinuing early (3 due to adverse event (AE) and 1 due to physician decision) and 2 still on dose at 88% of subjects experienced at least 1 AE, most common were peripheral edema and hypolactatemia. At least 1 low lymphocyte count was reported by 3 subjects (41%). Serious AEs occurred in 2 subjects (15%), including dehydration and COVID-19, with none deemed related to study treatment. Based on the 14 subjects that completed/terminated the study and had a post-baseline measure, there was a median 72% reduction in spot urine protein creatinine ratio (UPCR), resulting in high partial and complete response (PR and CR) rates (FIGURE). These responses occurred as early as prior to Week 4 on study.

Conclusions: EQUALISE Type B demonstrates that subjects with proteinuric apLN had high CR and PR rates with rapid and deep reduction in UPCR when itilizumab was added to MMF and steroids. Further controlled studies are warranted in this population at high risk of disease progression and end stage kidney disease.

Funding: Commercial Support - Equillium

EQUALISE Type B: % of responders at Weeks 12 & 36

SA-PO876

Long-Term Safety and Efficacy of Voclosporin in Black Patients with Lupus Nephritis

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Background: Black patients with lupus nephritis (LN) are reported to have more severe disease, are often refractory to treatment, and have worse long-term outcomes. Voclosporin in conjunction with low-dose glucocorticoids and mycophenolate mofetil (MMF) has shown significant benefit across ancestries and classes of LN. Here we report outcomes on up to three years of follow-up in patients identifying as Black and treated with voclosporin during the global Phase 3 AURORA studies.

Methods: Key inclusion criteria for the parent AURORA 1 study included biopsy-proven LN, urine protein creatinine ratio (UPCR) ≥1.5 g/g (≥2g/g for Class V) and estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m<sup>2</sup>. Patients completing AURORA 1 were eligible to enter the AURORA 2 continuation study on the same blinded therapy of voclosporin or placebo in combination with MMF and glucocorticoids for an additional two years. Programmed complete renal response (CR; UPCR ≤0.5 g/g, stable eGFR, low-dose steroids, and no rescue medication), partial renal response (PR; reduction in UPCR of ≥50% from baseline) and safety were assessed in patients self-identifying as Black or mixed Black.

Results: Twenty-six of 179 (14.5%) and 19 of 178 (10.6%) patients identified as Black or mixed Black in the voclosporin and control arms of AURORA 1. Baseline characteristics were similar between arms. CR rates at one year numerically favored voclosporin (46.2% vs 15.8%, OR 3.92 [CI 0.95, -9.99] p=0.0597) as did PR rates (69.2% vs 47.4%, OR 2.62 [CI 0.72, 9.45] p=0.1422). Eighteen voclosporin-treated patients and seven control-treated patients in the Black subgroup continued into AURORA.
Results: To date, 4 patients completed treatment, one patient discontinued treatment, and treatment is ongoing. Among 3/5 patients, 29 TEAEs occurred. All AEs were non-serious, except fever of unknown diagnosis in one patient. Injection site reactions arose in 3/5 patients—mild, mostly erythema. C4d/C4 ratio decreased with treatment in all 5 patients and returned to baseline after treatment cessation. Inhibition of C1q also resulted in normalization of downstream complement markers of activation and consumption for the entire pathway.

Conclusions: In this interim analysis, ANX009 administered subcutaneously was well tolerated and demonstrated C1q target engagement and complement inhibition in 5/5 patients; markers of all downstream active components, notably C3 and C5b-9, suggests the classical pathway, not the alternative pathway, is a key driver of complement activation in these LN patients. These interim results support further study of anti-C1q therapy in LN patients.

Funding: Commercial Support - Annexon Biosciences

SA-PO879

Long-Term Efficacy and Relapse in Lupus Nephritis Treated with Mycophenolate Mofetil and Tacrolimus Combination Therapy

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Background: Although recent research has shown the effectiveness of combination therapy with mycophenolate mofetil (MMF) and a calcineurin inhibitor for the initial treatment of active lupus nephritis (LN), its long-term outcomes still need to be explored.

Methods: We reviewed the medical records of 27 LN patients (4 males, 23 females) who underwent combination therapy with MMF and tacrolimus as an induction treatment from October 2009 to November 2018 in our department. Complete remission (CR) was defined by two criteria: 1) a urine protein to creatinine ratio (UPCR) of less than 0.5 g/gCr, and 2) a serum creatinine level (S-Cr) either normal or no more than 15% higher than the baseline. Both these criteria had to be met on the two consecutive visits. A relapse was defined as a doubling of UPCR and a 1.0 g/gCr on two consecutive visits or an intensification of immunosuppressive therapy after CR. Data are presented as median (IQR) or number (%).

Results: The median age was 38 (30-45) years, with 17 patients having new LN onset. Pre-treatment UPCR and eGFR were 4.21 (2.19-5.99) g/gCr and 62.6 (45.1-89.0) mL/min/1.73m², respectively. Renal histology (ISN/RPS 2003) showed: Class III in 1, III+V in 4, IV in 13, IV+V in 8, and V in 1. CR rates at 6 and 12 months were 59% and 74%, respectively. The combination regimen was administered for 25 (5.3-37.0) months, and the total observation period was 94.0 (63.0-111.5) months. During this period, one patient died from heart failure. No patient reached end-stage kidney disease or experienced a doubling of S-Cr. Although 26 (96.3%) patients achieved CR in total, 16 (59.3%) patients died from heart failure. No patient reached end-stage kidney disease or experienced a doubling of S-Cr. Although 26 (96.3%) patients achieved CR in total, 16 (59.3%) patients experienced a relapse. Kaplan-Meier analysis revealed that chronic lesions (A/C) in renal biopsy and the absence of a low C4 level were associated with relapse (P=0.006 and P=0.0007, respectively, by Log-rank test).

Conclusions: Combination therapy for LN was effective in inducing CR and preserving renal function over a long-term period. However, patients with chronic histological lesions or the absence of a low C4 level were more likely to relapse.

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

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Results: Overall, 446 patients were evaluated. High BL anti-C1q predicted a PERR with BEL or a CRR with PBO (Table). High BL levels of naïve B cells were predictive of PERR and CRR to BEL. Low BL plasmablasts, and a decrease in IgA at Wk 8 with BEL were predictive of PERR, and high BL levels of naïve B cells were predictive of PERR and CRR to BEL. Low BL plasmablasts, and a decrease in IgA or IgM at Wk 24 predicted a PERR in both groups and a decrease in IgA at Wk 24 predicted a CRR to BEL. A reduction in anti-C1q at Wk 52 and of sPCR at Wk 12 also predicted PERR and CRR in both groups. Changes in B-cell subsets were not predictive of a response in the BEL group. Changes of high levels of IgA and naïve B cells at BEL initiation, as well as early reductions in IgA, predicted attainment of PERR and/or CRR for BEL, but not PBO. Early reductions in sPCR predicted responses regardless of whether patients received BEL or PBO.

Funding: Commercial Support - GSK (GSK BEL1144054, NCT01939339)

| Table. Significant Bl biomarker and percentage change from BL to stated wk biomarker prediction of biomarker response at Wk 12 (treatment group). |
|---|---|---|---|
| Predicted | BL (n=229) | PBO (n=229) | BL (n=229) |
| IgA (g/g of Cr) | 0.565 | 0.565 | 0.565 |
| Odds ratio* | 0.506 | 0.506 | 0.506 |
| Change in IgA (g/g Cr) | 0.565 | 0.565 | 0.565 |
| Odds ratio* | 0.506 | 0.506 | 0.506 |
| Anti-C1q (μg/ml) b | 0.565 | 0.565 | 0.565 |
| Parameter estimate* | 0.565 | 0.565 | 0.565 |
| Odds ratio* | 0.506 | 0.506 | 0.506 |
| Change in anti-C1q (μg/ml) | 0.565 | 0.565 | 0.565 |
| Odds ratio* | 0.506 | 0.506 | 0.506 |
| Baseline plasmablasts (potential at BL) | 0.565 | 0.565 | 0.565 |
| Parameter estimate* | 0.565 | 0.565 | 0.565 |
| Odds ratio* | 0.506 | 0.506 | 0.506 |
| Change in baseline plasmablasts (potential at BL) | 0.565 | 0.565 | 0.565 |
| Odds ratio* | 0.506 | 0.506 | 0.506 |

Conclusions: High levels of IgA and naïve B cells at BEL initiation, as well as early reductions in IgA, predicted attainment of PERR and/or CRR for BEL, but not PBO. Early reductions in sPCR predicted responses regardless of whether patients received BEL or PBO.

SA-PO882
Outcome of Lupus Nephritis Patients Treated with a New Anti-CD40 Monoclonal Antibody According to Kidney Biopsy Features
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Background: Lupus Nephritis (LN) is responsible for SLE-related mortality and morbidity. A phase II trial tested different doses of the anti-CD40 monoclonal antibody BI655064 as add-on therapy to the standard of care in class III or IV LN patients with active renal disease. A post-hoc analysis showed that different potential biomarkers and therapeutic dosages were expressed differently. In this analysis, we predicted not only the efficacy of BI655064 but also the response of patients.

Methods: 101 renal biopsies of LN patients enrolled in the BI 655064 trial were scored centrally. eGFR and spot urine protein/urine creatinine ratio (UP/UC) were evaluated at every visit. Through a linear regression model (last available value vs. baseline), patients were divided according to their "Better" or "Worse" performance compared to the average. Biomarker parameters which differed between the two groups in the univariate analyses (p<0.1) were entered into a multivariate logistic regression model, and a routine model selection procedure (p<0.2) used to identify parameters predictive for proteinuria reduction or increase in eGFR (LN class IV vs III, Mesangial sclerosis, Lymphocytes, Microthrombi, Modified Chronicity index for UP/UC, Adhesions, Modified Activity index, Modified Chronicity index for eGFR). A logistic regression model adjusted for the same parameters was used to investigate whether the efficacy of BI655064 associated with the presence of renal monocytes.

Results: A lower modified activity index was predictive of UP/UC improvement (P=0.032); eGFR tended to be higher with a lower modified chronicity and a higher modified activity index. A higher treatment dose (BI655064 180/240mg vs Placebo/ BI655064 120mg) was associated with a greater proteinuria reduction when kidney biopsies contained glomerular monocytes (OR 3.72 (1.07–12.9), P=0.039). No substantial association between monocytes and eGFR change was detected.

Conclusions: In this post-hoc analysis, we showed that BI 655064 treatment in LN may improve the rate of proteinuria over time when monocytes are present in the biopsy, suggesting that specific renal biopsy characteristics could direct the choice of treatment for individual LN patients.

Funding: Commercial Support - Boehringer Ingelheim International GmbH, Biberach, Germany

SA-PO883
Abstract Withdrawn

SA-PO884
Atacicept in IgA Nephropathy (IgAN): Continued Protective Titers to Diphtheria and Tetanus vs. Placebo with a Focus on COVID-19
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Atacicept is a dual anti-BLyS/APRIL fusion protein currently in clinical development for IgA nephropathy (IgAN) treatment. Better understanding vaccine response and immunity with atacicept, especially to COVID-19, may help assess atacicept’s benefit risk profile. Atacicept has been studied in IgAN in the Phase IIa JANUS study which measured protective titers to diphtheria or tetanus toxin. Overall infections were balanced between atacicept and PBO. ORIGIN pts across atacicept and PBO arms had similar rates of overall and COVID-19 infections (Table). All pts with COVID-19 had protective to nonprotective status for diphtheria or tetanus toxin; overall infections were similar between atacicept and PBO. Atacicept 25, 75, or 150mg SC qw for 36w in ORIGIN (n=116). In JANUS, tetanus and diphtheria titers were measured at 1, 48 and 72w in addition to safety assessments. In ORIGIN, ORIGIN pts across atacicept and PBO arms had similar rates of overall and COVID-19 infections (Table). All pts with COVID-19 had protective to nonprotective status for diphtheria or tetanus toxin; overall infections were similar between atacicept and PBO.

Conclusions: Atacicept is a dual anti-BLyS/APRIL fusion protein currently in clinical development for IgA nephropathy (IgAN) treatment. Better understanding vaccine response and immunity with atacicept, especially to COVID-19, may help assess atacicept’s benefit risk profile. Atacicept has been studied in IgAN in the Phase IIa JANUS study which measured protective titers to diphtheria or tetanus toxin. Overall infections were balanced between atacicept and PBO. ORIGIN pts across atacicept and PBO arms had similar rates of overall and COVID-19 infections (Table). All pts with COVID-19 had protective to nonprotective status for diphtheria or tetanus toxin; overall infections were similar between atacicept and PBO.

Funding: Commercial Support - Boehringer Ingelheim International GmbH, Biberach, Germany

SA-PO884
Abstract Withdrawn
SA-PO885

IMAGINATION: A Global Phase 3 Trial of RO7434656, an Antisense Oligonucleotide Inhibitor of Complement Factor B, in IgA Nephropathy
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Background: RO7434656 (IONIS-FB-mex, ISIS 696441), a ligand-conjugated antisense oligonucleotide targeting complement factor B mRNA, was engineered for enhanced delivery to the liver as the primary site of factor B production. In a Phase 2 trial (NCT04014335), RO7434656 inhibited alternative complement pathway activation and enhanced delivery to the liver as the primary site of factor B production. In a Phase 2 trial (NCT04014335), RO7434656 inhibited alternative complement pathway activation and demonstrated a clinically meaningful reduction in UPCR resulting in a stable eGFR in patients with IgA nephropathy (IgAN). (Fig 1). Methods: IMAGINATION (NCT05797610), a Phase 3, randomized, double-blind, placebo-controlled trial will evaluate the efficacy and safety of RO7434656 in adults with biopsy-confirmed primary IgAN (placebo-controlled trial will evaluate the efficacy and safety of RO7434656 in adults with biopsy-confirmed primary IgAN). Fig 1: 428 patients will be divided into 2 cohorts: a primary cohort with eGFR ≥30 mL/min/1.73m² and an exploratory cohort with eGFR 20-29 mL/min/1.73m². Patients on maximally tolerated doses of ACEi/ARB will be randomized 1:1 to receive RO7434656 or placebo subcutaneously (SC) on Days 1, 15 and 29 and every 4 weeks (Q4W) thereafter for 105 weeks, with the option to continue double-blind or open-label treatment. The primary endpoint is change from baseline in 24h UPCR at Week 37. Key secondary endpoints include eGFR slope from baseline at Week 105, time to the composite kidney failure endpoint and patient-reported outcomes. Blood, urine and optional kidney biopsies will be collected throughout the study to assess biomarkers. Results: Expected upon study completion. Conclusions: The unique antisense modality and long tissue half-life of RO7434656 enables Q4W SC administration to inhibit the alternative complement pathway. IMAGINATION aims to evaluate the efficacy and safety of RO7434656 in adults with IgAN using a broad range of assessments over 105 weeks.

SA-PO886

Modeling Based on NefIgArd Two-Year eGFR Total Slope Predicts Long-Term Clinical Benefit of Nefecon in a Real-World IgA Nephropathy (IgAN) Population
Jonathan Barratt,1 Andrew M. Stone,2 Heather N. Reich,3 Richard A. Lafayette,4 College of Medicine Biological Sciences and Psychology, University of Leicester, Leicester, United Kingdom; 5Stone Biotestistics Ltd, Crewe, United Kingdom; 6Division of Nephrology, University Health Network, Department of Medicine, University of Toronto, Toronto, ON, Canada; 7Division of Nephropathy, Department of Medicine, Stanford University, Stanford, CA.

Background: Nefecon, a targeted-release budesonide formulation, is approved for the treatment of patients (pts) with immunoglobulin A nephropathy (IgAN). Data from the full Phase 3 NefIgArd trial showed that 9 months of Nefecon 16 mg/d preserved estimated glomerular filtration rate (eGFR) and reduced urine protein-creatinine ratio (UPCR) vs placebo. These effects were maintained during the 15-month off-drug follow-up period, indicating that Nefecon is disease-modifying. We conducted a modeling analysis to predict the potential long-term benefit of Nefecon on clinical outcome (i.e., a composite endpoint of end stage renal disease, eGFR <15 mL/min/1.73m², or sustained doubling of serum creatinine) in a real-world IgAN population. Methods: In the final analysis of the NefIgArd trial, there was a treatment benefit in 2-year eGFR total slope of 2.78 mL/min/1.73m² per year (95% confidence interval [CI] 1.39 – 4.17) with Nefecon vs placebo (linear spline mixed-effect model). This difference was applied to a published linear regression between treatment effects for the change in 2-year eGFR total slope and the log hazard ratio (HR) of clinical outcome, based on a meta-analysis involving >60K CKD pts (Inker et al. JASN 2019;30:1735-45). Median time to clinical outcome for a reference group receiving supportive standard of care (SoC) only was estimated by modeling long-term registry data from pts at Leicester General Hospital (LGH), UK, matching NefIgArd-recruited pts to individual LGH pt records based on their baseline UPCR and eGFR. Time to clinical outcome for SoC pts was estimated using a Weibull model. Results: 1,352/364 NefIgArd pts were matched with 886 unique records from 192 LGH pts, which contained 287 clinical event-times from 68 LGH pts. The NefIgArd 2-year eGFR total slope translated to a log HR for clinical outcome of 0.38 (95% CI 0.21 – 0.63), a 62% risk reduction vs placebo. Median time to clinical outcome was estimated at 9.6 years in SoC pts and 22.4 years in Nefecon-treated pts (median delay 12.8 [95% CI 4.8 – 27.9] years). 52% of SoC pts were predicted to have a clinical outcome within 10 years vs 24% of Nefecon-treated pts. Conclusions: Modeling analyses indicate that the clinical benefit seen with Nefecon predicts a substantial delay in progression to kidney failure.

Funding: Commercial Support - Vera Therapeutics

SA-PO887

Atacicept 150 mg Reduces Serum Gd-IgA1, a Biomarker Associated with Long-Term Outcomes in IgA Nephropathy (IgAN): 36W Results from the Ph2b ORIGIN Study
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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis and a significant contributor to ESRD worldwide, is characterized by elevated serum levels of galactose-deficient immunoglobulin A1 (Gd-IgA1). High Gd-IgA1 levels are associated with greater risk of renal function deterioration. Gd-IgA1 production is driven by the B Lymphocyte Stimulator (BLYS)-A PRofileration-Inducing Ligand (APRIL) signaling

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pathway’s effect on B cells and plasma cells. Atacicept is a dual anti-BLYS/APRIL fusion protein in clinical development for IgAN treatment. The Ph2b ORIGIN study of atacicept in IgAN met its primary endpoint. The objective of this analysis is to evaluate change in serum Gd-IgA1 quartiles over 36 weeks (w) with atacicept 150mg, the dose being evaluated in a pivotal Ph3 study, vs placebo (PBO).

Methods: The randomized, double-blind, Ph2b controlled Ph2b ORIGIN study included 116 patients (pts) with biopsy-proven IgAN, eGFR ≥30mL/min/1.73m², and proteinuria >0.75g/24h or UPCR >0.75g/g despite optimized renin–angiotensin system blockade. Pts were randomized 2:2:1:2 to atacicept 150, 75, or 25 mg vs PBO SC qw for 36w. At baseline (BL), 4, 12, 24, and 36w, Gd-IgA1 values were assessed and classified into quartiles using cutoffs derived from BL Gd-IgA1 values.

Results: Atacicept 150mg (n=30) achieved 64% mean Gd-IgA1 reduction vs 7% for PBO (n=29) at 36w (p<0.001) in pts with BL and 36w data. Atacicept 150mg led to steady Gd-IgA1 reduction to the lowest quartile 1 at 36w in 27/33 pts while most PBO pts transiently increased or decreased by 1 quartile (Figure). In the atacicept 150mg arm, 5/8 pts with BL quartile 4 had reductions to quartile 1 at 36w, while in the PBO arm 8/9 with BL quartile 4 remained in quartile 3 or 4 at 36w.

Conclusions: Atacicept 150mg achieved a durable and significant Gd-IgA1 reduction over 36w. Regardless of BL quartile, the vast majority of pts receiving atacicept 150mg for 36w had Gd-IgA1 reductions to the lowest quartiles, which has been associated with greater renal survival. These results provide further evidence supporting atacicept as a potential disease-modifying treatment for IgAN.

Funding: Commercial Support - Vera Therapeutics, Inc.

SA-PO888
Utilization of Corticosteroid Therapy in Patients with IgA Nephropathy and C1 Lesion
Jose Cabrales, Vivek Charu, Blake Shaw, Richard A. Lafayette. Stanford Medicine, Stanford, CA.

Background: IgA nephropathy (IgAN) frequently leads to chronic kidney disease and progressive kidney failure. Among the prognostic factors is the presence of crescents on renal biopsy, as a component of the MEST-C score, leading many to consider steroid treatment when crescents are found, even when seen in mild to moderate numbers (1-25%, C1 lesion). We wanted to assess if steroid treatment does indeed impact the outcome of IgAN patients with crescents.

Methods: Retrospective review of patient records from 2017-2022 who had biopsy proven IgAN with C1 lesions and adequate follow up was undertaken to assess patient characteristics, treatment and longitudinal follow up of outcomes of changes in eGFR and proteinuria. A multivariate model was created to relate steroid therapy to short to moderate term changes in kidney function (by eGFR slope).

Results: 68 of 176 consecutive patients met the study criteria, they had an average age of 41 years, 57% were women, mostly Asian, variable activity and chronicity in MEST characteristics, treatment and longitudinal follow up of outcomes of changes in eGFR and proteinuria.

Conclusions: We wanted to assess if steroid treatment does indeed impact the outcome of IgAN patients with crescents.

Funding: Private Foundation Support

SA-PO889
Kidney Outcomes with Corticosteroid Treatment in IgA Nephropathy
According to the Oxford-MEST-C Classification
Bancha Saitsarapi, Thapana Chueaboonchai, Narongrit Sirirattanasit, Narittaya Varothai, Naowanit Nata, Theerasak Tangwongler, Anmaat Chaiapraset, Ouppatham Supasaydh. Phramongkutklao College of Medicine, Bangkok, Thailand.

Background: Despite optimization of renin-angiotensin-aldosterone system (RAAS) inhibition, patients with IgA nephropathy remain at risk for kidney failure. The effect of steroids on kidney outcomes in IgA nephropathy with different renal pathologic lesions has been uncertain.

Methods: We retrospectively studied 67 patients with biopsy-proven IgA nephropathy who were receiving optimized RAAS inhibitor therapy and persistent proteinuria >1 g/day between January 2010 and December 2020. Clinical parameters including estimated glomerular filtration rate (GFR) decline were compared between corticosteroids and supportive treatment.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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SA-P0892

Analysis of the NefIgArd Part A Study Confirms Nefcon Reduces Levels of Dietary Antigen-Specific IgA in Patients with IgA Nephropathy
Viv Cottin, Irem Karaca, Roisin C. Thomas, Karen Molyneux, Jonathan Barratt, IgA Nephropathy Group. University of Leicester, Leicester, United Kingdom; University Hospitals of Leicester NHS Trust, Leicester, United Kingdom.

Background: Nefcon, the targeted-release formulation of budesonide, is delivered to the gut-associated lymphoid tissue (GALT) of the terminal ileum, a major site of immunoglobulin A (IgA) production. Results from the Phase 2b NEFIGAN and Phase 3 NefIgArd trials demonstrated that treatment with 16 mg/day of Nefcon significantly reduces proteinuria and loss of estimated glomerular filtration rate compared with placebo. A number of serum biomarkers have been measured in the 2 trials and many of those identified to be modulated by Nefcon in the Phase 2b NEFIGAN study have now been validated in Part A of the NefIgArd study. The aim of this study was to determine the effect of Nefcon treatment on serum protein levels and identify other potential biomarkers of IgA nephropathy (IgAN) disease activity.

Methods: Circulating levels of anti-gliadin IgA, anti-casein IgA, secretory IgA and a marker of gut permeability, fatty acid-binding protein 2 (FABP2) were measured in baseline serum samples and 3, 6, and 9 months after randomization during Part A of the NefIgArd trial using enzyme-based immunosorbent assays. Comparisons between placebo and Nefcon-treated groups were made at each study time point using unpaired t-tests, with a significance level of p<0.05.

Results: Treatment with Nefcon 16 mg/day significantly reduced levels of anti-gliadin IgA at 3 months (p<0.044), 6 months (p=0.029), and 9 months (p=0.027), and levels of anti-casein IgA at 9 months (p=0.023), compared with antibody levels at baseline. These data are consistent with Nefcon 16 mg/day results obtained in the Phase 2b NEFIGAN clinical trial. No significant changes were seen in levels of secretory IgA or FABP2.

Conclusions: Reductions in IgA antibodies against mucosally encountered antigens confirm a local mucosal effect of Nefcon in IgAN. This effect is likely mediated by a direct action on GALT B cell IgA production rather than an effect on gut permeability and increased antigen exclusion.

SA-P0893

Analysis of the NefIgArd Part A Study Confirms Nefcon Modulates Proteins Involved in the Intestinal Immune Network for IgA Production

Background: Nefcon, the targeted release formulation of budesonide, is delivered to the gut-associated lymphoid tissue (GALT) of the terminal ileum, a major site of immunoglobulin A (IgA) production. Results from the Phase 2b NEFIGAN and Phase 3 NefIgArd trials demonstrated that treatment with 16 mg/day of Nefcon significantly reduces proteinuria and loss of estimated glomerular filtration rate compared with placebo. A number of serum biomarkers have been measured in the 2 trials and many of those identified to be modulated by Nefcon in the Phase 2b NEFIGAN study have now been validated in Part A of the NefIgArd study. The aim of this study was to determine the effect of Nefcon treatment on serum protein levels and identify other potential biomarkers of IgA nephropathy (IgAN) disease activity.

Methods: Circulating levels of anti-gliadin IgA, anti-casein IgA, secretory IgA and a marker of gut permeability, fatty acid-binding protein 2 (FABP2) were measured in baseline serum samples and 3, 6, and 9 months after randomization during Part A of the NefIgArd trial using enzyme-based immunosorbent assays. Comparisons between placebo and Nefcon-treated groups were made at each study time point using unpaired t-tests, with a significance level of p<0.05.

Results: Treatment with Nefcon 16 mg/day significantly reduced levels of anti-gliadin IgA at 3 months (p<0.044), 6 months (p=0.029), and 9 months (p=0.027), and levels of anti-casein IgA at 9 months (p=0.023), compared with antibody levels at baseline. These data are consistent with Nefcon 16 mg/day results obtained in the Phase 2b NEFIGAN clinical trial. No significant changes were seen in levels of secretory IgA or FABP2.

Conclusions: Reductions in IgA antibodies against mucosally encountered antigens confirm a local mucosal effect of Nefcon in IgAN. This effect is likely mediated by a direct action on GALT B cell IgA production rather than an effect on gut permeability and increased antigen exclusion.
Conclusions: This systematic review demonstrates that incorporating TA in conjunction with other treatments, such as immunosuppressive therapy, is a successful strategy for managing severe renal involvement in CV patients. While PE, PP, and CF were all effective TA modalities, PE was the most commonly used approach.

SA-PO896

Mycophenolate Mofetil in Steroid Nonresponsive IgA Nephropathy
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Background: Immunosuppression use is suggested in patients of primary IgA nephropathy (IgAN) with persistent proteinuria≥1 g/day. We examined the role of mycophenolate mofetil (MMF) in steroid non-responsive IgAN.

Methods: In a retrospective study (2012-21) we included patients with primary IgAN who had received MMF for persistent proteinuria≥1 g/day despite treatment with oral steroids(1mg/kg/day) for at-least 8 weeks. All patients had received MMF 1-2g/day for at-least 3 months. Patients with C2 lesions were excluded. Primary outcome was deterioration of renal function defined as sustained decline in estimated glomerular filtration rate(eGFR) by ≥ 50% documented during at least 2 consecutive clinical visits with no recovery or progression to end stage kidney disease. Complete remission (CR) was defined as proteinuria <500 mg/d with stable eGFR and partial remission (PR) as proteinuria−1g/day, at least 50% reduction in proteinuria and decline of proteinuria to <3.5g/day with stable eGFR.

Results: 81 patients were included. Median age at presentation was 32(IQR 25-42) years and 67.9% were males. 67.9% had hypertension, 68(84%) had M1, 12(14.8%) had E1, 5(6.1%) had S1, 37(45.7%) had T1, 5(6.2%) had T2 and 16(19.8%) had C1 lesions. Median eGFR was 46.3(IQR 37.6-67.0) ml/min/173m2, median serum albumin was 3.9(IQR 3.4-4.3) g/dl and median proteinuria was 3.5(IQR 2.1-4.4) g/day at time of initiating MMF treatment. 70(90.1%) cases received renin angiotensin system (RAS) blockade therapy. 44(54.3%) patients achieved remission with MMF therapy (CR:24, PR:20) of whom 12/44(27.3%) relapsed. During a median follow up of 56.2 (IQR 30.8 to 96.1) months after diagnosis, 35(45.2%) patients had progressed to primary outcome. 53(63.2%) patients had adverse effects, 4 had diarrhea and 31 had infections. 7 patients developed tuberculosis.

Conclusions: MMF has limited efficacy in steroid non-responsive IgAN but with significant adverse effects.

SA-PO897

Mycophenolate Mofetil (MMF) and Corticosteroids in Crescentic IgA Nephropathy (IgAN)
Maria Jose Vargas-Brochez, Miriam Machado, Nancy Daniela Valencia-Morales, Ladan Zand, Yeshwanter Radhakrishnan, Maria Jose Sol,1 Fernando C. Fervenza, 1 Mayo Clinic Minnesota, Rochester, MN; 2 Hospital Clínico San Carlos, Madrid, Spain; 3 Hospital Universitari Vall d’Hebron, Barcelona, Spain.

Background: There is no gold standard for the treatment of crescentic IgAN.

Methods: Biopsy-proven crescentic IgAN patients treated with MMF plus corticosteroids 2000-2022(Figure1). Renal outcomes analyzed: hematuria, proteinuria, estimated glomerular filtration rate(eGFR), and end-stage kidney disease(ESKD) after one year.

Results: A total of 22 patients, 72.7% male, 86.4% white, age 38.9±15.3 years. Follow-up 3.9±2.2 years. Baseline serum creatinine(sCr) 2.0±0.78 mg/dl, and 100% had hematuria. Kidney biopsy showed MEST, M1 [90.9%], E1 [59.1%], S1 [86.4%], T0 [27.3%], T1 [27.3%], T2 [13.6%], C1 [72.7%], C2 [27.3%]. No previous treatment discontinuation. PH was defined as proteinuria <500 mg/d with stable eGFR and partial remission (PR) as proteinuria−1g/day, at least 50% reduction in proteinuria and decline of proteinuria to <3.5g/day with stable eGFR.

Conclusions: MMF plus corticosteroids is associated with 100% kidney survival at <3.5g/day with stable eGFR.

SA-PO898

Mycophenolate Mofetil in Immunoglobulin A Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
Marcelo A. Braga, 1 Nicole Felix, 1 Alleh Nogueira, 1 Jhonny W. Limachi Choque, 1 Sofia de Assis Oliveira, 1 Luis Claudio Santos Pinto, 1 Universidad Federal do Rio de Janeiro, Rio de Janeiro, Brazil; 2 Universidad Federal de Campina Grande, Campina Grande, Brazil; 3 Escola Bahiana de Medicina e Saude Publica, Salvador, Brazil; 4 Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of; 5 Centro Universitario Tocantinense Presidente Antonio Carlos, Araguaina, Brazil; 6 Centro Universitario Metropolitano da Amazônia, Belém, Brazil.

Background: Immunoglobulin A nephropathy (IgAN) is a prevalent primary glomerular disease worldwide. The efficacy of mycophenolate mofetil (MMF) for treating IgAN has yielded inconsistent findings in randomized controlled trials (RCTs).

Methods: In accordance with PRISMA guidelines, we systematically searched PubMed, Embase, Cochrane, and Web of Science in May 2023 for RCTs with long-term follow-up comparing MMF versus placebo or standard of care for IgAN with persistent proteinuria. Statistical analyses were performed using R software version 4.2.2.

Results: We included four RCTs comprising 276 patients with IgAN, of whom 51.81% were randomized to MMF. Average follow-up ranged from 24 to 72 months. MMF did not significantly reduce the incidences of end-stage renal disease (ESRD; RR 0.71; 95% CI 0.22-2.34; p=0.58; I2=53%; Fig. 1A) or doubling of serum creatinine (RR 0.53; 95% CI 0.18-1.56; p=0.25; I2=63%; Fig. 1B) as compared with placebo or standard of care in patients with IgAN.

Conclusions: In this meta-analysis of RCTs, there was no significant difference between MMF and placebo or standard of care in terms of ESRD and doubling of serum creatinine in patients with IgAN.
to October 2021. 60 nephrologists from China completed a structured online record for successive 387 IgAN patients, including treatment regimens and patient clinical characteristics.

**Results:** The proportion of different lines of treatments with ACEi/ARB, SGLT2i, corticosteroids and other therapy was analyzed and shown (Figure 1). Compared with EU5 and US, the proportion of ACEi/ARB use at first line was lower in Asia (EU5 84%, US 86%, China 74%, Japan 59%), while the use of corticosteroids in Asia as first line was higher (EU5 36%, US 44%, China 47%, Japan 63%). Main reasons to stop corticosteroids was when patient’s condition improved, treatment course completed, or side effects, of which weight gain (51%), acne (43%) and insomnia (30%) were most reported by Chinese nephrologists. Despite different lines of treatment, the proteinuria and eGFR levels were not well controlled (Table 1).

**Conclusions:** Despite attempts to alter various therapeutic regimens, IgAN remained poorly controlled. These data highlight an unmet need for the development of more effective drugs to treat and mitigate disease progression.

**Funding:** Commercial Support - Novartis Pharma AG

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**SA-PO999**

**Long-Term Follow-Up of Methylprednisolone (MP) Pulse and Mesenchymal Stem Cell (MSC) Therapy in Severe IgA Nephropathy**

**Byoung-Soo Cho,1 Won-Hee Cho,2 Dr. Cho’s Kidney Clinic, Seoul, Republic of Korea; 3 Soonmyung General Hospital, Seoul, Republic of Korea.**

**Background:** Up to date there is no specific treatment method for severe IgA nephropathy, but giving ARB, MRA, omega-3, antplatelet therapy, complement inhibitors, Neflexone, endostatin inhibitors, SGLT2 inhibitor etc. and eventually fall into ESRD and need dialysis or KTP. Cell based therapy especially autologous adipose derived stromal vascular fraction (SVF)/mesenchymal stem cells (MSC) is an emerging field in intractable immune-mediated disorders such as GVHD, multiple sclerosis, Crohn’s disease, osteoarthritis and even immune dysregulating infectious diseases, however reports in nephrology field are very rare. We firstly reported 2 years follow up results of MP pulse and MSC in severe IgAN in 2015 (ASN) with promising results. We tried MP pulse therapy followed by autologous MSC and follow up for 7 to 9 years in severe IgA nephropathy.

**Methods:** We selected severe IgA nephropathy as two groups, first group by clinical CKD stage 3B or more and A (and) or second group by pathologically severe group as Lee’s classification grade IV or V (B), and tried methylprednisolone pulse therapy followed by SVF/MSC one cycle of methyl PD pulse is (20-30mg/kg/day, max 1g/day) for 3 consecutive days. We tried to 17 cycles depends on the renal pathology, followed by autologous adipose derived SVF/MSC intravenously. Mean cell count was 3x10^7/ 

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**SA-PO900**

**Treatment of IgA Nephropathy in Chinese Patients: Evidence from Real-World Data**

**Weimin Wang,1 Runui Li,2 Ping Li,3 Fei Gao,2 Serge Smeets,3 Anечка T. George,4 Jonathan de Courcy,1 Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; 2 Beijing Novartis Pharma Co., Ltd., Shanghai, China; 3 Novartis Pharma AG, Basel, Switzerland; 4 Novartis Healthcare Private Limited, Hyderabad, India; 5 Adelphi Real World, Bollington, United Kingdom.**

**Background:** Immunoglobulin A nephropathy (IgAN) accounts for more than 50% of primary glomerulonephritis in China1. The aim of this real-world study was to describe and compare the treatment strategy of Chinese nephrologist with nephrologists across the world for patients with IgAN.

**Methods:** A point-in-time, cross-sectional survey utilizing data from Adelphi Real-world IgAN Disease-Specific Programme was conducted in China, Japan, United States (US) and Europe (EUS: France, Germany, Italy, Spain, United Kingdom), from June 2021 to October 2021. 60 nephrologists from China completed a structured online record for successive 387 IgAN patients, including treatment regimens and patient clinical characteristics.

**Results:** The proportion of different lines of treatments with ACEi/ARB, SGLT2i, corticosteroids and other therapy was analyzed and shown (Figure 1). Compared with EU5 and US, the proportion of ACEi/ARB use at first line was lower in Asia (EU5 84%, US 86%, China 74%, Japan 59%), while the use of corticosteroids in Asia as first line was higher (EU5 36%, US 44%, China 47%, Japan 63%). Main reasons to stop corticosteroids was when patient’s condition improved, treatment course completed, or side effects, of which weight gain (51%), acne (43%) and insomnia (30%) were most reported by Chinese nephrologists. Despite different lines of treatment, the proteinuria and eGFR levels were not well controlled (Table 1).

**Conclusions:** Despite attempts to alter various therapeutic regimens, IgAN remained poorly controlled. These data highlight an unmet need for the development of more effective drugs to treat and mitigate disease progression.

**Funding:** Commercial Support - Novartis Pharma AG

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**SA-PO901**

**Sparsentan as First-Line Treatment of Incident Patients with IgA Nephropathy: Preliminary Findings from the SPARTAN Trial**

**Chee Kay Cheung,1 Colleen Burns,2 Neeraj Dhawan,3 Sian V. Griffin,4 Alexandra L. Howson,1 Radko Komers,2 Alex Mercer,2 Matthew Sayer,2 Smeeta Sinha,2 Lisa C. Willcocks,3 Jonathan Barratt,1 University of Leicester & Leicester General Hospital, Leicester, United Kingdom; 2 Traverpe Therapeutics Inc, San Diego, CA; 3 Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; 4 University Hospital of Wales, Cardiff, United Kingdom; 5 JAMCO Pharma Consulting, Stockholm, Sweden; 6 Salford Royal Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom; 7 Addenbrooke’s Hospital, Cambridge University Hospitals, Cambridge, United Kingdom.**

**Background:** Sparsentan (SPAR) is a novel, non-immunosuppressive, single molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) approved by the US FDA for treatment of adults with IgA nephropathy (IgAN). SPARTAN is an open-label, single-arm, multi-center, exploratory trial, investigating the safety and efficacy of SPAR as first-line therapy in newly diagnosed IgAN patients. We report preliminary findings.

**Methods:** Patients were aged ≥18 yrs with biopsy-proven IgAN diagnosed within 6 months before enrollment, proteinuria ≥0.5 g/d, and eGFR ≥30 ml/min/1.73m^2 at screening. No previous treatment with ACEis/ARBs within the past 12 months was permitted. Patients receive SPAR for 110 wks with 4-wk safety follow-up. In addition to safety monitoring, assessments include proteinuria, estimated and measured GFR, 24h ambulatory blood pressure (BP), and total body water assessment (TBW, biopedimance). Renal and cardiac MRIs are performed at pre-defined time-points and repeat kidney biopsy at Wk 24.

**Results:** At data cutoff (4May2023) 6 patients had received ≥1 dose of SPAR with 12 wks follow-up. Mean (SD) age at enrolment was 42 (14) yrs (n=4 female). At baseline, median (IQR) proteinuria was 1.4 (0.6-2.0) g/d, mean (SD) eGFR 67 (27) ml/min/1.73m^2 and systolic/diastolic BP 122/80 (7/6) mmHg. Table 1 and Figure 1 summarize data over the first 12 wks. One patient discontinued due to hypotension.

**Conclusions:** As first-line treatment in newly diagnosed IgAN patients, preliminary findings show SPAR was safe and generally well-tolerated and reduced proteinuria >70% over 12 wks, with reduced total fluid and water over time.

**Funding:** Commercial Support - Traverpe Therapeutics, Inc.

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

Underline represents presenting author.

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**Table 1 Mean Proteinuria and eGFR levels in patients with different line* treatments**

**Table 1 Mean Proteinuria and eGFR levels in patients with different line* treatments**
SA-PO902
Sparsan and Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) in the PROTECT Open-Label Extension (OLE) Substudy and SPARTACUS: Trials in Progress

Isabelle Ayouby,1 Radko Komers,2 Alex Mercer,1 Priscila Preciado,3 Sydney C. Tang,1 Brad H. Rovin.1
1The Ohio State University Wexner Medical Center, Columbus, OH; 2Trave Therapeutics Inc, San Diego, CA; 3JAMCO Pharma Consulting, Stockholm, Sweden.

Background: Sparsan (SPAR) is a non-immunosuppressive, single-molecule dual endothelin and angiotensin II receptor antagonist (DEARA). In the ongoing PROTECT study, SPAR is compared to active control irbesartan in patients with IgAN. SGLT2i may slow disease progression in IgAN as suggested in subgroup analyses from DAPA-CKD and EMPA-KIDNEY. Combined DEARA and SGLT2i therapy may provide additional kidney-protective effects with unknown adverse events. Concomitant treatment with SGLT2i was prohibited during the PROTECT double-blind period (DB); however, SGLT2i are allowed in the OLE. We report the early clinical experience of SGLT2i added to ongoing SPAR treatment in patients with IgAN enrolled in the PROTECT OLE.

Methods: Patients who completed the PROTECT DB and met eligibility criteria were enrolled in the PROTECT OLE. All patients received SPAR with a target dose of 400 mg/day. Investigators, at their discretion, could initiate concomitant SGLT2i treatment at any time during the OLE. Body weight, systolic and diastolic blood pressure, and urine protein/creatinine ratio (UP/C) (based on 24-hour urine sample) were evaluated at baseline and at weeks 12, 24, and 36 after baseline. Baseline was defined as the OLE visit closest to SGLT2i start, ie, before or ≤14 days after. Treatment-emergent adverse events (TEAEs) were examined.

Results: At data cutoff, 21 patients (7 female) had received SPAR and add-on SGLT2i in the OLE. Mean (SD) age was 42 (11) years. Median (IQR) time from OLE start to SGLT2i start was 25 (11, 48) weeks. Summary data for selected variables are shown in Table. Eleven (52%) patients had TEAEs; most common were COVID-19, headache, hyperkalemia and hypotension in 2 patients (10%) each. Two patients discontinued SGLT2i and no patients discontinued SPAR.

Conclusions: Early clinical experience during the PROTECT OLE shows that SGLT2i added to stable dose of SPAR appears to be generally well-tolerated. Data are consistent with an additive benefit on proteinuria. A randomized sub-study within the PROTECT OLE will investigate the PROTECT OLE treatment set.

Funding: Commercial Support - Travere Therapeutics, Inc.
induction therapy. MEST-C scoring was performed by a single nephropathologist. The composite kidney endpoint was a 40% decline in eGFR, ESKD or eGFR < 15 ml/ min/1.73m².

Results: The baseline demographics, clinical characteristics and endpoints are shown in Table 1. Median duration of follow-up was 46 months (95% CI 20-84) in the full cohort. There was no significant difference in the proportion of patients with circulating anti-glomerular basement membrane antibodies across treatment groups (p=0.8). The only baseline difference between groups was in the severity of mesangial hypercellularity (MH) and crescentic involvement. MH was numerically lowest in the CT group and a25% crescents was numerically greatest in CYC group. The composite kidney endpoint was common, occurring in 60 (65%) of the total sample. Outcomes were similar across treatment groups, though there was a numerically lower risk for the composite kidney endpoint in the CYC group. The composite kidney endpoint was common, occurring in 60 (65%) of the total sample. Outcomes were similar across treatment groups, though there was a numerically lower risk for the composite kidney endpoint in the CYC group.

Conclusions: CYC may be superior for treatment of IgAN-C/IgA V-C. A randomized clinical trial is indicated to inform optimal therapy for this high-risk population.

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**SA-PO905**

**From Famine to Feast in IgA Nephropathy: New Treatments Present New Opportunities for Patients**

*Chris Dudzenksi, Meghan Weiss, Stephen Regan. Spheric Global Insights, Exton, PA.*

**Background:** As of only a few years ago, IgA nephropathy (IgAN), a common form of glomerulonephritis worldwide, had few treatment options beyond RAAS inhibitors and corticosteroids. The approval of SGLT2 inhibitors to treat non-diabetic CKD patients, genetic testing who were treated successfully with obinutuzumab. They were treated with LDL apheresis treatments via the Liposorber in addition to standard immune therapies. Atherogenic lipid metabolites (Lp-PLA2, oxLDL) and cytokines (TNFα, IL-6, IL-1β) were collected pre and post-treatment at set intervals and measured via ELISA. Proteinuria was measured by urine protein to creatinine ratio (UPC) and cystatin C GFR was monitored pre and at the completion of LDL apheresis treatment. Results expressed as meansSEM.

**Results:** OxLDL was reduced from 94.7 ± 3.0 to 78.6 ± 11.4 µL (p=0.019) at the completion of LDL apheresis. Lp-PLA2 showed a trend of reduction from 137.6 ± 36.8 to 117.0 ± 15.7 ng/mL (p=0.077). Interestingly, the mean baseline ox-LDL levels were significantly elevated, comparable to patients with extreme obesity. UPC was reduced from 10.3 ± 2.5 to 5.7 ± 1.8 mg/mg (p<0.005). Mean cystatin C GFR was 57 ml/min at baseline and was unchanged over the study period.

**Conclusions:** We demonstrated that children and adolescents with FSGS have elevated levels OxLDL and Lp-PLA2, increasing the risk for long term atherogenesis and cardiovascular morbidity. We propose that monitoring and normalizing these lipid metabolites will promote cardiovascular health in patients with FSGS. LDL apheresis represents a safe and effective method of reducing oxLDL and Lp-PLA2 in patients with FSGS. This was accompanied by a significant reduction in proteinuria inducing disease remission. Larger studies are needed to further assess the effects of LDL apheresis and antilipemic treatments on cardiovascular outcomes in this patient population.

**Funding:** Commercial Support - Kaneka Medical America LLC

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**SA-PO906**

**Low-Density Lipoprotein (LDL) Apheresis Removes Atherogenic Mediators in Focal Segmental Glomerulosclerosis**

*Jacob A. Humphrey,1 James Rose,1 Kelli A. Krallman,1 Joshua Zartitsky,2 Michael L. Mortitz,2 Stuart Goldstein,1 Efif Erkan,1* *1 Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2 Children’s Hospital of Pittsburgh of UPMC, Pittsburgh, PA; 3 Phoenix Children’s Hospital, Phoenix, AZ.*

**Background:** Focal Segmental Glomerulosclerosis (FSGS) is the most common cause of end stage kidney disease in adolescents. EdNA dysregulation causes cardiovascular morbidity and disease progression in FSGS. Unregulated lipoprotein associated phospholipase A2 (Lp-PLA2) activity causes increased oxidation of low-density lipoprotein (oxLDL) and production of inflammatory cytokines, leading to atherosclerosis and poor cardiovascular outcomes. However, this has not been explored in children with FSGS. We hypothesize that LDL apheresis can improve cardiovascular outcomes by removal of atherogenic mediators in patients with FSGS.

**Methods:** We enrolled 10 patients with FSGS from 4 centers (mean age 15.3 years, M:F 6:4). Five patients had post-transplant FSGS recurrence. Patients received 12 LDL apheresis treatments via the Liposorber in addition to standard immune therapies. Atherogenic lipid metabolites (Lp-PLA2, oxLDL) and cytokines (TNFα, IL-6, IL-1β) were collected pre and post-treatment at set intervals and measured via ELISA. Proteinuria was measured by urine protein to creatinine ratio (UPC) and cystatin C GFR was monitored pre and at the completion of LDL apheresis treatment. Results expressed as meansSEM.

**Results:** OxLDL was reduced from 94.7 ± 3.0 to 78.6 ± 11.4 µL (p=0.019) at the completion of LDL apheresis. Lp-PLA2 showed a trend of reduction from 137.6 ± 36.8 to 117.0 ± 15.7 ng/mL (p=0.077). Interestingly, the mean baseline ox-LDL levels were significantly elevated, comparable to patients with extreme obesity. UPC was reduced from 10.3 ± 2.5 to 5.7 ± 1.8 mg/mg (p<0.005). Mean cystatin C GFR was 57 ml/min at baseline and was unchanged over the study period.

**Conclusions:** We demonstrated that children and adolescents with FSGS have elevated levels OxLDL and Lp-PLA2, increasing the risk for long term atherogenesis and cardiovascular morbidity. We propose that monitoring and normalizing these lipid metabolites will promote cardiovascular health in patients with FSGS. LDL apheresis represents a safe and effective method of reducing oxLDL and Lp-PLA2 in patients with FSGS. This was accompanied by a significant reduction in proteinuria inducing disease remission. Larger studies are needed to further assess the effects of LDL apheresis and antilipemic treatments on cardiovascular outcomes in this patient population.

**Funding:** Commercial Support - Kaneka Medical America LLC

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**SA-PO907**

**Obinutuzumab in Treatment-Resistant Primary Focal Segmental Glomerulosclerosis (FSGS): A Report of Four Cases**

*Yashwanth Radhakrishnan,1 Amit Sethi,2 Ladan Zandi,2 Fernando C. Fervenza,1 Mayo Clinic Minnesota, Rochester, MN; 2 University of Minnesota Twin Cities, Minneapolis, MN.*

**Background:** There is no definite approach in treating patients with primary FSGS who fail to respond to immunosuppressive (IS) therapy including corticosteroids and calcineurin inhibitors. Other IS therapy such as rituximab (RTX), Achar gel and mycophenolate have been used with sub-optimal response. Obinutuzumab is type II anti-CD20 monoclonal antibody that has been shown to be effective in treating patients who have been resistant to RTX in diseases such as ANCA associated vasculitis or membranous nephropathy.

**Methods:** We report 4 patients with treatment-resistant primary FSGS with negative genetic testing who were treated successfully with obinutuzumab. They were treated with an average of 4 other IS with sub-optimal response as shown in Table 1.

**Results:** The mean age was 48 years and 50% were males. The mean serum creatinine and mean serum albumin at the time of presentation was 2.2 mg/dl and 2.0 g/dl, respectively. The mean proteinuria at the time of diagnosis and before initiation of obinutuzumab was 10.7 ± 2.4 g/dl and 1.5 ± 0.9 g/dl, respectively. The mean proteinuria at 6 and 12 months after the infusion was 0.3 ± 0.2 g/dl and 0.5 ± 0.3 g/dl, respectively. Mean serum albumin improved to a mean of 4.0 g/dl and 4.3 g/dl at 6 months and 12 months respectively. None of the patients experienced any adverse effects or infusion reactions. CD20+ B cells remained depleted over an average of 10.5 months.

**Conclusions:** We report 4 cases of treatment-resistant primary FSGS that were treated successfully with obinutuzumab infusions with 1 complete remission and 3 partial remissions. The efficacy of Obinutuzumab on treatment-resistant FSGS should be evaluated through a randomized clinical trial to determine short- and long-term outcomes and adverse effects.
SA-PO908

**Intravenous Rituximab vs. Oral Mycophenolate Mofetil in Sustaining Remission in Calcineurin Inhibitor-Dependent Steroid-Resistant Nephrotic Syndrome: An Open-Label Randomized Controlled Trial**

_**Aditi Sinha, Arvind Bagga. Division of Nephrology, Dept of Pediatrics, Nephrotic Syndrome Study Group. All India Institute of Medical Sciences, New Delhi, India.**_

**Background:** Retrospective unicenter studies in patients with steroid-resistant nephrotic syndrome (NS) show that switching of calcineurin inhibitors (CNI) to oral mycophenolate mofetil (MMF) or IV rituximab enables remission and is corticosteroid- and CNI-sparing, while avoiding therapy-associated adverse effects (AE). However, prospective controlled studies are lacking.

**Methods:** This open-label multicenter RCT will examine the superiority of IV rituximab versus oral MMF in maintaining satisfactory remission in patients with steroid-resistant NS who were in complete or partial remission while on therapy with tacrolimus or cyclosporine for over 2-yrs, but continued to show steroid-sensitive relapses. Eligible consenting patients with steroid-resistant NS, 1-18 yr-old, with complete or partial remission and steroid sensitive relapses while on ≥2-yr therapy with CNI, will be randomized to switch therapy to either oral MMF for 1-yr or IV rituximab (2 doses a week apart; 1 dose 6-months later). The primary outcome, on intention-to-treat analysis, will be the proportion of patients with satisfactory remission (sustained remission or infrequent relapses) at 1-yr (Fig. 1). Secondary outcomes are the proportions of patients with frequent relapses, steroid resistance & serious AE, incidence of relapses, prednisolone exposure, and changes in anthropometry & biochemistry (CTRI/2022/10/046890).

**Results:** The study began enrolment in October 2022 and will close enrolment in February 2025.

**Conclusions:** Findings from the study shall have important implications for guiding the choice of non-nephrotoxic therapies following induction and maintenance of remission with CNI for childhood idiopathic steroid-resistant NS.

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

SA-PO909

**Monthly Mini-Dose Rituximab for Primary Membranous Nephropathy: A Different Approach**

_Song Wang, Zhenling Deng, Danxia Zheng, Sijia Zhou, Wen-Han Bao, Yue Wang. Peking University Third Hospital, Beijing, China._

**Background:** The currently recommended dose of rituximab for primary membranous nephropathy is as high as that for lymphoma. This study assessed the efficacy of monthly 100 mg rituximab monotherapy in patients with primary membranous nephropathy.

**Methods:** This retrospective study included 32 patients with primary membranous nephropathy treated at Peking University Third Hospital between March 2019 and January 2021. All patients were anti-phospholipase A2 receptor (PLA2R) antibody-positive and received rituximab 100 mg intravenously monthly for at least 3 months without other immunosuppressive therapy.

**Results:** The baseline parameters included: proteinuria, 8.5±3.6 g/day; serum albumin, 24.8±3.4 g/L; and anti-PLA2R antibody, 160 (20-2659) RU/mL. B-cell depletion was achieved in 87.5% patients after the first dose of rituximab 100 mg and in 100% after the second equivalent dose. The median follow-up was 24 months (range 18-38). Twenty-seven (84%) patients achieved remission, with 11 (34%) patients achieving complete remission by last follow-up. The relapse-free survival from the last infusion was 13.5 months (range 3-27). Patients were stratified into the low-titer (<150 RU/mL, n=17) and high-titer groups (≥150 RU/mL, n=15) based on the anti-PLA2R titer. Sex, age, urinary proteins, serum albumin, and estimated glomerular filtration rate at baseline did not differ significantly between the two groups. At 18 months, compared to the low-titer group, the rituximab dose (960±387 vs 694±270 mg, p=0.030) was higher, while serum albumin (37.0±5.4 vs 41.3±5.4 g/L, p=0.033) and the complete remission rate (13% vs 53%, p=0.000) were lower in the high-titer group.

**Conclusions:** Monthly rituximab 100 mg appeared as a potential effective regimen for treating anti-PLA2R-associated primary membranous nephropathy with a low anti-PLA2R titer.

**Funding:** Government Support - Non-U.S.
Felzartamab Reduces aPLA2R Ab by Selectively Depleting CD38+ Plasma Cells and Plasmablasts, the Main Pathogenic Cellular Drivers of Disease in Primary Membranous Nephropathy (PMN)

**Background:** Felzartamab (felza) is a fully human monoclonal antibody that binds to CD38 with high affinity and depletes CD38+ antibody-producing cells such as plasma cells/plasmablasts primarily via antibody-dependent cellular cytotoxicity & phagocytosis. In studies of high-risk PMN patients, felza substantially reduced aPLA2R with associated improvements in UPCR and serum albumin. To further characterize felza with respect to efficacy biomarkers and preservation of protective immunity, we analyzed samples collected prospectively during the M-PLACE (NCT04145440) and NewPLACE (NCT04733040) trials.

**Methods:** Serum and whole blood were collected pre/post-felza treatment in patients with aPLA2R+ PMN. Biomarker analyses were performed for aPLA2R (ELISA), total IgG (turbidimetry), anti-Tetanus Toxoid (TT) (ELISA), and B cell populations (flow cytometry).

**Results:** Felza reduced aPLA2R comparably in patients with baseline levels ≤150 and ≥150 RU/mL (Table 1). A dose-dependent effect on aPLA2R reduction at 6 months was observed across both M-PLACE (9 infusions) and NewPLACE (5 or 2 infusions). Depletion of detectable CD38+ plasmablasts was observed 1 wk after felza treatment. Treatment did not impact other B cell populations, as absolute counts of total, naive, and memory B cells were unchanged. Total IgG decreased on treatment then recovered above the protective threshold (0.1 IU/mL).

**Conclusions:** Felza selectively depleted CD38+ plasmablasts and plasma cells, reducing pathogenic aPLA2R to a greater extent than protective anti-TT titers and total IgG, which was dose-dependent and durable. Treatment of PMN with Felza suggests an efficient and selective treatment concept with preservation of vaccine response compared to conventional immunosuppressive therapies.

**Funding:** Commercial Support - Human Immunology Biosciences Inc, MorphoSys AG

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### Table 1. Median baseline values and % change in key biomarkers in M-Place and NewPlace trials

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Values</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>aPLA2R Ab (RU/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>206</td>
<td>+15</td>
</tr>
<tr>
<td>Middle</td>
<td>191</td>
<td>+10</td>
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<td>182</td>
<td>+5</td>
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<tr>
<td><strong>Total IgG (µmol/l)</strong></td>
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<tr>
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</tr>
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<td><strong>Ant-TT (IU/mL)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.4</td>
<td>-10</td>
</tr>
<tr>
<td>Middle</td>
<td>0.1</td>
<td>-20</td>
</tr>
<tr>
<td>High</td>
<td>0.0</td>
<td>-30</td>
</tr>
</tbody>
</table>

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SA-PO911

**Combined Rituximab and Cyclophosphamide Therapy in PLA2R-Associated Membranous Nephropathy (MN)**

**Background:** Optimal treatment of MN is debated: oral high-dose cyclophosphamide (CP) is effective (>90% immunological remission (IR)), but associated with toxicity. Rituximab (RTX) is less toxic, but also less effective (IR 65%). We evaluated the “McAdoo” treatment regimen (RTX 2×1000mg; CP 1.5mg/kg/day×8 weeks and prednisone (iv 2×1 gr+3 weeks oral starting at 1mg/kg) in high risk MN. In this preliminary analysis, we evaluated PLA2R and immunological remission, a surrogate biomarker for later onset clinical remission.

**Methods:** We assessed data of incident patients with MN, at high risk for progression, treated according the prescribed protocol. aPLA2R Ab levels were measured by ELISA in available samples collected at baseline (n=26), and 2 (n=18), 4 (n=20), 8 (n=20) and 12 (n=23) weeks after start of therapy.

**Results:** We included 26 patients (MF 15/11, age 60 [47-68] years, Scrntime 128 µmol/l [102-136], Salbumin 18 g/l [14-21] and UPCR 7.1 gram/10 mmol [5.7-10.0]). Baseline aPLA2R Ab levels were 176 RU/ml [115-460]. Overall, there was a very fast decrease of aPLA2R Ab levels, with a decrease >50% within 2 weeks in all but two patients. Within 8 weeks complete IR (ELISA < 2RU/ml) was 83 %. IR was associated with baseline aPLA2R Ab tertile (Table). The lower IR rate at 8weeks in patients in the highest tertile was not merely explained by the high baseline aPLA2R Ab levels, but more likely the consequence of a prolonged PLA2R half-life (Table). Most patients with high baseline PLA2R Ab levels have received additional therapy (mostly RTX 2×1) within 8 weeks after start of therapy may enable to identify patients who need more intensive therapy.

**Conclusions:** Our study showed early and high immunological response rate in patients with PLA2R associated MN. The longer T1/2 in patients with very high PLA2R Ab levels suggest immunological differences (increased B cell proliferation, presence of long-lived plasmacells). Assessment of PLA2R Ab levels within 2-4 weeks after start of therapy may enable to identify patients who need more intensive therapy.

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**SA-PO912**

**Analysis of the Efficacy and Influencing Factors of Rituximab in the Treatment of Primary Membranous Nephropathy**

**Background:** Membrane nephropathy (MN) is the most common primary glomerular disease that causes adult nephrotic syndrome in the world. Primary membranous nephropathy (pMN) can progress to end-stage renal disease. Rituximab (RTX) has been listed as the first-line treatment for patients with medium and high risk pMN.

**Methods:** This study retrospectively analyzed 83 patients with pMN in XX Hospital who were confirmed by renal biopsy and received RTX treatment. According to the clinical outcome, the patients were divided into complete remission (CR), partial remission (PR) and no response (NR). CR, PR were considered effective in treatment while NR was considered ineffective in treatment. The baseline values of patients with different clinical outcomes were compared to explore the influencing factors that affect the efficacy of RTX in the treatment of pMN patients.

**Results:** After a follow-up of 10.66 (7.25, 16.46) months, 65.1% of those pMN patients achieved clinical remission, of which 27.7% had complete remission and 37.3% had partial remission. Patients with effective treatment (CR, PR) showed a significant decrease in urinary protein creatinine ratio after RTX treatment, while creatinine and eGFR remained stable. Patients with ineffective treatment (NR) showed no decrease in urinary protein creatinine ratio after RTX treatment, while creatinine significantly increased and eGFR significantly decreased. During follow-up, 9 patients (10.8%) experienced infection related adverse reactions. Multivariate Cox regression analysis showed that the combined use of glucocorticoids (p=0.027, HR=2.05), serum albumin (p=0.006, HR=1.10), and urinary light chain LAMBDA/KAPPA ratio (>0.622)(p=0.011, HR=0.35) were independent influencing factors on the effectiveness of RTX in treating pMN patients.

**Conclusions:** RTX has a good therapeutic effect on pMN, which can reduce urinary protein and increase albumin in patients, maintain the stability of blood creatinine and eGFR, and have a low incidence of adverse reactions. The combined use of glucocorticoids, serum albumin and urinary LAMBDA/KAPPA ratio are independent factors affecting the effectiveness of RTX in the treatment of pMN.

**Funding:** Clinical Revenue Support
SA-PO913

Personalized and Standard Treatment of Rituximab in Primary Membranous Nephropathy: A Prospective Multi-Center Trial in the East Coast Region of China

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Background: Guidelines recommend standard rituximab therapy (1000mg/2 or 375mg/m2) for patients with idiopathic membranous nephropathy (IMN) at high risk of progression to ESRD. This study assessed the safety and efficacy of B cell and anti-PLA2R antibody targeted low-dose rituximab therapy in patients with IMN.

Methods: In this prospective study, we compared the partial and complete remission, serious and non-serious events between the personalized treatment group and standardized protocols group. Patients were followed once every 2 months for 12 months. The primary outcome was a composite of complete or partial remission of proteinuria. In addition, laboratory indexes and safety were assessed.

Results: A total of 101 were available for statistical analysis out of 140 participants at inclusion. At 12 months, 34 out of 55 patients (61.8%) in the personalized group and 29 out of 46 (63.04%) in the standardized group had complete or partial remission. Kaplan-Meier curves indicated no difference for the cumulative incidence of participants with IMN who progressed to the end point according to the two arms (Figure 2). The median (quartile) of total RTX dose at one year was 700 (600,1100) mg per patient with a total cost of RMB (yuan) 18786 (17388, 24378) per unit utility in the personalized group, which was progressed to the end point according to the two arms (Figure 2). The median (quartile) of total RTX dose at one year was 700 (600,1100) mg per patient with a total cost of RMB (yuan) 18786 (17388, 24378) per unit utility in the personalized group, which was statistically significant differences in the frequency of adverse events between groups (P=0.02).

Conclusions: B cell and anti-PLA2R antibody targeted rituximab therapy was as effective as standard protocols. It was a more economical and safer strategy for IMN patients.

Funding: Government Support - Non-U.S.

SA-PO914

Impact of Time to Treatment on Outcomes in Primary Membranous Nephropathy

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Background: Despite treatment, progression of renal dysfunction remains a significant burden globally in patients with primary MN (pMN). Clinicians use individualized risk assessment to choose immunosuppression therapy after ‘watchful wait’ to help avoid side-effects in those who could otherwise have achieved remission spontaneously. Here we describe features of renal disease during the ‘watchful wait’ period and its association with longer term outcomes.

Methods: Retrospective longitudinal cohort study of patients with pMN (biopsy-proven or positive serology in the absence of secondary causes). Data collected from three specialist centres in the North of England, with patients presenting as proteinuric kidney disease from Jan 2003 to July 2019, with follow-up data to Sept 2021. Risk markers included initial eGFR and baseline demographic and clinical features. Primary outcomes were CKD5 and Partial Remission (PR). Secondary outcomes were Progression (composite of doubling of creatinine, CKD5, and death). Analysis investigated the change in eGFR based on risk categorisation. Cox proportional hazard models were used to assess the association of outcomes with risk markers.

Results: 312 patients were included. Using eGFR and uPCR, patients in the low and moderate risk groups were more likely to achieve spontaneous PR (Fig 1A). The strongest predictor of renal outcome was eGFR at the start of immunosuppression (IS), irrespective of baseline function, and the longer patients waited to start treatment, the worse the renal decline (Fig 1B).

Conclusions: Combined eGFR and uPCR can be used to predict patients who are more likely to attain SR and that in patients who require IS, the longer it takes to initiate treatment, the worse their renal outcomes. This has significant implications for future guidelines in the management of pMN.

SA-PO915

Anticoagulation Thrombophrophylaxis Is More Effective than Antiplatlet Thrombophrophylaxis for Individuals with High-Risk Membranous Nephropathy

Ayman Al Jurdi,1 Christopher El Mounhayar,2 Karim Yatim,3 Orhan Efe,1 Saif A. Mulhsin,2 Leonardo V. Rieila,1 Reza Zonozi,1 Karen A. Laliberte,1 John Niles,1 Anushuya Jeyabalan,1 Massachusetts General Hospital, Boston, MA; 2 Brigham and Women’s Hospital, Boston, MA.

Background: Data on the use of apixaban and antiplatelet therapies for thromboprophylaxis in MN are limited.

Methods: We conducted a multicenter retrospective cohort study of all individuals with high-risk MN, defined as having a serum albumin nadir ≤ 2.5 g/dL in the setting of nephrotic-range proteinuria. The primary outcome was the incidence of thrombotic events within 12 months, stratified by thromboprophylaxis strategy.

Results: 66 individuals met the study’s inclusion criteria. Median serum creatinine was 1.2 mg/dL (IQR 0.9-1.5), median uPCR was 22.2 mg/g (IQR 8.5-16.6), and mean nadir serum albumin level was 1.9 ± 0.4 g/dL. 23 (35%) received no thromboprophylaxis, 20 (30%) received antiplatelet [AP] prophylaxis, and 23 (35%) received anticoagulant [AC] prophylaxis. Thrombotic events occurred in 11 subjects (17%). 1: in the AC group, 4 in the AP group, and 6 in the no prophylaxis group. No thrombotic events occurred in individuals who received apixaban (n = 11), while one individual in the warfarin group (n = 7) developed a recurrent ischemic stroke. The incidence of thrombotic events was lower in the AC group compared to both AP and no prophylaxis groups (log-rank P = 0.041, Fig 1A). In individuals with anti-PLA2R antibody-associated MN, higher anti-PLA2R antibody levels were associated with a higher risk of thrombotic events (Fig 1B) at various levels of serum albumin (Fig 1C). Three subjects had significant bleeding events, 1 in the AP group and 2 in the AC group.

Conclusions: AC prophylaxis, including apixaban, is associated with a lower risk of thrombotic events compared to AP or no prophylaxis in individuals with high-risk MN.
C3 Glomerulopathy Current Treatment Options and Real-World Management: Results from a Multi-Country Study

Richard A. Lafayette,1 Katharina Pannagl,2 Bríana C. Ndife,3 Serge Smeets,4 Kathleen Murphy,1 Jonathan de Courtye,1 Susanna Libby,1 Clare Proudfoot,1 1Stanford University School of Medicine, Stanford, CA; 2Novartis Pharmaceuticals Corporation, East Hanover, NJ; 3The University of Iowa Stead Family Department of Pediatrics, Iowa City, IA; 4Novartis Pharma AG, Basel, Switzerland; 5Adelphi Real World, Bollington, United Kingdom.

Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease, with an estimated incidence of 1-2/million/year. C3G is associated with a high risk of disease progression, approximately 50% of patients reach kidney failure within 10 years of diagnosis. KDIGO guidelines recommend treating with renin-angiotensin-aldosterone system inhibitors (RAASi) and in some patients, corticosteroids (CS) or mycophenolate mofetil (MMF), or eculizumab. This analysis aimed to better understand the treatment of C3G in the US, Europe, and Asia.

Methods: Data were drawn from the Adelphi C3G Disease Specific Programme, a real-world cross-sectional survey of C3G-treating nephrologists in US, France, Germany, Italy, Spain, UK (EU5), China and Japan from August 2022 to April 2023. Nephrologists completed forms via online links for consecutive patients presenting with C3G. Forms included patients’ demographics, clinical characteristics and C3G treatments.

Results: 111 nephrologists completed records for 385 C3G patients (US 100, EU5 321, China 60, Japan 36). 321 (83%) patients were receiving treatment at time of survey. Of these, median patient age was 41 years, and 60% were male. Median proteinuria was 1.3 g/day. 63% of patients had proteinuria ≥1 g/day. Of these, median patient age was 41 years, and 60% were male. Median proteinuria was 1.3 g/day. This highlights the need for targeted therapies to treat the root cause of C3G.

Conclusions: C3G is a rapidly progressing disease with no approved therapy. Most patients in this study were treated with both conventional immunosuppressants and biologics frequently added to RAASi. Despite this, proteinuria remained high, in most patients ≥1 g/day. This highlights the need for targeted therapies to treat the root cause of C3G.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Table 1: Current therapy and proteinuria levels by region

<table>
<thead>
<tr>
<th>Region</th>
<th>Treatment Initiation</th>
<th>Proteinuria (g/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (100)</td>
<td>LAASi, CS, MMF, ECZ</td>
<td>≥1</td>
</tr>
<tr>
<td>EU5 (321)</td>
<td>LAASi, CS, MMF, ECZ</td>
<td>≥1</td>
</tr>
<tr>
<td>China (60)</td>
<td>LAASi, CS, MMF, ECZ</td>
<td>≥1</td>
</tr>
<tr>
<td>Japan (36)</td>
<td>LAASi, CS, MMF, ECZ</td>
<td>≥1</td>
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SA-PO917
Change in GFR and UPC (Urinary Protein:Creatinine Ratio) Before and After Eculizumab in C3 Glomerulopathy

Tina Liu,1 Lauren O. Fergus,1 Monica D. Hall,1 Patrick D. Walker,2 Richard J. Smith,1,2 Carla M. Nester,1,3 University of Iowa Molecular Otolaryngology and Renal Research Laboratories, Iowa City, IA; 1Arkana Laboratories, Little Rock, AR; 2The University of Iowa Stead Family Department of Pediatrics, Iowa City, IA; 3University of Iowa Hospitals and Clinics, Iowa City, IA.

Background: C3 Glomerulopathy (C3G) is an ultra-rare kidney disease characterized by alternative complement pathway dysregulation. Most patients reach end-stage renal disease (ESRD) within 10 years of diagnosis. The complement inhibitor, eculizumab, has been used to treat C3G with mixed results. In this study, we compared differences in GFR and UPC trends in a cohort of C3G patients before and after eculizumab treatment.

Methods: 14 patients from the University of Iowa’s C3G Natural History Study were included in the cohort. Inclusion criteria: baseline native biopsy diagnosis of C3G and ≥2 years of clinical data (C3, GFR, UPC) prior to and after starting eculizumab. Exclusion criteria: treatment with other complement inhibitors, dialysis, and kidney transplant. Simple linear regression of the change in GFR and UPC before and after eculizumab initiation was measured. Paired t-test with p values were used to evaluate the significance of GFR and UPC change pre/post treatment; p ≤ 0.05.

Results: GFR changes per year pre/post eculizumab were insignificant (p = 0.201). Trends showed a pattern of GFR decline with a median difference from pre- to post-eculizumab of -0.47. UPC change per year was also not significant (p = 0.981). General patterns showed improvement with a median difference in UPC change per year pre/post eculizumab of -0.26.

Conclusions: Most patients showed no significant change in disease trajectory following eculizumab therapy. There was a general trend towards worsening kidney function following eculizumab, though with a slight decrease in UPC. Limitations include sample size and gross slope estimation with only simple linear regression. Future directions include examining the baseline C3G histology, complement biomarkers, and other clinical markers to determine if outcome may be predicted.

Funding: NIDDK Support, Private Foundation Support
SA-PO918

CPV-104, a Recombinant Variant of Human Complement Factor H Produced in Moss, to Be Studied in a Phase 1/2 Clinical Trial in Patients with C3 Glomerulopathy (C3G)

Karin Heidenreich,1 Björn Cochlovius,1 Martin Bauer,1 Andreas Busch,1 Paulina Dabrowska-Schleppe,1 Andreas Schaal,1 Fabienne C. Zeiter,1 Karsten Häffner,2 Joerg Koehl,3 Tilman Schmidt,4 Thorsten Wiech,4 Peter F. Zipfel.5 Eleva Clinical Trial Group.1 Eleva GmbH, Freiburg, Germany; 2Albert-Ludwigs-Universität Freiburg Medizinische Fakultät, Freiburg, Germany; 3Universität zu Lubeck Sektion Medizin, Lubeck, Germany; 4University Hospital Hamburg, Hamburg, Germany; 5Leibniz-Institute for Natural Product Research and Infection Biology, Jena, Germany.

Background: Human complement factor H (CFH) is the main regulator of the alternative pathway (AP). CFH deficiency is associated with several complement-mediated diseases, such as C3 Glomerulopathy (C3G) or atypical hemolytic uremic syndrome (aHUS). CF3G is caused by an uncontrolled overactivation of AP in fluid phase and on cell surfaces with overlapping clinical and pathophysiological features. AP dysregulation leads to predominant C3 fragment deposition within the glomeruli. C3G appears with proteinuria, microhematuria, acute kidney injury, and chronic kidney failure. About 50% of patients develop end-stage renal disease within 10 years. Recurrence of C3G after kidney transplantation is common. Currently there is no established disease-modifying treatment available. CPV-104 is produced in the suspension culture of moss Physcomitrium patens in 500L single-use bioreactors.

Methods: The current clinical program aims to develop CPV-104 for treatment of C3G. Preclinical in vivo (FH (-/-) knockout mice) and in vitro studies with CPV-104 demonstrated comparable or superior efficacy to that achieved with serum-derived CFH.

Conclusions: CPV-104 is a promising candidate for the 1st disease modifying treatment option in C3G. In preclinical studies CPV-104 demonstrated a strong potential to rebalance the dysregulated complement pathway, simultaneously maintaining its natural defense potential against infectious agents and pathogens. Following successful phase 1 and a proof-of-concept clinical trial in C3G, CPV-104 may also become a new treatment option for a broader spectrum of complement mediated diseases.

Funding: Commercial Support - eleva GmbH

Clinical Trial Design

SA-PO919

Outcome of Kidney Transplantation in Atypical Hemolytic Uremic Syndrome (aHUS): Eculizumab Prophylaxis vs. Rescue Therapy

Caroline Duineveld,1 Emily Glover,2 Romy N. Bouwmeester,1 Nicole Van De Kar,1 David Kavanagh,3 Jack F. Wetzels,1 Neil S. Sheerin,2 1Radboudumc, Nijmegen, Netherlands; 2Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom.

Background: Prophylactic eculizumab therapy is advised in aHUS kidney transplant recipients in view of high risk of recurrence. However, historical recurrence rates may be overrated and early start of eculizumab therapy at relapse (“rescue”) may prevent graft loss. The efficacy, safety, and costs of different treatment strategies have not been compared in RCT’s. We performed a comparative cohort study, including patients from a previously described Dutch cohort (NL) treated with eculizumab rescue therapy [PMID 37069997] and a UK aHUS cohort using eculizumab prophylaxis [PMID 36413152].

Methods: NL: we selected all adult aHUS patients who received a kidney transplantation between 2010-2021 in the Radboudumc (n=30) and enriched this cohort with 8 patients who received rescue therapy in other centers. UK: all adult aHUS patients transplanted between 2013 and 2017 were included.

Results: We included 38 NL patients (29 F, median age 45y, range 22-68) and 35 UK patients (24 F, median age 42y, range 17-64). Overall characteristics were comparable, although the UK cohort included more patients with a mutation in CFH SCR 20 / hybrid gene (31% versus 5%; p<0.01), whereas NL patients more often received a living donor kidney (66% versus 20%; p <0.001). The majority of the NL patients (74%) was transplanted using low dose tacrolimus (TAC). Eighteen (47%) NL patients were treated with eculizumab rescue therapy. Follow-up was comparable, NL 70.8m (range 10-134), and UK 55.4m (range 2-95). There were no significant differences in death-censored graft survival between the two cohorts (Figure).

Conclusions: Eculizumab rescue therapy was not inferior to eculizumab prophylaxis with respect to death-censored graft survival. Limitation: this conclusion holds for use of rescue therapy in a population characterized by low prevalence of “very high risk” genes, low TAC levels, and predominant use of living donor kidneys.

Funding: Commercial Support - This work was supported by research grants from the Dutch Board of Health Insurance Companies (Zorgverzekeraars Nederland), Government Support - Non-U.S.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO920

Ravulizumab Is Associated with Positive Clinical and Quality-of-Life Outcomes in Patients with Atypical Hemolytic Uremic Syndrome in a Real-World Setting

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Background: Ravulizumab (RAV) is a complement C5 inhibitor first approved in 2019 for the treatment of atypical hemolytic uremic syndrome (aHUS), a rare disease characterized by hemolytic anemia, thrombocytopenia, and organ damage. This study assessed real-world clinical and quality of life (QoL) outcomes in patients with aHUS treated with RAV.

Methods: Data were drawn from the Adelphi aHUS Disease Specific ProgrammeTM, a cross-sectional survey of physicians reporting on their consulting patients with aHUS (data collected August–December 2022). This analysis included physician-reported, patient data from Germany, Italy, Spain, the UK, and the USA. Patients included had physician-diagnosed aHUS and were treated with RAV at time of survey.

Results: Overall, 65 patients were included: 31 had switched from eculizumab (ECU; switch cohort) and 34 had not received ECU before RAV initiation (naive cohort). Median (range) age at time of survey was 34 (15–75) and 39 (14–66) years in the switch and naive cohorts, respectively; 10% (n = 29) and 16% (n = 32) had family history of kidney disease. For switch and naive cohorts, respectively, median (interquartile range) time from aHUS diagnosis was 531 (233–1043) and 257 (152–456) days and RAV treatment duration was 163 (93–293) and 201 (106–476) days; and time since aHUS diagnosis was 531 (233–1043) and 257 (152–456) days. Data from patient records showed high physician satisfaction with RAV (Table). In 84% of patients in the switch cohort, physicians reported higher satisfaction with RAV vs ECU (n=26, top reasons were fewer infusions required [92%] and less burden to patient/caregiver [54%]); no physicians reported higher satisfaction with ECU. From the patient survey, RAV satisfaction was 100% (switch cohort; n=8) and 83% (naive cohort; n=11).

Conclusions: There was concordance in high satisfaction with RAV between physicians and patients, regardless of prior ECU treatment. No dissatisfaction with RAV was reported.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease. The Disease Specific ProgrammeTM is an Adelphi Real World product. Alexion was a subscriber to the Disease Specific ProgrammeTM and did not influence the original survey through either contribution to the design of questionnaires or data collection.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
SA-PO922
Characteristics and Outcomes of Patients with Atypical Hemolytic Uremic Syndrome Switching to Ravulizumab from Eculizumab: A Global Registry Analysis
Franz S. Schaefer,1 Imad Al-Dakkak,2 Ekatetina Anokhina,2 David J. Cohen,3 Larry A. Greenbaum,4 Maria Arieta,5 Heidelberg University Hospital, Heidelberg, Germany; 2Alexion, AstraZeneca Rare Disease, Boston, MA; 3Columbia University Medical Center, New York, NY; 4Emory University School of Medicine and Children’s Healthcare of Atlanta, Atlanta, GA; 5Vall d’Hebron Hospital, Barcelona, Spain.

Background: There are currently no real-world cohort data on clinical characteristics and outcomes in patients with atypical hemolytic uremic syndrome (aHUS) who switched to ravulizumab (RAV) from eculizumab (EUC). This study aimed to address this need.

Methods: This was a post-marketing, observational, non-interventional, multinational registry study of patients diagnosed with aHUS who switched to RAV from EUC up to 27-Mar-23 (NCT01522183).

Results: Overall, 60 patients (24 pediatric) were included from Germany (45%), UK (18%), USA (18%), Denmark (10%), Spain (5%), and Israel (3%). Median (range) age at RAV initiation was 34 (2-72) years and 70% of patients were female. Overall, 58% of patients had a pathogenic variant or anti-complement factor H antibodies. Median (range) time on treatment was 21 (2–40) months for RAV and 62 (11–155) months for EUC. No new events of dialysis, kidney transplant, or thrombotic microangiopathy (TMA) relapse were reported during RAV treatment. Estimated glomerular filtration rates (eGFR) remained stable during the evaluation period (Figure).

Conclusions: Switching to RAV from EUC resulted in sustained maintenance of kidney function without evidence of new events of dialysis, kidney transplant, or TMA relapse over the median treatment period of 21 months. These results support the real-world effectiveness of RAV in patients with aHUS who switched from EUC.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease, Boston, MA, USA.

SA-PO923
Efficacy of 12-Week Pegcetacoplan in Kidney Transplant Recipients with Recurrent C3 Glomerulopathy (C3G) or Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN)
Andrew S. Bomback,1 Erica Daina,2 John Kanelis,3 David Kavanagh,4 Matthew C. Pickering,5 Gere Sunder-Plassmann,6 Patrick D. Walker,7 Zhongshen Wang,8 Zurish Ahmad,9 Fadi Fakhouri,10 Columbia University Irving Medical Center, New York, NY; 11Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; 12Monash Medical Centre Clayton, Clayton, VIC, Australia; 13National Renal Complement Therapeutics Centre, Newcastle University, Newcastle upon Tyne, United Kingdom; 14Imperial College London, London, United Kingdom; 15Medizinische Universität Wien, Wien, Austria; 16Arkana Laboratories, Little Rock, AR; 17Apellis Pharmaceuticals Inc, Waltham, MA; 18Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Background: Pegcetacoplan (PEG; C3 inhibitor) may prevent C3G or IC-MPGN progression. NOBLE (NCT04572854) is the first prospective randomized controlled trial of PEG vs standard of care (SOC) in kidney transplant recipients (KTRs) with primary C3G or IC-MPGN recurrence.

Methods: Adult patients (pts) were randomized 3:1 to subcutaneous PEG 1080 mg twice weekly plus SOC (n=10) or SOC only (n=5). Primary endpoint: reduction in renal biopsy C3c staining (a2 orders of magnitude [OOM]) from baseline to Week 12 (W12). Additional W12 endpoints: changes in eGFR, uPCR, C3G activity score, serum C3, and serum SC5b-9.

Results: 9 (69.2%) pts had C3G and 4 (30.8%) had IC-MPGN. At W12, 5 (50%) PEG pts had ≥1 OOM reduction in C3c staining (4 had 0 intensity), 8 (80%) had ≥1 OOM reduction (Figure). (90%) PEG pts had reduced C3G activity score at W12. In subgroup (≥1000 mg/g), uPCR decreased with PEG (-39.2%) at W12. eGFR remained stable, serum C3 increased, and SC5b-9 decreased with PEG (Table). There were no dose-limiting deaths due to treatment-emergent adverse events.

Conclusions: As early as W12, pegcetacoplan reduced C3c staining and proteinuria with stable eGFR, supporting the pathophysiology of C3 dysregulation, and was well tolerated in KTRs with recurrent C3G or IC-MPGN.

SA-PO924
Efficacy of Combined Rituximab (Anti-CD20) and Daratumumab (Anti-CD38) in Steroid-Resistant Nephrotic Syndrome and in Post-Transplant Recurrent FSGS
Andrea Angeletti,1 Maurizio Bruschi,1 Francesca Lugani,1 Enrico E. Verria,1 Gianluca Caridi,1 Edoardo La Porta,2 Shiuliya Kajana,3 Sonia Spinelli,4 Paola Magnaghi,5 Alberto Magnasco,5 Paolo Cravedi,5 Gian Marco Chioggeri,5 1Istituto Giannina Gaslini, Genova, Italy; 2University of Florence, Florence, Italy; 3Mount Sinai Health System, New York, NY.

Background: Multidrug-resistant nephrotic syndrome (MRNS) accounts for 15% of overall cases of nephrotic syndrome (NS) in childhood. MRNS is associated with high risk of kidney failure and recurrence after kidney transplant (KT). Common treatments, including rituximab and plasma exchange (PEX), are poorly effective.

Methods: We ran a phase II proof-of-concept clinical study (NCT05704400) including patients with MRNS (lack of antiproteinemic effect of therapy based on steroid plus CN1 and MMF for at least 12 months before enrolment) and post-transplant FSGS recurrence (FSGSr) resistant to rituximab and PEX. We administered rituximab (single infusion of 375 mg/m²) + daratumumab (single infusion of 10 mg/kg) in 8 patients: 5 with MRNS and 3 FSGSr (Figure). Rituximab continued for at least 2 years.

Results: We enrolled 8 patients: 5 with MRNS and 3 FSGSr (Figure). MRNS resulted resistant to previous infusion of rituximab alone (last infusion at least 9 months before enrolment). Combined rituximab + daratumumab therapy induced CR or PR in 3 and 2 subjects with MRNS, respectively (Figure). In 1 patient with other history of MRNS (5yrs), proteinuria remission was transient, but she refused a second treatment. All 3 FSGSr achieved CR/PR and PEX was stopped. Relapse occurred after 4 months in all pts. We repeated the combined treatment in 2 pts that after initial reduction, had a second relapse after 4 months. Therefore, administration of daratumumab alone obtained remission as well (Figure). Treatment was well tolerated and all patients are in active follow-up.

Conclusions: Combined treatment with rituximab and daratumumab is effective in inducing proteinuria remission in MRNS and FSGS recurrence. In KT, relapse-free time was 4 months and repeated infusions were needed. Therefore, targeting CD20 and CD38 may represent a valid therapeutic strategy in MRNS and FSGS recurrence.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only. Underline represents presenting author.
SA-PO925

The Type II Glycoengineered Anti-CD20 Antibody MIL62 or Cyclosorpin in Chinese Primary Membranous Nephropathy: Updated Results of an Ongoing, Multicenter, Randomized, Open-Label Phase Ib/2 Trial

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Background: A novel glycoengineered type II anti-CD20 antibody, MIL62 with a nearly completely afucosylated N-glycans in Fc region, has demonstrated superior activity compared with rituximab and obinutuzumab in vitro and in vivo, respectively. We have many clinical data of MIL62 in lymphoma, so we chose two doses to evaluate the safety, tolerability, and efficacy of MIL62 in pMN.

Methods: Eligible pts with pMN diagnosed by kidney biopsy, proteinuria of at least 3.5 g per 24 hours received intravenous MIL62 (two infusions, 600 or 1000 mg each administered 14 days apart; repeated at 6 months) or Cyclosorpin (CsA, starting at a dose of 3.5 mg per kilogram of body weight per day for 12 months). Patients were followed up for up to 104 weeks. The primary outcome was immunological remission (IR) at 12 weeks and a composite of complete or partial remission of proteinuria with stable eGFR at 24 weeks.

Results: From Feb. 23th, 2022 to Dec. 21th, 2022, 86 patients (pts) were randomly enrolled. As of Mar. 23th, 2023, median follow up time was 24 weeks. 22/35 (62.9%) pts in the MIL62 group and 6/18 (33.3%) pts in the CsA group achieved remission at 24 weeks (P<0.05). In the 69 pts positive for anti-PLA2R Abs (aPLA2R U/mL) at baseline, 41/47 (87.2%) pts in the MIL62 group achieved IR, which was superior to the CsA group [12/22 (54.5%), P=0.05] at 12 weeks. The remission to MIL62 in our study was faster than Rituximab-based therapy [23/35 (65.7%)] of patients achieved complete or partial remission at 24 weeks compared with the 33% (23/67) 6-month response rate reported in the Mentor study. Treatment-related adverse events occurred in 73.3%, 77.1% and 88.5% pts in the MIL62 600mg, MIL62 1000mg and CsA group respectively; no therapy-related deaths occurred.

Conclusions: The 12-week IR and 24-week overall remission of MIL62 was significantly higher than CsA, and had a manageable safety profile. A phase III clinical trial of MIL62 in pMN is ongoing (NCT05862233).

SA-PO926

An Exploratory Trial of an Investigational RNA Therapeutic, IONIS-FB-LRx, for Treatment of IgA Nephropathy: New Interim Results

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Background: Overactivity of the complement Alternative Pathway (AP) has been proposed to contribute to pathogenesis of IgA nephropathy (IgAN). An antisense oligonucleotide to complement factor B (FB), IONIS-FB-LRx (IIONIS696844, RO7434566) targets FB mRNA in the liver. IONIS-FB-LRx, treatment led to inhibition of AP and reduction in proteinuria in IgAN patients (2022 ASN Abstract#SA-PO714).

Methods: An exploratory, single-arm, multi-national open-label Ph2 study (NCT04014335) recruited patients with biopsy-confirmed IgAN, proteinuria>1.5 g/d, eGFR<60mL/min/1.73m2, and hematuria despite maximum tolerated RAAS blockade. Patients received monthly SC administration of IONIS-FB-LRx, for 24 weeks. Primary outcome was change in 24-hr proteinuria at Wk29 (4 weeks after last dose) compared to baseline (BL).

Results: 13 subjects have completed study to date, 25-62 yr, 40% Female, 7 Asian, and 6 White. There was a selective reduction of plasma complement FB levels, serum AP activity, urinary Ba and urinary sC5b-9 (mean % change of -69%, -36%, -92%, and -26% respectively). Median 24-hr proteinuria at BL was 1.80 g/g (IQR 1.23, 2.33 g/g). At Wk29, a 47% geometric mean ratio reduction was observed. There was no change in eGFR Wk29 compared to BL (meanSD IONIS-FB-LRx, but prior to use of SGLT-2 inhibitors (Wk27), demonstrated a 47% reduction in proteinuria. IONIS-FB-LRx demonstrated an acceptable safety profile with no Treatment Emergent SAE. The only clinically meaningful safety signal (moderate TEAE) was a reversible ALT elevation without a change in bilirubin in 1 subject.

Conclusions: This Ph2 open-label study provides continuing clinical evidence that IONIS-FB-LRx reduces complement levels and proteinuria in patients with IgAN, supporting Ph3 development (NCT05797610) to determine the potential of IONIS-FB-LRx to reduce the progression of IgAN.

Funding: Commercial Support - Ionis Pharmaceuticals

SA-PO927

Plasma Osteopontin Differentiates Active and Inactive Lupus Nephritis and Is Associated with Response to Therapy

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Background: New biomarkers are needed to differentiate activity from chronic damage in Lupus nephritis (LN) & to monitor response to treatment. Osteopontin (OPN) is an N-linked glycoprotein with integrin-binding ligands that has been identified as a potential biomarker of activity in systemic lupus erythematosus (SLE).

Methods: This is a diagnostic study with a cross-sectional and a longitudinal phase to describe the course of plasma (pOPN) & urinary OPN (uOPN) in a LN cohort. We recruited 62 patients with biopsy-proven active LN. As disease controls, we included 88 patients with non-renal activity, chronic LN on kidney biopsy, & inactive SLE. To evaluate the diagnostic yield of OPN we built ROC curves from the cross-sectional data. In the longitudinal phase, we included 36 active LN patients with prospective follow-up and plasma/urine samples collected at 3, 6, & 12 months. Response to therapy was evaluated at 6 & 12 months. Linear mixed models were fitted to evaluate the association between pOPN, uOPN, and response to therapy.

Results: Active LN patients had the highest levels of pOPN (81.18 ng/mL, IQR 53.73-169.46). Elevated pOPN levels correlated with SLEDAI-2K activity score (r=0.51, p=0.001), SLICC/ACR damage index (r=0.24, p=0.005), ISRN/RPS class IV LN (r=0.24, p=0.03), histologic activity index (r=0.46, p=0.001) and eGFR <60 mL/min/1.73m2 (r=0.35, p=0.001). There were no differences in uOPN between the groups. pOPN >58 ng/mL had 72% (95%CI 0.60-0.82) sensitivity and 81% (95%CI 0.71-0.88) specificity to distinguish active LN from inactive patients. The course of pOPN in responsive therapy was associated with the type of response, with continuous reduction in complete responders and persistent elevation in non-responders. There was no association between uOPN and response to therapy.

Conclusions: Plasma OPN correlates with LN activity, it has a fast reduction within the first 3 months of therapy and is associated with response to therapy.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only; Underline represents presenting author.
SA-PO928

Identification of New Therapeutic Targets of Arsenic Trioxide for Lupus Nephritis: Machine Learning Bioinformatics and In Vitro Studies
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Background: Lupus nephritis (LN) is a serious complication of systemic lupus nephritis (SLE). Preliminary study suggested that low-dose ATO treatment in active SLE patients was associated with reduced flare rates, but the underlying mechanisms have not well characterized.

Methods: The potential targets of differentially expressed genes (DEGs) from human SLE and LN PBMCs datasets were identified by bioinformatic analysis and network pharmacology. Characteristic hub genes were further selected using machine learning method. The relationship between the potential targets and immune cells was also examined.

Results: Twelve predicting immune related intersection DEGs in SLE were identified. KEGG pathway analysis indicated that ATO could attenuate IL-17 signaling pathway (p=1.67E-18), and TNF signaling pathway (p=5.77E-11) in SLE. Five genes of features importance were selected by three machine learning models, in which MMP9 showed the highest performance in predicting SLE development (ROC AUC: 0.942). MMP9 also showed positive correlations with macrophages and neutrophils in ssGSEA analysis (r=0.88 and 0.66 respectively). Our in vitro studies further demonstrated that ATO treatment downregulated MMP9 expression in PBMCs obtained from LN patients during disease remission (n=5).

Conclusions: ATO can attenuate LN via reduction of MMP9 expression in PBMCs and different inflammatory pathways.

Figure 1. Intersection immune associated genes of arsenic trioxide in systemic lupus erythematosus (SLE).

Figure 2. MMP9 was selected as the hub target in systemic lupus erythematosus (SLE).

SA-PO929

Genetic Determinants of Lupus Nephritis and Kidney Function in Systemic Lupus Erythematosus
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Background: Lupus nephritis (LN) is one of the most common and severe manifestations of SLE. We completed an LN genome wide association study (GWAS) in a multi-ethnic cohort of children and adults with SLE.

Methods: We included SLE patients from dedicated Lupus clinics and the SLICC cohort. All patients met ACR and/or SLICC SLE classification criteria and were genotyped on a multi-ethnic Illumina array. LN was defined by SLE criteria. Kidney function (eGFR) was estimated using the Schwartz Bedside formula for measures <18 years and CKD-EPI (without ancestry) for >18 years of age, collected longitudinally over time. Wilcoxon rank sum or Chi-square test were used for significance between LN and Non-LN patients. We completed GWAS of LN in marginal and multivariable adjusted regression models with principal components for ancestry, sex and cohort site.

Results: We included 2981 patients with SLE, 88% female, 46% of European ancestry, 27% childhood-onset SLE. LN was present in 45%. People at time of LN diagnosis were younger and more likely of African American or East Asian ancestry. People with LN had significantly lower within-person mean eGFR, greater eGFR variability and slope over time compared to those without LN (Table). GWAS of LN demonstrated a peak on chromosome 8, yet did not reach a genome-wide significance (p < 5x10^-8).

Conclusions: Our GWAS did not identify a significant locus for LN. We plan to repeat GWAS of repeated eGFR measures, as it is a more informative outcome that may improve power for detecting genetic loci for LN.

Funding: Government Support - Non-U.S.
SA-PO930

Discovery and Validation of Novel Circulating Auto-Antibodies in Lupus Nephritis Using Peptide Array Technology
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Background: Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN) are prototypes of autoimmune. Autoantibodies determining the first hit in LN have been identified; autoantibodies involved in renal progression remain an open issue.

Methods: We investigated sera of SLE, LN, rheumatologic and normal controls (20/20/60/40) using a high-density peptide array (17,402 peptides) covering the coding sequences of 464 proteins involved in rheumatologic/immunologic processes. The immune- fluorescence intensity was calculated by repeating incubation of sera with peptides 20 times to reduce variability for an overall of 348,040 peptide spots. The noise cutoff was set at IF=50. Validation of results was done by either specific assays (ELISAs) in many more patients (130 SLE, 91 LN) and by renal immunohistochemistry (12 LN).

Results: Overall, 133 proteins reactive with SLE and LN sera were identified by the peptide array. Annexin A1 (ANXA1) and Formin-like 1 Protein (FMNL1) had the highest probability to be true antigens. Anti-ANXA1 antibodies have been already associated with LN and SLE, FMNL1 is a new identified antigen. Anti-ANXA1 and anti-FMNL1 IgG2 (ELISAs) were high in serum of LN and SLE patients (LN > SLE); FMNL1 co-stained with macrophage markers (CD68) in glomeruli, high expression being associated with proliferative LN (stage IV). FMNL1 was recognized in macrophage cell lysates ‘in vitro’ by sera of LN patients with high anti-FMNL1 IgG2.

Conclusions: Overall, these findings show many potential antigens in SLE and LN based on an innovative peptide array technology. Circulating anti-ANXA1 and anti-FMNL1 IgG2 were high in both conditions. Anti-FMNL1 antibodies target a protein of macropolages associated with proliferative LN, suggesting that targeting cells potentially involved in tissue damage and/or repair might have a definite role in determining that disease outcome.

Funding: Government Support - Non-U.S.

SA-PO931

Disease Reactivation in Lupus Nephritis Correlates with Disease Biomarkers: Results from Two Observational Studies
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Background: Lupus nephritis (LN) is an autoimmune-mediated disease that can activate C1q and the classical complement pathway. Pathogenic anti-C1q antibodies (PACAs) are often present, amplifying classical pathway inflammation and contributing to progressive kidney damage. Elevated C4d and reduced C4 are markers of classical complement activation and consumption, respectively. For LN patients in the CLUES/UCSF Study, C4d/C4 ratio positively correlated with PACAs and urine protein-creatinine ratio (UPCR). To validate this correlation, the Sanguine Bio study was conducted.

Methods: Samples were collected from 40 LN patients (plus 20 healthy controls) from the CLUES/UCSF Study and 24 LN patients (plus 10 healthy controls) from the Sanguine Bio study. All samples were processed in a blinded fashion. For both cohorts, C4d/C4 ratio was measured using a high-density peptide array (17,402 peptides) and confirmed using specific assays. Demographic data and clinical informations were noted for all subjects. To validate this correlation, the investigators completed the immunohistochesmistry (IHC) stain of PLA2R, EXT-1 and NCAM-1. Demographic datas and clinical informations were also collected and evaluated.

Results: Among the 55 subjects, there are 52 subjects with successful HIC stain for EXT-1 and 49 subjects with successful HIC stain for NCAM-1. All the subjects are negative of IHC stain for PLA2R. EXT-1 and NCAM-1 expression could be found with 26.9% (14/52) and 2.0% (1/49), respectively. Comparing with other group, the positive rate of IHC stain for EXT-1 and NCAM-1 were postulated recently in lupus membranous nephropathy. Therefore, we conducted a prospective study to evaluate the prevalence of EXT-1/EXT-2 and NCAM-1 expression in patients with lupus membranous nephropathy.

Conclusions: This prospective investigation is conducted at a tertiary medical center in Taiwan. During the study period, there are totally 55 patients with pathologic diagnosis of lupus membranous nephropathy. In addition to routine histologic examination by experienced renal pathologist, the investigators completed the immunohistochesmistry (IHC) stain of PLA2R, EXT-1 and NCAM-1. Demographic data and clinical informations were also collected and evaluated.

Results: Among the 55 subjects, there are 52 subjects with successful HIC stain for EXT-1 and 49 subjects with successful HIC stain for NCAM-1. All the subjects are negative of IHC stain for PLA2R. EXT-1 and NCAM-1 expression could be found with ratio of 26.9% (14/52) and 2.0% (1/49), respectively. Comparing with other group, the positive rate of IHC stain for EXT-1 and NCAM-1 were postulated recently in lupus membranous nephropathy. Therefore, we conducted a prospective study to evaluate the prevalence of EXT-1/EXT-2 and NCAM-1 expression in patients with lupus membranous nephropathy.

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SA-PO933

Urinary sCD163/Creatinine Ratio Is a Potential Biomarker of Disease Severity in Patients with IgA Nephropathy
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Background: IgA nephropathy is the most common glomerular disease in adults. There are several prediction models postulated for IgAN but no one could be validated successfully. In addition, no any one biomarker was proved to predict severity and survival for patients with IgA nephropathy. Recently, one urinary metabolite from macrophage, soluble CD163 (usCD163) was found remarkably elevated in patients with IgA nephropathy. Gong et al demonstrate urine sCD163/creatinine ratio seems correlated to disease severity of IgA nephropathy. Thus, the investigator conducted a prospective study to elucidate the role of urine sCD163/creatinine in IgA nephropathy.

Methods: The investigators initiated a prospective cohort of glomerular disease at a tertiary medical center in Taiwan. Mid-stream spot urine sample was prospectively obtained before renal biopsy. During the study period, there are 150 subjects with pathologic diagnosis of IgA nephropathy. After exclusion as criteria, there are totally 70 subjects believed as primary IgA nephropathy was studied. Pre-stored urine sample were used to check the level of soluble CD163 and creatinine.

Results: The level of urine soluble CD163/creatinine could be divided into 3 tertiles. Between these tertiles, there are no remarkable difference in serum creatinine and GFR. Greater tertiles of usCD163/Cr have greater severity of hyperalbuninemia, proteinuria, hypercholesterolemia and hypertension. Greater tertiles of usCD163/Cr have also more obsoleted glomeruli, greater severity of tubulointerstitial fibrosis, and more crescents formation. ±50% decline of estimated glomerular filtration rate (eGFR) and entering dialysis during study period didn’t achieve statistical difference between 3 tertiles of usCD163/Cr. Survival analysis toward a 50% eGFR decline and entering dialysis, however, revealed lower survival probability in tertile 3 compared to tertile 1/2.

Conclusions: Urine sCD163/creatinine ratio seems correlated to proteinuria and the symptoms associated with nephrosis. It also correlated to histologic injury of glomerular sclerosis and tubulointerstitial fibrosis. Although there are no statistical significance of ±50% eGFR decline and entering dialysis between these tertiles, survival analysis proved that lower survival probability in tertile 3 compared to tertile 1/2.

SA-PO934

Urinary Proteomics Identifying Novel Biomarkers for Predicting the Activity of ANCA-Associated Nephritis
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Background: Despite the pathogenic role of ANCA in ANCA-associated glomerular nephritis (AAGN), it’s still challenging to determine the active stage. Urinary proteomics, specifically data-independent acquisition (DIA) proteomics, might be the non-invasive and efficient method to find potential biomarkers to identify the active AAGN.

Methods: The urine samples used for proteomic analysis were from patients diagnosed as AAV at Peking Union Medical College Hospital from May 2022 to April 2023. We performed LC-MS/MS analysis with quality control and identified differentially expressed genes (DEGs). Weighted gene co-expression network analysis (WGCNA), Least Absolute Shrinkage and Selection Operator (LASSO), and Random Forest analysis were used to figure out the target molecule and validated in the validation cohort by ELISA.

Results: In this study, 40 patients performed the urine DIA analysis, and the other 50 patients were in the validation group, with 56.7% female, with an average of 58.15 years old. In the 338 DEGs identified between AAV with and without renal involvement, the top pathways were the complement, coagulation cascade, and cholesteryl mechanism. After WGCNA, Lasso, and Random forest analysis, four urine proteins, marked complement factor D (CFD), coagulation factor II (F2), fibrinogen Alpha Chain (FGA), and plasminogen (PLG) were highly associated with AAGN in the active stage and confirmed by ELISA (Figure 1). The receiver operating characteristic curve (ROC) values of F2 combined CFD in AA V patients with active renal involvement was 0.922 (P<0.001) with a sensitivity of 75% and a specificity of 97.1%.

Conclusions: Several biomarkers from the complement and coagulation cascade might be potential urinary biomarkers for AAGN in the active stage.

Funding: NIDDK Support

Figure 1. ELISA analysis of F2, CFD, FBG and PLG.

SA-PO935

Citrullinated Histone H3-Positive Neutrophils May Be Associated with Disease Activity in ANCA-Associated Vasculitis

Background: Neutrophil extracellular traps (NETs) formation is reportedly involved in the onset of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV). Citrullinated histone H3 (H3Cit) is an important component of NETs. Previously, we reported that the presence of H3Cit (+) neutrophils is more specific in AAV than in other glomerular diseases and H3Cit staining is useful for identifying activated neutrophils. However, there were no detailed analysis of association between H3Cit neutrophils and AAV disease activity.

Methods: We selected kidney biopsy cases with AAV at Nippon Medical School Hospital during 2011 to 2022. Clinical findings included age, gender, serum creatinine (sCr) level, CRP, MPO/PR3-ANCA titer, and urinary findings (urinary protein (U-P) level, urinary β2-microglobulin (uβ2-MG)). Histological findings were assessed as follows: rates of global sclerotic glomeruli, crescent formation, interstitial fibrosis, and arteritis activity score. MPO (neutrophil marker) and H3Cit (NETs marker) staining were performed.

Results: A total of 49 cases with AAV were selected and were divided into two groups : H3Cit (+) group (n=44) and H3Cit (-) group (n=5) according to the presence or absence of H3Cit+ neutrophils in renal tissues. Clinically, sCr level and uβ2-MG level were significantly higher in the H3Cit (+) group although there were no significant differences in age, CRP, ANCA titer and U-P level. Histologically, H3Cit (+) neutrophils were observed in tubulointerstitial lesions in 43 cases, and in both tubulointerstitial lesions and glomeruli in 13 cases. Only one case showed glomerular involvement. H3Cit (+) neutrophils were observed mainly in peritubular capillaries, and around necrotic lesions of arteries and glomeruli. The rates of crescent formation and interstitial fibrosis were significantly higher in the H3Cit (+) group while there was no differences in rates of global sclerotic glomeruli and arteritis activity score.

Conclusions: The H3Cit (+) group exhibited significantly worse renal function and urinary findings, as well as higher tissue activity. The presence of H3Cit+ neutrophils serves not only a disease-specific marker but also a potential indicator of disease activity in AAV.

SA-PO936

Clinical Implication of Platelets and Complement C3 as Link Between Innate Immunity and the Coagulation System in ANCA-Associated Renal Vasculitis with Myeloperoxidase (MPO) ANCA Seropositivity
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Background: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a potentially life-threatening systemic small vessel vasculitis (SVV). It is well established that AAV patients feature an increased risk of developing thrombotic events, and platelets are activated in AAV patients being triggered by the alternative complement pathway. We here aimed to systematically assess the relevance of platelet counts and systemic complement system activation regarding distinct histopathological lesions in ANCA associated renal vasculitis (AAV).

Methods: A total of 53 patients with biopsy proven AAVR were retrospectively enrolled in a single center observational study. Multivariate regression analysis was performed to identify parameters associated with platelet counts in AAVR compared to disease controls. Finally, the relevance of platelets for disease course and recovery was assessed by survival analysis.

Results: Lower platelet counts correlated with markers of kidney injury including eGFR loss (p=0.0094) and lower complement C3 levels (p=0.0017). Multivariate and subgroup analysis revealed that this association was only present in the MPO ANCA subgroup (eGFR loss: p=0.009, lower C3: p=0.0032). Lower platelet counts correlated with interstitial fibrosis (p=0.0313), and tubulitis in areas of interstitial fibrosis and

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tubular atrophy (r=0.0035). Finally, we observed significant differences with increased requirement of kidney replacement therapy or death in the subgroup below median platelet counts (HR: 4.1, 95% CI: 1.6-10, p=0.0047), associated with a prolonged hospitalization in this subgroup (HR: 0.5, 95% CI: 0.3-0.9, p=0.0113).

Conclusions: Based on our observed association between platelets and complement system activation in the MPO ANCA subgroup, we here show an impact on disease course and histopathological lesions implying distinct damage modes in different subtypes of AAVR.

Methods: We used a 24-serum-sample quality-control set that spans the Gd-IgA1 concentration range reported in the literature. A 5-hour detection protocol for Gd-IgA1 has been validated using standard curves. This approach included intra- and inter-assay performance and serial measurements to ensure freeze-thaw stability. Additionally, multiple batches of key reagents were evaluated over time to ensure assay consistency.

Results: Our validation analysis demonstrated high-quality assay performance, with less than 10% plate-to-plate error. Furthermore, the assay demonstrated six-month stability of the components. The entire range of the calibrated assay was 29-2000 ng/mL. The lower limit of detection was determined to be 0.425 ng/mL. The lower limit of quantitation was 29 ng/mL. The GaD test is fully scalable to enable testing across multiple sample plates, dates, or users, and with same-day readout.

Conclusions: Our GaD test now brings the ability to measure serum Gd-IgA1 concentration to any laboratory while assessing the full spectrum of galactose-deficient IgA1 present in serum samples.

Funding: NIDDK Support

SA-PO939

Single-Cell RNA Sequencing Reveals Immune Cell-Specific Genes and Pathways Associated with IgA Nephropathy
Le Wang, Honghui Zeng, Yi Xiao, Siweiier Luo, Xiaoqiang Yang, Yiming Zhou. Sun Yat-Sen Memorial Hospital, Guangzhou, China.

Background: IgA nephropathy (IgAN) is one of the most common primary glomerulonephritis globally. Increasing evidence suggests the importance of host immunity in the development of IgAN, but its dynamics during the early stage of IgAN pathogenesis are still largely unclear. Single-cell RNA-sequencing is a high-throughput sequencing technology with cells as minimal units, which could be applied to explore the pathogenesis of IgAN.

Methods: Peripheral venous blood samples were collected from 6 healthy controls and 10 newly diagnosed IgAN patients. Peripheral blood mononuclear cells (PBMCs) were isolated by FACS sorting with above 80% cell viability. Then single cell RNA-sequencing was performed on the BD Rhapsody platform. Downstream analysis was performed with the Seurat V3.0. Meanwhile, the clinical data of the IgAN patients were co-analyzed with single-cell RNA-sequencing results. Experimental and research procedures were approved by and in accordance with the internal review board and human subject guidelines of the Sun Yat-sen Memorial Hospital and Sun Yat-sen University.

Results: First, we generated a single immune cell landscape of early IgAN. The differentially expressed genes (DEGs) between the control and IgAN groups were mainly related to the NK cell-mediated cytotoxicity and NK cell killing pathways. We found that decreased NK cell numbers and cytotoxicity genes. Interestingly, we discovered that NK cell numbers and marker genes were negatively correlated with many clinical parameters, including urinary protein creatinine ratio (UPCR) and serum galactose-deficient IgA1 and IgA. In contrast, DEGs of B cells were enriched in different viral infection pathways, and these B cell subgroup exhibiting the inhibition of NFκB signaling, was positively correlated with IgAN clinical parameters. In addition, a subpopulation of monocytes expressing interferon-inducing genes was positively associated with clinical severity of IgAN. Finally, we identified vast dynamics in intercellular communications of NK cells and monocytes in IgAN.

Conclusions: We constructed a landscape of peripheral blood mononuclear cells from early IgAN patients by using scRNA-seq and found significant alterations in the number and gene expression pattern of immune cells, some of which are closely related to clinical manifestations.

SA-PO940

Low eGFRcys/eGFRcreat Ratio Indicates Glomerular Filtration Impairment in the Patients with IgA Nephropathy

Background: Most glomerular diseases are characterised by disruption of the glomerular filtration barrier (GFB). The reduced pore size of GFBS as a result of endothelial damage is thought to result in lower clearance of medium-sized molecules (5000-3000 Da) such as cystatin C (cys) compared to small molecules (<900Da) such as creatinine (creat). Recently, GFR was used to determine the reduction in renal function. However, with less than 10% plate-to-plate error. Furthermore, the assay demonstrated six-month stability of the components. The entire range of the calibrated assay was 29-2000 ng/mL. The lower limit of detection was determined to be 0.425 ng/mL. The lower limit of quantitation was 29 ng/mL. The GaD test is fully scalable to enable testing across multiple sample plates, dates, or users, and with same-day readout.

Conclusions: Our GaD test now brings the ability to measure serum Gd-IgA1 concentration to any laboratory while assessing the full spectrum of galactose-deficient IgA1 present in serum samples.

Funding: NIDDK Support

SA-PO937

Clinical Application of IgA-Type Autoantibodies Against Mesangial Autoantigen, βII-Spectrin, in IgA Nephropathy
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Background: Half a century has passed since the first report of patients with IgA nephropathy (IgAN), however, the whole pathogenesis of IgAN remains elusive. In particular, the important question why IgA antibodies (Abs) are selectively deposited in the mesangial region, a hallmark of IgAN, remains unanswered. Recently, we have uncovered the answer to this critical question by identifying IgA type autoantibodies directed against mesangial autoantigen, βII-spectrin, in sera of patients with IgAN (Y. Nihei et al. Science Advances, 9, eadd7734, 2023). We confirmed that serum anti-βII-spectrin IgA was positive in 60% of patients with IgAN by Western blot. In present study, we aim to elucidate the specificity of serum levels of anti-βII-spectrin in patients with IgAN and to clarify clinical aspects of serum anti-βII-spectrin IgA.

Methods: To evaluate the specificity of anti-βII-spectrin IgA, serum anti-βII-spectrin IgA were measured by enzyme-linked immuno sorbent assay (ELISA) in patients with biopsy-proven IgAN (N=70) or other kidney diseases (N=32). The clinical parameters were compared between patients with IgAN who were positive for anti-βII-spectrin IgA and those who were negative. To test whether serum anti-βII-spectrin IgA titers correlate with disease activity, we compared the titers before and after steroid treatment in IgAN patients with positive for anti-βII-spectrin IgA.

Results: We found that 24 of 70 patients with IgAN have serum anti-βII-spectrin IgA while only 2 of 32 were positive for anti-βII-spectrin IgA in patients with other kidney diseases. No differences in eGFR, proteinuria, or histopathological findings were found between IgAN patients with positive and negative for serum anti-βII-spectrin IgA. To evaluate the specificity of anti-βII-spectrin IgA at the mesangial region, a hallmark of IgAN, we measured anti-βII-spectrin IgA by Western blot. In present study, we aim to elucidate the specificity of serum levels of anti-βII-spectrin IgA in patients with IgAN and to clarify clinical aspects of serum anti-βII-spectrin IgA.

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In contrast, and **Prevotella Anaerobutyricum**, in all of the individuals. In comparing between two groups, the abundance of genus level, there were 32 microbiomes that indicated a detection rate of more than 70%.

**SA-PO941**

**Exploring Differently Expressed Proteins in Plasma Extracellular Vesicles for Early Detection of IgA Nephropathy**

Chih-chin Kao, Taipei Medical University College of Medicine, Taipei, Taiwan.

**Background:** IgA nephropathy (IgAN) is the most common primary glomerulonephritis and may develop end stage renal disease. The overproduction of galactose-deficient IgA1 (Gd-IgA1) leads to the production of autoantibodies, resulting in the formation of nonglomerular immune complexes. Extracellular vesicles (EVs) are cell-derived membranous vesicles encapsulating various proteins, lipids, and miRNAs. We aimed to develop EV-biomarkers for the early diagnosis of IgAN.

**Methods:** Size exclusion chromatography was used for isolating plasma EVs. A total of 60 plasma samples from individuals with IgAN, chronic kidney injury (CKD), and control group were utilized in this study. Each plasma had been reduced by dithiothreitol (DTT), alkylated by iododeacetic acid (IAA), and digested by trypsin. Tryptic peptides were analyzed using nano-liquid chromatography-mass spectrometry. PEAKS Proteomics, Reactome Pathway Database, FunRich, and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to identify differently expressed proteins in IgAN patients.

**Results:** There were 86 differentially expressed proteins between the three groups. Of these, 92.9% of the cellular component was associated with the extracellular protein. After analyzing by Reactome Pathway Database, our results showed that the main functional pathways of the EVs from clinical plasma samples were the immune system pathway and the vesicle-mediated transport. We also compared the protein components of plasma-EVs from clinical samples. 12 out of 19 proteins showed significant differences, which may be served as EV markers for IgAN.

**Conclusions:** We have developed and validated a workflow to isolate plasma-EVs for proteomics analysis, and proteins that showed statistical differences among the three groups were identified. Potential EV biomarkers were discovered in this study and are undergoing validation as well.

**SA-PO942**

**Gut Microbiota Profiles Representing Pathogenic Severity in IgA Nephropathy Patients**

Yaejin Kim, Jin Hyuk Peak, Woo Yeong Park, Kyubok Jin, Seungyeup Han, Jung Pyo Lee, Dong Ki Kim. Keimyung University School of Medicine, Daeug, Republic of Korea; Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.

**Background:** Although immunoglobulin A nephropathy (IgAN) is not a definite genetic disease, it has an autoimmune trait of complex architecture with a solid genetic predisposition. Hence, we aimed to evaluate the difference in microbiota profile among patients with IgAN and healthy controls. In addition, we tried to evaluate the microbiome representing the disease severity.

**Methods:** We prospectively recruited subjects with IgAN and healthy control between July 2019 and December 2021. Gut microbiota was analyzed using the Illumina MiSeq system based on the 16S rRNA gene. We compared the abundance of the microbiome in each level of phylum, class, order, family, and genus between the groups using Mann–Whitney U test. Also, we tried to find a specific genus representing the disease severity based on the Oxford classification.

**Results:** A total of 87 subjects (IgAN 59, healthy control 24) were finally included in the study. The mean age was 40.3 and 38.1 years old in IgAN and healthy controls, respectively. The mean eGFR was 89.2 and 107.6 ml/min/1.73 m², respectively. At the genus level, there were 32 microbiomes that indicated a detection rate of more than 70% in all of the individuals. In comparing between two groups, the abundance of *Blautia, Anaerobutyricum, Dorea, Roseburia, and Clostridium* was higher in IgAN patients. In contrast, *Prevotella* and *Lachnospira* were significantly lower in IgAN patients. According to the Oxford classification, the microbiome responsible for the difference in the T score was discovered the most, while the microbiome responsible for the difference in the E and S score was discovered the least. The abundance of *Blausia* was higher in T1, *Prevotella, Lachnospiraceae, Escherichia, Kineothrix, Lachnospir* and *Veillonella* were lower in T1 compared to T0. In contrast, C. *Coprooccus* was detected at a higher level in E1, while *Parabacteroides* was detected at a lower level in S1.

**Conclusions:** The gut microbiota was well discriminated in subjects with IgAN from healthy controls. In addition, it was also differentially observed according to the status of the pathologic findings of IgAN. These results may provide a basis for further metagenomics analysis of IgAN.

**SA-PO943**

**Urinary Exosomal miRNA Signature of IgA Nephropathy: A Case-Control Study**

Mvthri Shankar, Institute of Nephrology, Bangalore, India.

**Background:** IgAN is a progressive disease. The current gold standard for diagnoses is kidney biopsy-invasive procedure with life-threatening complications. The hour needs a non-invasive, reliable, stable & accurate biomarker.miRNAs are small, non-coding endogenous RNA. Urinary exosomes are rich in miRNA and can be used as novel non-invasive biomarkers. We aim to study the urinary exosomal miRNA signature of pts with IgAN.

**Methods:** 50 biopsy-proven IgAN pts & 50 healthy controls were recruited in India. Urinary exosomes were isolated & miRNA extracted. Analysis was done with digital multiplexed nCounter® human miRNA Expression Assay which contains 799 unique miRNA barcodes. Lasso regression & consensus clustering were performed to discover significant miRNA.

**Results:** Mean age:36.8yrs. Male:Female=3:1. Mean creatinine & proteinuria : 2.2 mg/dl and 2.9 gms/day respectively. Majority miRNAs were significantly downregulated. A group of 5 candidate miRNAs hsa.miR.146b.3p+hsa.miR.599+hsa.miR.4532+hsa.miR.664b.5p+hsa.miR.221.5p which could successfully differentiate between IgAN cases and healthy controls with very high sensitivity and specificity.

**Conclusions:** The group of five candidate urinary exosomal miRNAs hsa.miR.146b.3p+hsa.miR.599+hsa.miR.4532+hsa.miR.664b.5p+hsa.miR.221.5p has the potential to serve as novel non-invasive biomarkers for IgA nephropathy.

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

**Model using the group of 5 miRNAs for diagnosis**

**Heat map showing the 5 miRNAs with biomarker potential giving a accuracy of 99%**

**SA-PO944**

**Relevance of Serum A Proliferation-Inducing Ligand (APRIL) as a Biomarker in South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort (GRACE-IgANI)**


**Background:** The role of serum APRIL as a biomarker in a prospective longitudinal South Asian IgAN cohort (GRACE-IgANI) and the impact of immunosuppression (IS) is not known.

**Methods:** Serum APRIL levels were measured in baseline and longitudinal sera (1year, 2year & 3year) in IgAN patients, and at baseline in disease controls and healthy controls by ELISA (R&D Systems; Catalog No: DY884B). Short course IS was...
Correlation of Immunoglobulin A/Complement Factor 3 (IgA/C3) Ratio with the Clinico-Histological Characteristics and Outcome in IgA Nephropathy

Anutha Swamy,1 Adarsh Barwad,2 Geetika Singh,3 Arunkumar Subbiah,1 Raj K. Yadav,1 Sandeep Mahajan,1 Dipankar M. Bhowmik,1 Sanjay K. Agarwal,1 Soumya Bagchi,1 and All India Institute of Medical Sciences, New Delhi, India.2 All India Institute of Medical Sciences, Bhubaneshwar, India.

Background: IgAN is a heterogeneous disease and has an aggressive clinical course in Asians. The serum IgA/C3 ratio at biopsy has been shown to correlate well with the prognosis of IgAN in few studies. We conducted this study to evaluate this non-invasive biomarker in our patients.

Methods: In an ambispective study we evaluated the baseline serum IgA and C3 levels, and IgA/C3 ratio in patients with biopsy-proven primary IgAN and eGFR ≥ 30 ml/min/1.73 m². For the patients recruited retrospectively, the same was determined from serum samples stored in a biorepository at the time of kidney biopsy. The ratio was evaluated in relation to the clinical severity at the time of presentation in terms of eGFR and proteinuria and histological severity assessed using the Oxford classification. We also assessed the role of the baseline IgA/C3 ratio as a prognostic biomarker in this cohort.

The primary outcome assessed was renal survival which was defined as absence of ≥ 40% decline in eGFR and/or progression to end stage renal disease. Remission of proteinuria was defined as urinary protein creatinine ratio(UPCR)<1g/g with stable renal function (± 25% decline in eGFR).

Results: 106 patients with a median follow-up period of 17.3 months with a median serum creatinine of 1.3 (0.4-2.6) mg/dl at presentation were analyzed. 46 patients (43.4%) had a baseline eGFR < 60 ml/min/1.73 m². The mean UPCR at baseline was 2.1 ± 1.6 g/g with 18 patients (17.0%) having nephrotic range proteinuria. The median IgA/C3 ratio in the population was 2.5 (0.79-4.75). The serum IgA/C3 ratio at baseline did not correlate with the baseline eGFR, proteinuria and the MEST-C characteristics. The ratio did not predict the primary outcome or the remission of proteinuria.

Conclusions: Future studies with larger sample size, milder cases, longer follow up period and a serial measurement of IgA/C3 are warranted for better clarification of any possible role of this biomarker in IgAN in our population.

SA-PO946

Glomerular Diseases: Translational Studies and Biomarkers

Poster/Saturday

Guangzhou, China

SA-PO945

The Level of Poly-Iga Immune Complexes in the Short-Term Efficacy Evaluation and Disease Activity Monitoring of IgA Nephropathy (IgAN)

Yulei Chen, Xiao Zhang, Yuxin Luo, Junzhe Chen, Ying Tang. Nephrology Dept. The Third Affiliated Hospital of Southern Medical University, Guangzhou, China.

Background: The formation of Poly-Iga immune complexes play a key role in IgA nephropathy (IgAN). The levels of poly-Iga in patients with IgAN is related to the severity of the disease. Whether Poly-Iga changes after treatment can evaluate the therapeutic effect, whether Poly-Iga level is an independent risk factor for non-remission, and whether it can be combined with other indicators to achieve a more accurate individual evaluation of IgAN patients still needs research.

Methods: 74 IgAN patients in Department of Nephrology, The Third Affiliated Hospital of Southern Medical University from March 17, 2022 to March 28, 2023 were recorded. Serum samples stored in a biorepository were used to evaluate the levels of Poly-Iga before and after treatment. Patients with serum creatinine of 1.3 (0.4-2.6) mg/dl at presentation were analyzed. 46 patients (43.4%) had a baseline eGFR < 60 ml/min/1.73 m². The mean UPCR at baseline was 2.1 ± 1.6 g/g with 18 patients (17.0%) having nephrotic range proteinuria. The median IgA/C3 ratio in the population was 2.5 (0.79-4.75). The serum IgA/C3 ratio at baseline did not correlate with the baseline eGFR, proteinuria and the MEST-C characteristics.

Results: Future studies with larger sample size, milder cases, longer follow up period and a serial measurement of IgA/C3 are warranted for better clarification of any possible role of this biomarker in IgAN in our population.

Conclusions: The formation of Poly-Iga immune complexes play a key role in IgA nephropathy (IgAN). The levels of poly-Iga in patients with IgAN is related to the severity of the disease. Whether Poly-Iga changes after treatment can evaluate the therapeutic effect, whether Poly-Iga level is an independent risk factor for non-remission, and whether it can be combined with other indicators to achieve a more accurate individual evaluation of IgAN patients still needs research.

Funding: Government Support - Non-U.S.
SA-PO948
Rate of Loss of eGFR and Time-Averaged Proteinuria in IgA Nephropathy (IgAN) Patients Progressing from Early-Stage Disease to Kidney Failure
David Pitcher,1 Fiona E. Braddon,1 Bruce M. Hendry,1 Alex Mercer,1 Kate Osmaston,1 Moin Saleem,1 Reha D. Steenkamp,1 Wu Gong,2 A. Neil Turner,2 Jonathan Barratt,3 Daniel P. Gale.1 1UK Renal Registry, Bristol, United Kingdom; 2Travere Therapeutics Inc, San Diego, CA; 3JAMCO Pharma Consulting, Stockholm, Sweden; 4University of Bristol & Bristol Royal Hospital for Children, Bristol, United Kingdom; 5University of Leicester & Leicester General Hospital, Leicester, United Kingdom; 6Royal Free Hospital & University College London, London, United Kingdom; 7University of Edinburgh, Edinburgh, United Kingdom.

Background: Cohort studies in IgAN have analyzed time-averaged proteinuria (TA-PU) and eGFR decline over long-term follow-up (Fu), and randomized controlled trials typically measure proteinuria and eGFR over 1-2 years, but none compare disease progression in early vs later stages of disease. In this study, patients enrolled into the UK National Registry of Rare Kidney Diseases (RaDaR) with biopsy-proven IgAN and Fu data spanning early-to-late CKD stages, we present preliminary findings comparing the extent of proteinuria (PU) and eGFR decline prior to and after entering CKD stage 3B. Methods: Linear regression of eGFR values from baseline (first PU value after diagnosis) until kidney replacement therapy initiation or end of Fu was used to define patient’s Time0 as the estimated date their eGFR passed 45. Longitudinal PU was analyzed using multilevel models and paired t-test; patients were required to have ≥2 eGFR and ≥2 PU values before and after Time0.

Results: eGFR decline was rapid and comparable in the 2 periods, either unadjusted or adjusted for age and sex (Table 1A; Figure). TA-PU was 41.4% greater in patients after progressing through the 45 ml/min/1.73m² threshold than before reaching this mark (Table 1B).

Conclusions: Given the comparability of eGFR decline prior to and after passing an eGFR of 45ml/min/1.73m², slope measurements in early disease stages may be useful in estimating future eGFR loss. Comparability of eGFR slopes but differences in TA-PU suggest patients with stable rates of eGFR loss suffer increasing damage to the glomerular filtration barrier.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table 1: Mean annualized eGFR slope (95% CI) pre and post an eGFR threshold of 45 ml/min/1.73m² (A) and TA-PU prior to and after the eGFR threshold (B).

<table>
<thead>
<tr>
<th>A (n=184)</th>
<th>B (n=185)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized mean slope (95% CI) per eGFR 65 threshold</td>
<td>TA-PU prior to eGFR 65 threshold</td>
</tr>
<tr>
<td>Pre-renal Fu</td>
<td>Post-renal Fu</td>
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<td>Pre-renal Fu</td>
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<tr>
<td>Pre-renal Fu</td>
<td>Post-renal Fu</td>
</tr>
<tr>
<td>A. Unadjusted</td>
<td>-7.7 (6.6, 8.8)</td>
</tr>
<tr>
<td>A. Age-adjusted</td>
<td>-7.2 (6.4, 8.0)</td>
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Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

SA-PO949
Comparative Analysis of Clinical and Pathological Traits in IgA Nephropathy with Nephrotic Range Proteinuria Based on Serum Albumin Level
Sang Hun Fam,1,9 Ji Won Min,1,9 Eun Sil Koh,1,9 Tae Hyun Ban,1,9 Seyoung Hong,1,9 Yu Ah Hong,2,10 Byung ha Chung,1,9 Yong Kyun Kim,3,9 Soo Joon Shin,1,9 Hye Eun Yoon,1,9 Incheon St. Mary's Hospital, Incheon, Republic of Korea; 2Bucheon St. Mary's Hospital, Bucheon, Republic of Korea; 3Yeouido St. Mary's Hospital, Seoul, Republic of Korea; 4Eunpyeong St. Mary's Hospital, Seoul, Republic of Korea; 5Uijeongbu St. Mary's Hospital, Iujeongbu, Republic of Korea; 6Daejeon St. Mary's Hospital, Daejeon, Republic of Korea; 7The Catholic University of Korea, College of Medicine, Seoul, Republic of Korea.

Background: Presently, the clinical outcomes associated with IgA nephropathy exhibiting heavy proteinuria and the potential correlation between decreasing serum albumin levels and adverse prognosis have not been conclusively established. The present study was designed to elucidate the clinical and pathological characteristics of IgA nephropathy patients who present with nephrotic-range proteinuria, particularly in relation to serum albumin levels.

Methods: This retrospective study was conducted using data from biopsy-confirmed IgA nephropathy patients presenting with nephrotic-range proteinuria between 2017 and 2022 from eight university-affiliated hospitals in South Korea. Patients were stratified into two groups based on a serum albumin level of 2.5g/dl. The study involved a comparative assessment of clinical and pathological characteristics across these two groups, as well as an evaluation of clinical prognosis with respect to the end-stage kidney disease (ESKD).

Results: The analysis included a total of 105 patients. Of these, 86 patients had a serum albumin level above 2.5g/dl (designated as the preserved albumin group, or PA group), while 19 patients had levels below 2.5g/dl (designated as the decreased albumin group, or DA group) in the PA group. The baseline characteristics of the two groups were found to be statistically similar. The mean age of the patients was 46.25 years, and 45.71% were male. Serum erythrocyte sedimentation rate, total cholesterol and low-density lipoprotein-cholesterol levels were significantly higher in the DA group. Pathological findings revealed more pronounced global sclerosis, interstitial fibrosis, and tubular atrophy in the PA group. Diffuse foot process effacement was more prominent in the DA group. During a median follow-up period of 23.64 months (range 0.03-69.53 months), 22 patients (25.58%) in the PA group progressed to ESKD, compared with 1 patient (5.26%) in the DA group. There was no statistically significant difference between the two groups in terms of progression to ESKD (P = 0.005).

Conclusions: In patients with IgA nephropathy presenting with nephrotic-range proteinuria, a decline in serum albumin levels was associated with less chronic lesions, and it was not found to be associated with adverse prognosis.

SA-PO950
Application of Prediction Tools in Patients with IgA Nephropathy: A Single-Center Cohort
José Agapito Fonseca,1 João Riesenberger,1 Islanda Godinho,1 Marta Pereira,1 Jose A. Lopes,2 Joana Gameiro.1 1Serviço de Nefrologia e Transplantação e Renal, Hospital de Santa Maria, Centro Hospitalar e Universitário Lisboa Norte, Lisboa, Portugal; 2Faculdade de Medicina da Universidade de Lisboa, Lisboa, Portugal.

Background: IgA nephropathy (IgAN) is the most common glomerular disease. Despite the development of prognostic scores, such as then IgAN Prediction Tool (IgAN-PT), long-term clinical course is difficult to predict. The Korean Fungibility Risk Equation (KFRE) is a four-variable equation which allows to predict the two and five-year probability of requiring kidney replacement therapy (KRT), but its accuracy on IgAN has not been established. The aim of this study was to assess the discriminative ability of the KFRE compared to the IgAN-PT to predict KRT in patients with IgAN.

Methods: We conducted a retrospective analysis of patients with IgAN followed by the Nephrology and Kidney Transplantation Department in Centro Hospitalar Universitário Lisboa Norte for five years. The primary outcome was the need for KRT within five years after kidney biopsy. The IgAN-PT and the four-variable KFRE were calculated for multiple follow-up points.

Results: Twenty-nine patients were included and 58.6% were male. At presentation, mean age was 41.3 ± 13.6 years, serum creatinine was 1.60 ± 1.17 mg/dl, and proteinuria was 1360 ± 1120 mg/g. At biopsy, the five-year KFRE score was 13.9 ± 25.6% and the five-year IgAN-PT score was 14.7 ± 15.9%. Three patients started KRT (10.3%) during follow-up. Proteinuria at presentation (3032 mg/dl vs. 1159 mg/dl, p=0.004) and serum creatinine on kidney biopsy (2.81 mg/dl vs. 1.35 mg/dl, p=0.003) were associated with need for KRT. Both the IgAN-PT and the KFRE correctly identified patients with higher risk for KRT, with the KFRE equation at clinical presentation exhibiting a slight superiority over the IgAN-PT (AUC 0.885 vs. 0.846).

Conclusions: The KFRE score at five-years after clinical presentation in patients with IgAN has shown excellent discriminative ability for identifying patients at risk of KRT. Moreover, it has demonstrated equivalent accuracy compared to the more specific IgAN-PT, being easier to apply and allowing for longer-term prognosis.
SA-PO951

Cnm-Positive Strepococcus mutans, a Major Pathogen of Dental Caries, May Cause IgA Nephropathy via Tonsils

Taro Misaki,1,2 Shuhei Naka,1 Yasuyuki Nagasawa,1 Daiki Matsuo,1 Seigo Ito,1 Saaya Matayoshi,1 Ryota Nomura,1 Michiyu Matsumoto-Nakano,1 Kazuhiko Nakano,1 Division of Nephrology, Seirei Hamamatsu General Hospital, Hamamatsu, Japan; 2Department of Nursing, Faculty of Nursing, Seirei Christopher University, Hamamatsu, Japan; 3Okayama Daigaku, Okayama, Japan; 4Hyogo Ika Daigaku, Nishinomiya, Japan; 5Japan Self-DefenseIrma Hospital, Iruma, Japan; 6Osaka Daigaku, Suita, Japan; 7Hiroshima Daigaku, Higashihiroshima, Japan.

Background: The presence of Strepococcus mutans, a major pathogen of dental caries, expressing Cnm protein encoded by cnm in the oral cavity has been associated with the pathogenesis of IgA nephropathy (IgAN). Although tonsillectomy is applied for the treatment of IgAN, the effectiveness in the patients harboring cnm-positive S. mutans in the oral cavity is not clear. This study aimed to investigate the effects of tonsillectomy on patients with IgAN who harbor cnm-positive S. mutans in the oral cavity.

Methods: The presence of cnm-positive S. mutans was analysed by polymerase chain reaction in saliva specimens from 117 patients with IgAN. The patient’s history of tonsillectomy was examined, and they were divided into four groups based on the results of cnm-positive S. mutans detection and tonsillectomy history: group A (n=52) (tonsillectomy (-), cnm-positive S. mutans (-)); group B (n=55) (tonsillectomy (+), cnm-positive S. mutans (-)); group C (n=16) (tonsillectomy (-), cnm-positive S. mutans (+)); and group D (n=14) (tonsillectomy (+), cnm-positive S. mutans (+)). The subjects’ clinical parameters were analysed.

Results: The proportion of patients with an estimated glomerular filtration rate <60 mL/min was significantly higher in group C than the other groups (p < 0.0083). The proportion of proteinuria 2+ or higher was significantly higher in group C than the other groups (p < 0.0083). In the cnm-positive S. mutans (+) groups, serum IgA was significantly lower in tonsillectomy group than in non-tonsillectomy group (266.9mg/dl vs 350.0mg/dl, p = 0.05).

Conclusions: These results suggest that the exacerbation of IgAN by cnm-positive S. mutans may be mediated by the tonsils and tonsillectomy may be effective in patients with IgAN who harbor cnm-positive S. mutans in the oral cavity.

SA-PO952

Porphyromonas gingivalis Infection in Oral Cavity Is Associated with Elevated Galactose-Deficient IgA1 in IgA Nephropathy

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Background: The association between Porphyromonas gingivalis, a major periodontal bacteria, and the pathogenesis of IgA nephropathy (IgAN), with a focus on galactose-deficient IgA1 (Gd-IgA1) in IgA nephropathy has not been fully understood.

Methods: Saliva samples were obtained from 30 IgAN patients and 44 patients with chronic kidney disease (CKD) to analyze the presence of P. gingivalis using PCR with a specific set of primers. The association between P. gingivalis detection and clinical parameters, including plasma Gd-IgA1, was analyzed for each group.

Results: P. gingivalis-positive group had a significantly higher serum Gd-IgA1 level than P. gingivalis-negative group in IgAN and CKD patients (p < 0.05). P. gingivalis-positive group in IgAN patients also showed a significantly higher serum Gd-IgA1 level than P. gingivalis-negative group in IgAN patients (p < 0.05). As for kidney biopsy findings, P. gingivalis-positive group exhibited a significantly higher frequency of the existence of segmental glomerulosclerosis than P. gingivalis-negative group when examining the Oxford classification of IgAN (p < 0.05).

Conclusions: These results suggest that P. gingivalis presence in oral cavity may be associated with IgAN pathogenesis due to induction of elevated level of Gd-IgA1.

SA-PO953

Validation of the International Immunoglobulin A (IgA) Risk Prediction Tool in American Indians and Hispanics

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Background: The International IgA risk prediction equation performance has not been studied in the Hispanic and American Indian population. Studies have reported a higher frequency of IgAN in American Indians. Therefore, we conducted this single-center study based in New Mexico to assess the performance of the International IgA risk prediction tool without racial discrepancy.

Methods: We searched the University of New Mexico kidney biopsy registry - a repository of kidney biopsies from 2002 -2016 - for instances of IgA nephropathy. We calculated the 5-year risk of developing kidney failure and assessed the equation performance using the metrics of calibration, discrimination, and overall prediction error for patients with primary IgA nephropathy on whom the predictions variables were available.

Results: Thirty-four patients were included, most of whom identified as of Hispanic race/ethnicity (44.1%), or as American Indians (26.5%). At biopsy, the median (IQR) age, serum creatinine, and spot urine protein to creatinine ratio were 38 years (27-45), 2.15 mg/dl (1.51-3.04), and 2.7 g/g (1.5-5.8), respectively. The equation identified patients at high risk of developing kidney failure early with a concordance statistic of 0.79 (95% CI 0.68 – 0.89). The agreement between observed and predicted outcomes at 5 years was marginal, with over-estimation of risk for patients with low observed risk and vice versa. Overall prediction error was optimal in this cohort [index of prediction accuracy 0.34 (0.03-0.51)].

Conclusions: The International IgA risk prediction equation without race adjustment identified patients at elevated risk of developing kidney failure. At 5 years, the agreement between the observed and predicted outcomes was sub-optimal, possibly due to advanced kidney disease in this cohort. A diverse development population may improve the risk prediction.

SA-PO954

Challenges and Lessons Learnt from Industry-Driven Multi-Centre Global Clinical Trials in IgA Nephropathy (IgAN): Site Investigators’ Perspective

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. Recently, many promising bio-molecules are being studied in clinical trials which are industry sponsored, multi-centre and global. Does the uniform protocol across the centers really reflect the regional practices or standard of care in a geographically varied disease like IgAN?

Methods: This was the site investigators’ perspective after being involved in 5 ongoing industry driven phase 2/3/OLE multi-centre clinical trials in IgAN. More than 20 eligible patients were enrolled from one of the largest not-for profit quaternary medical centre in South India over a span of 3 years. We are highlighting some of the best practices and some of the regional challenges for participants.

Results: Consent process - The entire process of providing trial related information, informal consultations with relatives and family doctors before providing an informed written consent could take 3-4 months. The strength of this long-drawn pre-consenting phase is improved overall retention of minimal drop-outs. Screening phase - In India, it is common to test positive for latent tuberculosis using IGRA tests due to community exposure. This is one of the major impediments for recruitment as otherwise they would have received immunosuppression in the absence of active disease. Another major road block was the anti-hepatitis B core antigen testing in the absence of hepatitis B surface antigen or hepatitis B viral DNA positivity. Recruitment and Retention phase - Flexible appointment times, frequent reminders and good rapport with the clinical trial team gained the participants’ trust and helped in retention. Reimbursement of actual expenses is vital to ensure proper visits and compliance to treatment. Investigators meetings and regular newsletters helped us to track recruitment and SAEs at a global scale. Post trial access - Indian regulatory approval for open label extension is long drawn which has directly affected the post-trial access to potentially valuable bio-molecules for participants in phase 2/3 clinical trials.

Conclusions: Industry driven global clinical trials are indispensable but sponsors could consider some regional modifications in the entry criteria and post-trial access. This also highlights the need for academic trials that repurpose the already available molecules.
Methods: We implemented a multi-targeted serologic screening procedure, which allows for detection of ab directed against sensitive, conformational epitopes of multiple antigens within one experiment. Results were validated using ELISA, Western blot and immunohistochemistry of kidney biopsies. The clinical applicability of this system was tested in 410 patients with biopsy-proven MN.

Results: A PLA2R MN was diagnosed in 307 (74.9%) of 410 patients. Using our multi-targeted serology screening approach, we identified 17 (4.2%) NELL1-1ab positive patients, 10 (2.4%) THSD7A-ab positive patients and 12 (2.9%) patients with circulating ab against one of the other antigens (PCDH7, HTRA1, NTNG1, CNTN1, or SEMA). Interestingly, 5 of these 12 patients showed ab against two different antigens simultaneously. Every ab result was validated using Western Blot showing concordance of results in 95% of cases. 20 (31.2%) of the remaining 64 sera showed reactivity to different preparations of human glomerular extract (HGE), indicating that for each antigen, 3D detectability is strongly dependent on the experimental protocols used to extract the HGE antigens. 83% of patients with no reactivity to any antigen or the HGE in any experimental condition, had a remission of proteinuria, in 66% of them it was a spontaneous remission without use of immunosuppression.

Conclusions: We report a multi-targeted serologic approach, which allows an antigen-specific diagnosis of MN within days and is therefore applicable in clinical routine. To fully accomplish an antigen-specific MN diagnosis in every patient, sera with reactivity to HGE are used for antigen identification via immunoprecipitation. The 10% of cases with no serologic activity allow a good prognosis, while antigen identification is performed by tissue-based mass spectrometry. For the implementation of the later two steps into clinical routine further adjustments are required, especially concerning the turnaround time for antigen identification.

Funding: Government Support - Non-U.S.

SA-PO956
Monoclonal Characterization of Auto-reactive PLA2R1 Antibody Responses in Membranous Nephropathy (MN)
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Background: Membranous nephropathy (MN) is caused by circulating antibodies, which in 70-80% of cases are directed against PLA2R. The CysR domain of the PLA2R is the immune dominant domain and all patients with PLA2R1-induced MN exhibit antibodies against this domain of the protein. Today, all treatment options for MN are unspecific concerning the molecular disease pathogenesis.

Methods: We isolated PBMCs from patients with PLA2R1-induced MN. Using tagged PLA2R1, PLA2R1-specific B cells were isolated and the corresponding B cell receptors were cloned, in order to produce monoclonal human PLA2R1-antibodies (PLA2R1-mAb). PLA2R1-mAb originating from patients with MN. The inhibitory potential of each PLA2R1-mAb was tested in vitro by competition ELISA using 60 sera from patients with PLA2R1-induced MN and in vivo in a rat model, which expresses the human PLA2R1 (hPLA2R1) specifically on podocytes.

Results: In total, four PLA2R1-mAb were cloned from PLA2R1-specific B cells from patients with MN and bound epitopes on the CysR domain. Every PLA2R1-mAb was tested for its inhibitory capability using 60 PLA2R1-antibody positive sera from patients with PLA2R1-induced MN. The PLA2R1-mAb inhibited the PLA2R1-antibody binding capacity of the patient sera by 45% - 96%. The inhibitory effect of each PLA2R1-mAb was independent of the PLA2R1-antibody level of the sera; i.e. the PLA2R1-mAb with the highest inhibitory potential of 90% exhibited a PLA2R1-antibody inhibition of 95%, 96% and 98%, when sera with PLA2R1-antibody level of 40-79 U/ml, 80-250 U/ml and > 250 U/ml were used, respectively. PLA2R1-mAb were injected in a rat with podocyte-specific hPLA2R1-expression prior to passive transfer of human PLA2R1-antibodies from patients with MN. This PLA2R1-mAb led to an inhibition of PLA2R1-antibody binding by 80% in vivo.

Conclusions: We report for the first time the characterization of human monoclonal antibodies specific for PLA2R1 derived from memory B cells of MN patients. Cloned autoantibodies showed strong inhibition of PLA2R1 autoantibody binding both in vitro and in vivo, opening the possibility of a potential PLA2R1 epitope specific treatment.

Funding: Commercial Support - Novartis, Basel, Switzerland, Government Support - Non-U.S.

SA-PO958
Efficacy of Rituximab in T Lymphocyte Subsets in the Treatment of Idiopathic Membranous Nephropathy and Its Significance
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Background: We studied T lymphocyte subsets in patients with idiopathic membranous nephropathy (IMN) and examined the impact and significance of rituximab (RTX) on these subsets.

Methods: We examined peripheral blood lymphocyte subsets in 58 patients with IMN and 25 normal controls by flow cytometry. We followed up the above indicators in 33 patients for 6 months after RTX administration. We also evaluated the changes of anti-PLA2R antibody titers and 24-hour urinary protein before and after treatment.

Results: 1. Compared to the control group, peripheral blood CD3+CD4+CD19+ B cells, CD3+ T cells, CD3+CD4+ T cells, CD4+CD8+ T cells and CD4+CD25+ T cells were significantly higher in patients with MN group(P<0.05). The levels of peripheral blood Treg cells (CD4+CD25+CD127-) and CD3+ T cells in IMN group were higher(P<0.05). 2. After 6 months of RTX treatment, all the above abnormal indicators were reversed, especially Treg and CD4+CD25+ T cells(P<0.05). 3. Before and after RTX treatment, the changes of peripheral blood CD4+ T lymphocyte subsets of IMN patients were not correlated with B lymphocyte counts and anti-PLA2R antibody titers.

Conclusions: IMN patients exhibit an abnormality in T lymphocyte subsets, particularly in CD4+ T cell subsets. RTX could restore the balance of CD4+ T lymphocyte subsets and enhance the levels of Treg cells. Importantly, this effect is not solely dependent on B lymphocyte depletion or changes in anti-PLA2R antibody titers. These findings suggest that RTX may have a beneficial impact on cellular immunity in IMN patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
African ancestry, in whom non-APOL1 Mendelian variants were much less common. Overall, the highest rate of discovery was in steroid-resistant pediatric patients. In adults, onset disease, there was also a significant rate of monogenic variant discovery, including in steroid-sensitive patients -- most of this group featured heterozygous COL4A4 variants. Pathway analysis showed that GBM-related variants were most common in adult-onset cases, while podocyte genes predominated in pediatric disease. APOL1 high-risk genotypes were associated with risk of ESKD within individuals of African ancestry, as well as further eGFR decline even in steroid sensitive cases.

Conclusions: In this large cohort of patients with idiopathic NS, exome sequencing analyses provide a diagnostic roadmap for clinical-genetic correlations across the lifespan, ancestry, phenotype, and response to immunosuppression.

SA-P0961

B-Cell Lymphocyte Precipitating Identities Steroid-Dependent Forms of Nephritic Nephropathy Disease Onset

Background: The clinical evolution of steroid-sensitive forms of idiopathic nephritic syndrome (SSNS) is highly heterogeneous, ranging from non-relapsing or infrequently relapsing patients (NRNS/IRNS), treated only with standard protocols of glucocorticoids (GC), to patients who present frequent relapses (FRNS) and lastly to severe patients showing a steroid-dependent course of disease (SDNS). This last group invariably require second-line steroid-sparing agents. Recently, the therapeutic benefit of anti-CD20 monoclonal antibodies in treating SSNS and the discovery of anti-neprin antibodies in patients with minimal change disease have pointed to a role of B cells in disease pathogenesis. In particular, we and others have shown that memory B cells predict relapse following and before receiving anti-CD20 (rituximab) infusion in patients with mainly SDNS forms of disease. However, a prospective characterization of B cell subsets from disease onset, before GC and other immunosuppressive treatment, is lacking.

Methods: In this study, we characterized by flow cytometry the profile of circulating B-cell subsets in 19 SSNS children (11 males) at disease onset, before starting GC treatment. All patients were then followed for 12 months in order to define the clinical subtype of their form of SSNS based on the frequency of relapses in relation to GC treatment in the subsequent months.

Results: During follow-up, 6 patients never relapsed (NRNS), 3 were classified as FRNS and 10 as SDNS. Mean (SD) age was higher in NRNS patients (5.5±1.4 years) compared to FRNS patients (4.7±2.3 years, p=0.07) or SDNS patients (4.1±1.8 years, p<0.01). When compared with FRNS patients, FRNS patients showed similar amount of total CD19+ (p=0.66), transitional (p=0.43), mature-naive (p=0.25), and memory (p=0.62) B cells. In contrast, SDNS patients had significantly higher levels of all these B-cell subsets compared to NRNS patients (p=0.05). Moreover, they had similar levels of total CD19+ (p=0.16), transitional (p=0.31) and mature-naive B cells (p=0.77), but a significantly higher amount of memory B cells (p=0.04), when compared to FRNS patients.

Conclusions: Increased levels of circulating memory B cells may allow to discriminate SDNS from FRNS starting from disease onset.

Funding: Private Foundation Support
Conclusions: Though hypertension is an important risk factor for progression of kidney disease, BP was not associated with differential gene expression in kidney tissue after adjusting for common confounders in patients with MCD/FSGS enrolled in NEPTUNE.

Funding: NIDDK Support

SA-PO963

Proteinuria Trajectories Among Patients with Minimal Change Disease (MCD) and FSGS in NEPTUNE

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Background: Proteinuria is a primary symptom of nephrotic syndrome and known risk factor for disease progression. Our objective was to identify patient-groups based on longitudinal proteinuria trajectories.

Methods: Patients with minimal change disease (MCD, n=151) and focal segmental glomerular sclerosis (FSGS, n=173) enrolled at the time of biopsy in the Nephrotic Syndrome Study Network (NEPTUNE) were included. Group based trajectory modeling was applied to UPCR measurements from the first 2 years post-biopsy; groups were compared on demographics, clinical presentation, histopathologic features, and eGFR trajectories.

Results: Three groups were identified; Group 1 (n=32) had low proteinuria on average over the first 2 years post-biopsy; Group 2 (n=130) had nephrotic range proteinuria by 2 years post-biopsy (63%) compared to Groups 2 and 3 (38% and 24%, respectively). By 2 years post-biopsy 92%, 85%, and 66% of Groups 1, 2, and 3 respectively had normal proteinuria. Group 1 was more likely to be treated with immunosuppression (IST, mostly glucocorticoids) prior to biopsy (63%) compared to Groups 2 and 3 (38% and 24%, respectively). By 2 years post-biopsy 92%, 85%, and 66% of Groups 1, 2, and 3 respectively had normal proteinuria. Group 1 was more likely to be treated with immunosuppression (IST, mostly glucocorticoids) prior to biopsy (63%) compared to Groups 2 and 3 (38% and 24%, respectively). By 2 years post-biopsy 92%, 85%, and 66% of Groups 1, 2, and 3 respectively had normal proteinuria. Group 1 was more likely to be treated with immunosuppression (IST, mostly glucocorticoids) prior to biopsy (63%) compared to Groups 2 and 3 (38% and 24%, respectively).

Conclusions: Proteinuria trajectories identified patient phenotypes that did not completely align with traditional histopathologic diagnosis. These groups also differ on baseline clinical and histopathologic features that may help predict response to treatment.

Funding: NIDDK Support

SA-PO964

Patients with Primary Focal Segmental Glomerulosclerosis with Detectable Urinary CD80 Are More Similar to Patients with Minimal Change Disease in ClinicoPathological Features

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Background: Focal segmental glomerulosclerosis (FSGS) is an important cause of refractory nephrotic syndrome (NS) in children and adults. Urinary CD80 is elevated in patients with primary FSGS, however, its clinical value is not fully clarified. This study aims to evaluate the clinical and pathological significance of urinary CD80 in patients with primary FSGS.

Methods: Sixty-one adult patients with biopsy-proven primary FSGS, with standard treatment and long-term follow-up, were enrolled retrospectively. Urinary CD80, at the day of kidney biopsy, was measured using commercial ELISA kits and adjusted for urinary creatinine excretion. Their associations with clinical and pathological parameters were investigated.

Results: Urinary CD80 was detectable in 30/61 (49.2%) patients, who presented with a higher level of proteinuria (10.7 vs. 5.8 g/d; \( P = 0.01 \)), a lower level of serum albumin (19.3±3.9 vs. 24.2±8.2 g/L; \( P = 0.005 \)), a higher prevalence of hematuria (70.0 vs. 38.7%; \( P = 0.01 \)), and showed lower percentage of segmental glomerulosclerosis lesion [4.8 (3.7-14.0) vs. 9.1 (5.6-21.1)%; \( P = 0.06 \)]. The cumulative relapse rate was remarkably high in these patients (log-rank, \( P = 0.001 \)). Multivariate analysis identified that the elevated urinary CD80 was an independent risk factor for steroid-dependent NS (OR 8.81, 95% CI 1.41-54.89; \( P = 0.02 \)) and relapse (HR, 2.87; 95% CI 1.29-6.38; \( P = 0.01 \)).

Conclusions: The elevated urinary CD80 is associated with mild pathological change and steroid-dependent cases of primary FSGS adults, which indicates these patients are more similar to minimal change disease (MCD).

SA-PO965

Clinical Significance of IgM and C3 Immunofluorescence Deposition Patterns in Patients with Focal Segmental Glomerulosclerosis

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Background: The presence of IgM and C3 deposits on immunofluorescence in some patients with Focal Segmental Glomerulosclerosis (FSGS) are considered to be a trapping of these molecules by mesangial sclerosis. However, there are studies that associate these deposits with a worse renal prognosis when compared to patients with negative immunofluorescence or only IgM deposit. We conducted this study aimed to evaluate the association of worse renal outcome with the presence of IgM and C3 deposits in glomeruli of patients from a Brazilian cohort with FSGS.

Methods: This is a retrospective study of clinical, laboratory, light microscopy histopathological and immunofluorescence (IF) data of patients diagnosed with FSGS, in the Nephrology Service of the Hospital das Clínicas of the School of Medicine of USP, from 2009-2017. Through immunofluorescence the patients were divided into four groups: with concomitant IgM + C3 deposition, IgM only, C3 only and without any deposition. These groups were compared to each other regarding data at diagnosis and at the end of follow-up.

Results: In the stipulated period, 114 patients were eligible for the study. The most commonly found IF patterns were concomitant IgM + C3 deposits in 46 patients (40.4%) and no deposits in 43 (37.7%). The other two patterns found were, exclusive IgM or C3 deposition, which occurred in seven (6.1%) and 18 patients (15.8%), respectively. When comparing these four groups, baseline creatinine, final creatinine and final proteinuria were significantly higher in the immunofluorescence groups with IgM + C3 and exclusive C3 deposition. The pattern of Collapsing Glomerulopathy was statistically significantly more frequent in the groups with IgM + C3 and exclusive C3 immunofluorescence (28.2 and 22.2% respectively) compared to those with negative immunofluorescence and exclusive IgM deposition (11.6 and 0% respectively) with \( P < 0.0001 \). These two groups also had the highest percentages of end-stage renal disease compared to the last two groups.

Conclusions: Our study showed that the presence of IgM and C3 on immunofluorescence is related to a worse renal prognosis. There is a need to return to the theme of a probable participation of the complement system in this disease.

SA-PO966

Identification of Biomarkers for Minimal Change Disease Based on LMD-DIA Technology Quantitative Proteomics

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Background: Minimal change disease (MCD) accounts for 80%-90% of idiopathic nephrotic syndrome in children and 10%-15% in adults. There is no apparent pathological change in the kidney tissue under the light microscope, but the podocyte foot process is diffusely disappeared under the electron microscope.

Methods: The kidney tissues of 5 MCD patients and 5 normal patients were selected as the experimental and control group. The three regions of kidney: the glomerulin, renal tubule, and renal interstitium were sequentially cut by using a laser microdissection device. The fold change ≥1.5 was used as the criterion of significant difference to screen different proteins. GO enrichment analysis, KEGG pathway analysis, Gene Set Enrichment Analysis and PPI analysis were performed on the identified differential proteins to determine the target protein.
Results: We found that 552 differentially expressed proteins (DEPs) in the glomerular group, 61 DEPs in renal interstitium group, 108 DEPs in renal tubular group. After bioinformatics analysis of the DEPs in the glomerular group, we found that the oxidative phosphorylation pathway and regulation of actin cytoskeleton pathway were play a significant role in MCD. In the renal interstitium group, Heterogeneous nuclear ribonucleoprotein K (hnRNP-K) were the most up-regulated DEPs and 4-hydroxyphenylpyruvate dioxygenase (HPD) were most down-regulated DEPs. In renal tubes group. Down-regulated HSP90AB1 have great influence in Akt to increase the apoptosis of renal tubule cell by PI3K–Akt signaling pathway.

Conclusions: ACTN4, ZXY, CSK and CAN1 are potential biomarkers for early diagnosis of MCD. COPD, HPRT, FIBG, HEMO, GTR1 and WBP2 may be the key proteins interacting with the immune compartment of the MCD kidney.

Funding: Government Support - Non-U.S.

SA-PO967
Differential Contributions of C5b-9 and C5a/C5aR1 Pathways to Thrombosis in Thrombotic Microangiopathy (TMA) Patients
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Background: This study aimed to clarify the critical role of C5a/C5aR and C5b-9 pathways in macrovascular thrombosis (MAT) and renal microthrombosis (MIT) formations based on a complement-mediated thrombotic microangiopathy (C-TMA) cohort.

Methods: Seventy-three renal biopsy-proven C-TMA patients from 2012 to 2019 in Peking University First Hospital were collected. Amongst 73 C-TMA patients, 9 patients with pure MAT and 13 patients with pure MIT were selected. Their plasma and urinary C5a and soluble C5b-9 (sC5b-9) levels were evaluated, respectively. C5a receptors and C5b-9 depositions in renal biopsied specimens were assessed.

Results: Compared to patients with pure MAT, patients with pure MIT had lower levels of hemoglobin (P=0.008) and eGFR (P=0.049), and higher renal acute arterial scores (P=0.011). Plasma C5a and sC5b-9 levels were significantly higher in C-TMA patients with MAT than those with MIT (P=0.008, P=0.041, respectively). The mean optical density (MOD) of C5aR1 in the kidney was significantly higher in MAT patients than in those with MIT (P<0.001). No significant difference was found in MOD of C5b-9 or C5L2 in the kidney or urinary C5a and C5b-9 levels between the two groups. However, urinary sC5b-9 level and renal depositions of C5b-9 were both associated with renal MIT formations (P=0.009; P=0.031, respectively).

Conclusions: MAT was not rare in C-TMA patients. The local C5b-9 and C5a/C5aR1 pathways might have differential contributions to MIT and MAT formations in the disease.

Funding: Government Support - Non-U.S.

SA-PO968
Ex Vivo Test of Complement Dysregulation in Atypical Hemolytic Uremic Syndrome Kidney Transplant Patients: A Pilot Study
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Background: In 2014 the ex-vivo complement assay, which evaluated C5b-9 deposition on cultured endothelial cells, was proposed as a possible biomarker for patients with aHUS. In our center eculizumab prophylaxis is not used in aHUS patients after kidney transplantation (Tx). A sensitive biomarker could improve management. The endothelial assay has not been studied in kidney transplant patients.

Methods: Pilot study. Serum samples of transplanted patients with aHUS who were in remission without eculizumab treatment, and transplanted patients with other primary kidney diseases (controls) were blindly evaluated in the complement assay (Noris lab).

Results: We included 13 patients (M 4; F 9) with aHUS, age 54 yrs (range 35-69), time after Tx 5.8 yrs (range 1.6-11.7). All but 1 patient were treated with a calcineurin inhibitor. There were no significant differences in C5b-9 deposits on resting (R) or activated (A) endothelial cells between aHUS patients (R 136%, range 93-382%, A 196%, range 113-260%, Figure 1). Three aHUS patients and 4 controls showed elevated C5b-9 deposits on resting cells, which should correspond to active aHUS or TMA. None of these patients has laboratory signs of TMA, and during follow-up of 15.8 m (range 6-21), eGFR has remained stable in all. Notably, in 3 aHUS patients with a genetic variant no increase in deposits were found on activated endothelial cells, which contrasts with literature suggesting that a positive test should identify carriers of a genetic variant.

Conclusions: Our data questions the accuracy of the ex-vivo complement assay in kidney transplant patients. We hypothesize that endothelial injury due to transplantation related factors may result in a positive test result. Further study is necessary before the test can be used in routine care for aHUS transplant patients.

Funding: Commercial Support - This work was supported by a research grant from the Dutch Board of Health Insurance Companies (Zorgverzekeraars Nederland), Government Support - Non-U.S.
Urinary Acanthocytes and Red Blood Cell Casts for the Diagnosis of Glomerulonephritis and Its Crescentic Forms


Background: Identification of urinary acanthocytes (uAc) is fairly specific for the diagnosis of glomerulonephritis (GN), but it is perceived as having suboptimal sensitivity. We hypothesized that combining the finding of urinary red blood cell casts (uRBCC) with uAc for the diagnosis of GN, the sensitivity of urine microscopy (uMICRO) as a whole can be optimized. Furthermore, whether uAc provides diagnostic value for identification of more severe (ie, crescentic) forms of GN is unknown.

Methods: Records of patients seen in nephrology consultation who had a uMICRO over a 5-year period were reviewed. We identified cases in which a kidney biopsy was performed within 2 weeks of the uMICRO. We assessed the performance of uAc alone and that of uAc in combination with uRBCC for the diagnosis of biopsy-proven GN or for any glomerular disease (GD). In addition, we evaluated the performance of uAc for identification of crescentic forms of GN.

Results: Of 747 patients who underwent uMICRO, 217 underwent kidney biopsy. Mean age was 56, 51% women, 47% White, 7% Hispanic, 41% Black. Mean serum creatinine was 3.5 mg/dL. Biopsy diagnosis was GD in 77%, GN in 54%, and others in 23%. The sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) of uAc for diagnosing GN were 62%, 85%, 75% and 76%, respectively. Combining the presence of either uAc or uRBCC, the SENS, SPEC, PPV and NPV changed to 69%, 100%, 100% and 64%, respectively. When examining uAc to predict any form of GD, the SENS, SPEC, PPV and NPV were 45%, 100%, 100% and 35%, respectively. As for crescentic GN, either uAc or uRBCC were found in 29 out of 33 (88%). The SENS, SPEC, PPV and NPV of uAc for crescentic GN were 88%, 42%, 47% and 86%, respectively. Notably, uAc were common in IgA nephropathy (71%), pauci immune ANCA (81%), and infection-related GN (IRGN) (83%), but uncommon in lupus GN (29%).

Conclusions: With proficient examiners and well-equipped laboratory, identification of uAc and uRBCC by uMICRO aid in the diagnosis of GN. uAc are pathognomonic of GN and certain pathologies (IgA nephropathy, pauci immune ANCA, IRGN) most commonly present with uAc and/or uRBCC.

SA-PO970

Anti-Nephrin Autoantibodies Broadly Detected in the General Population and in Non-Kidney Disease Patients

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Background: Nephrin is the key structural component of the interpodocyte-spanning slit diaphragm, and mutations of NPHS1 are associated with congenital nephrotic syndrome. Recently, Watts and colleagues discovered anti-nephrin autoantibodies in patients with MCD (J Am Soc Nephrol. 2022 Jan;33:238-252.), suggesting these autoantibodies may be directly contributory to the etiology of podocytopathy and also might play a role in primary FSGS. With our own focus on FSGS, we collected plasma samples from patients with kidney and non-kidney diseases and had them examined for anti-nephrin antibodies.

Methods: We tested a total of 126 plasma samples of recurrent vs nonrecurrent FSGS, primary and secondary FSGS, MCD, MN, LN, IgAN, TX, T1D with no kidney involvement, and health controls (Fig). Anti-nephrin antibody titers were measured using ELISA coated with recombinant Nephrin extracellular domain (R&D Systems, Cat#399-NN-050). In addition, we performed Western blotting (WB) analyses of the antisera against nephrin (C-FLAG tagged full-length nephrin from CHO cell transfection with plasmid). Results: Based on an arbitrary cutoff, a majority of the plasma samples were positive for anti-nephrin antibodies, whereas between 5% and 38% of the patients were tested positive for the antibody with varying titers. However, positive antibodies were broadly detected across the spectrum of the disease types, with the highest titer from a nonrecurrent FSGS.
Impact of Kidney Biopsy Findings Including Oxford MEST-C Scores on Kidney Outcomes in IgA Vasculitis Nephritis (IgA VN): A Study of the International IgA Nephropathy Network

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Background: Nephritis is a common manifestation of IgAV and is morphologically indistinguishable from IgA nephropathy (IgAN). However, while MEST-C scores are predictive of outcomes in IgAN, their value in IgAV has not been widely studied.

Methods: Biopsies from 361 patients with IgAV (262 children, 99 adults) from 17 centers in N. America, Europe and Asia were independently scored by 3 pathologists. Median time from clinical onset to biopsy was 2.0 mo, median post-biopsy follow-up was 2.7 y, 309 (85.6%) patients received immunosuppression (IS) during follow-up. As few patients developed ESKD or ≥30% eGFR decline, Latent Class Mixed Models (LCMM) were used to analyze eGFR trajectory post-biopsy in patients treated with IS. Association of clinical and histologic parameters with the different classes of eGFR trajectory was examined by logistic regression.

Results: Two classes were identified by LCMM (Figure), one with initial improvement in eGFR followed by a more notable decline (Class 1, n = 91) and one with stable disease (Class 2, n = 218). Among MEST-C scores, only E1 was predictive of Class 1 by multivariable analysis (OR 2.3; 95% CI 1.1,4.5); other scores were not although only 4.5% of patients had T>0. Other predictors of Class 1 were age ≤18 y, male sex, lower eGFR at biopsy, and extrarenal, non-cutaneous disease. Fibrous crescents were predictive of Class 2.

Conclusions: The clinical course of biopsied and treated patients with IgAV is determined by active lesions, notably endocapillary hypercellularity (E1) which is not part of the ISKDC classification for IgAV. The results support including MEST-C scores in biopsy reports of IgAV. Patients with IgAV, even those with initial therapeutic response, require long-term follow-up due to risk of late renal function decline.

Funding: Private Foundation Support

SA-PO973

ANCA Renal Risk Score (ARRS) 2023: The Updated and Revised ARRS

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Background: Reliable prediction tools are needed to improve prognostication and personalisation of treatment in anti-neutrophil cytoplasmic antibody (ANCA) glomerulonephritis (GN). We aimed to update the ANCA Renal Risk Score (ARRS) prediction model.

Methods: We collated a retrospective multicentre international longitudinal cohort from referral centres and registries across the globe to revise the ARRS in a validation and recalibration study. The primary endpoint was end stage kidney disease (ESKD) and patients were censored at last follow-up. Cox proportional hazards models were used to reweight risk factors and develop a modified scoring system. Kaplan-Meier estimates, Harrel’s C statistics and calibration plots were used to assess model performance.

Results: Of a total of 1591 patients, 1439 were included in the final analyses (959 in the development cohort, 520 male, median age 64 years). The ARRS demonstrated a discrimination of C=0.80, comparable to the original cohort. Updating the model found an additional useful cut-off for kidney function (K), and serum creatinine replaced glomerular filtration rate which provided higher reliability (Kt: <250 µmol/l = 0 points, Kt: 250-450 µmol/l = 4 points, Kt: >450 µmol/l = 11 points). The risk points for the percentage of normal glomeruli (N) and interstitial fibrosis and tubular atrophy (T) were reweighted (N: ≥25% = 0 points, N1: 10-25% = 4, N2: < 10% = 7, T0: none, mild or < 25% = 0 points, T1: mild-moderate or ≥ 25% = 3 points). We created four risk groups based on the sum of points: low (0 – 4 points), moderate (5 – 11), high (12-18) and an additional very high-risk (≥19). The model discrimination was C=0.811 and a supplemental continuous model was developed to supply a patient-specific annual risk. Three-year kidney survival was 96%, 79%, 54%, and 19%. The ARRS23 performed similarly well in the validation cohort with excellent calibration.

Conclusions: We demonstrated the out-of-sample validity of the ARRS and present the modified and improved score to optimise prognostication and risk stratification for clinical practice and trials.

Funding: Government Support - Non-U.S.

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

Underline represents presenting author.
Voclosporin Ameliorates Both Proteinuria and Dyslipidemia in a Model of Noninflammatory Glomerular Disease

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Background: Idiopathic nephrotic syndrome (INS) is one of the most frequent glomerular diseases in children. There is a critical need for the development of more effective and less toxic INS treatments. Voclosporin (VCS) is a novel calcineurin inhibitor (CNI) approved in the USA, EU, Great Britain and Switzerland on a background of immunosuppressive therapy for the treatment of adult with active lupus nephritis. VCS does not require therapeutic drug monitoring due to an improved pharmacokinetic profile. We thus investigated whether VCS could reduce proteinuria in non-inflammatory glomerular disease using an animal model of nephrotic syndrome (NS).

Methods: Male Wistar rats received 50 mg/kg purocine animinosuccinamide (PAN) or saline via tail vein injection on day 0. Rats were gavaged twice daily with vehicle (VEH), VCS (4 mg/kg/dose), or cyclosporine (CsA, 10mg/kg/dose) at clinically relevant doses. Rats were euthanized on Day 11 and proteinuria, lipid profile, glomerular cell injury (TUNEL), and hypercoagulability (TGA) were measured.

Results: PAN induced proteinuria in all disease groups. VCS ameliorated proteinuria more effectively vs. CsA (mean reduction vs. disease control was 81% vs. 17%, respectively). Mean triglyceride (TG) levels increased by 74% vs. controls in the PAN + Veh group vs. 22% in the PAN + CsA group vs. -26% in the PAN + VCS group. Similarly, PAN induced increases in all other lipid levels vs. controls, while VCS reduced these lipid levels. Flow cytometry TUNEL positivity of isolated glomeruli revealed injury of 2.1% in control podocytes vs. 5.3% in PAN + VEH cells (152% increase) vs. 8.5% in PAN + CsA cells (305% increase) vs. 4.1% in PAN + VCS cells (95% increase). TGA assay revealed that VCS effectively improved PAN-induced hypercoagulopathy.

Conclusions: Voclosporin is a clinically relevant dose of VCS ameliorated PAN-induced proteinuria, hypercoagulopathy, and in situ glomerular injury in a model of non-inflammatory glomerular disease, without apparent exacerbation of NS-associated dyslipidemia. Compared to CsA, VCS more effectively ameliorated proteinuria, hypercoagulopathy, and glomerular injury and led to a better lipid profile.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.
expressed primarily on lymphocytes, we hypothesize that podocyte-derived IL-1X recruits inflammatory cells to the glomerulus to propagate injury. We will use in vitro models to define the role of IL-1X in the pathogenesis of FSGS and to determine its utility as a therapeutic target in FSGS.

Funding: NIDDK Support, Private Foundation Support

SA-PO978
Podocytopathy with a Novel Variant in ARHGAP24 and an APOL1 Risk Allele
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Introduction: Genetic mutations cause up to 30% of steroid resistant nephrotic syndrome (SRNS) cases. A missense mutation responsible for hereditary podocytopathy was first described in ARHGAP24, a gene that encodes a GTPase activating protein (GAP) required for regulating podocyte motility. In 2011, we report a case of SRNS with an ARHGAP24 variant that has not been previously reported to our knowledge and a concurrent APOL1 risk allele.

Case Description: A 16-month-old male presented with anasarca, nephrotic range proteinuria, hypoalbuminemia, hypertension, microscopic hematuria, and severe anemia. Infectious work-up (hepatitis, HIV, COVID) was negative, and serum complement levels were within normal limits. Renal biopsy showed severe podocytopathy. Genetic testing showed a G1 APOL1 risk allele and a heterozygous missense mutation (c.584 A>C; p.K195T) in ARHGAP24. After a lack of response on 8 weeks of high dose steroids, the patient was transitioned to tacrolimus.

Discussion: Our patient’s ARHGAP24 mutation is in the critical GAP domain that regulates podocyte motility. The ARHGAP24 mutation described in 2011 was also in the GAP domain, causing reduced GAP activity and increased podocyte motility with a dominant effect attributed to heterodimerization of the mutated and wildtype (WT) proteins. Our patient’s mutation replaces lysine (positively charged) with threonine (neutral). This lysine residue, per Alphafold, is predicted to form a cation-pi interaction with a tyrosine residue in the GAP domain of the WT protein. Lysine is also highly conserved at this position across species. Therefore, we hypothesize that the positively charged lysine residue is required for preserving the GAP domain’s integrity, and changing the residue to a neutral amino acid (threonine in our patient’s case) disrupts the GAP domain. Despite the genetic findings, we opted to treat with tacrolimus, as the pathogenicity of this variant has not been confirmed. The patient also has a G1 APOL1 risk allele – while 1 allele is not expected to confer the risk associated with having 2 APOL1 risk alleles, the combination of 1 risk allele with a possibly pathogenic mutation is expected to confer an increased risk.

Conclusion: Our patient represents multiple genetic findings that require further investigation to define their contribution to his podocytopathy and to determine if and how the two variants interact with each other.

SA-PO979
Circulating Hypo-Sialylated IgM by FSGS Subjects Induce Proteinuria and Podocyte Injury
Andrea Angelelli, Maurizio Bruschi, Giovanni Candiano, Xulianna Kajana, Francesca Lugani, Enrico E. Verrina, Gianluca Cardi, Sonia Spinelli, Gian Marco Ghiglieri, Istituto Giannina Gaslini, Genova, Italy.

Background: Sialylation is an important regulator of protein function. Previous data showed that sialylation of total circulating IgM in Idiopathic Nephrotic Syndrome is significantly reduced compared to healthy subjects. The role of hypo-sialylated IgM (bIgM) on podocytes in FSGS pathogenesis is unknown.

Methods: We characterized IgM derived by patients affected by multi-drug resistant FSGS (defined as lack of antiproteinuric effect of a double therapy based on steroid plus CNL and MMF for at least 12 months before enrolment). IgM were first analysed through a one-dimensional electrophoresis. Sialylation levels were measured in total circulating IgM through incubation with biotinylated Sambucus nigra agglutinin (SNA). Then, sialylated and hypo-sialylated-IgM were put in culture with human podocytes. Incubation of podocytes with medium was used as control. IgM purified from serum of a patient were injected in rats.

Results: We enrolled 10 patients with resistant FSGS and 5 healthy controls, matched for age and sex (Fig1a). IgM derived from FSGS subjects induced significantly higher proteinuria than IgM from HC when injected in rats (Fig1b). IgM purified from serum of FSGS patients resulted significantly more cationic than IgM of HC (Fig1c), and as previously demonstrated, IgM cationic charge derived by hypo-sialylation (Fig1d). Co-incubation with bIgM, significantly induced human podocytes damage as opposed to sialylated IgM, which had no injurious effect (Fig1e).

Conclusions: Pathobiology of FSGS is still largely unknown and common treatments often result poorly effective. We here reported that sialylation of IgM may be of relevance in this context, showing that bIgM induce in vivo proteinuria and in vitro podocytes structural damage. Therefore, bIgM may represent a promising therapeutic target for FSGS.

SA-PO980
Potential Roles of Autoantibodies Targeting the Podocyte in the Idiopathic Nephrotic Syndrome
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Background: The idiopathic nephrotic syndrome (INS) is characterized by heavy proteinuria, hypoalbuminemia, and edema. In both forms of INS, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), podocytes are injured by mechanisms that are still mostly unknown. This injury causes changes in their actin cytoskeleton, leading to the effacement of their foot processes. Recent evidence suggests that autoantibodies targeting the podocyte might play a role in this process. Our objective is to establish if such autoantibodies are implicated in the pathogenesis of INS and to understand how they contribute to podocyte injury and foot process effacement.

Methods: As previously published (Hada and al., J Am Soc Nephrol. 2022;33(11):2008-2025.), INS was induced in C3H/HeN mice by immunization with recombinant Crb2, a transmembrane protein expressed both at the murine and human podocyte’s slit diaphragm. Immortalized podocytes expressing mouse Crb2 were incubated with serum from Crb2-immunized and control mice, then stained for phospho-ezrin, the phosphorylated form of ezrin, a protein that links Crb2 to the actin cytoskeleton. Serum from human INS patients in active disease and healthy controls were tested with quantitative ELISA specific for anti-Crb2 and anti-nephrin antibodies.

Results: C3H/HeN mice developed significant anti-Crb2 antibody titer and proteinuria 4 weeks after immunization. Podocytes incubated with Crb2-immunized mouse serum showed a significant increase in ezrin phosphorylation compared to podocytes incubated with control mouse serum (average staining intensity per cell of 1370 vs 68, p=0.0001). Among 67 INS patients in active disease, 22 (32%) had a positive anti-Crb2 antibody titer and 6 (9%) had a positive anti-nephrin antibody titer, while no healthy controls had a positive titer of either antibody.

Conclusions: Mice immunized with the podocyte protein Crb2 develop an INS-like disease, and their anti-Crb2 antibodies induce phosphorylation of ezrin, which links Crb2 to the cytoskeleton. Such anti-Crb2 antibodies are also present in human INS patients in active disease along with anti-nephrin antibodies, indicating that autoantibodies targeting human podocyte proteins may contribute to the crosstalk changes and podocyte injury seen in INS.

SA-PO981
Prospective Study of B-Cell Subsets in New-Onset Primary Podocytopathy in Adults
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Background: Data on children suggests the involvement of an altered B-cell immunophenotype in the pathogenesis of nephrotic syndrome (NS) due to primary podocytopathy. Characterization of the immune signature in NS patients will likely improve therapeutic strategies. We examined B-cell subsets in a cohort of adults with new-onset NS.

Methods: This was a prospective study at a tertiary care center in India. Adults with new-onset NS due to biopsy-proven primary minimal change disease or focal segmental glomerulosclerosis were included. Three sequential visits for blood sampling were: 1(on the day of starting prednisolone), 2 (2 weeks after visit 1), and 3 (6 months after visit 1 and 2 weeks after stopping prednisolone). B-cell subsets studied were: naïve B cells (CD19+27+), memory B-cells (CD19+27+), and transitional B-cells (CD19+27-38+/24+). Patients were categorized based on steroid responsiveness as steroid resistant (SR), infrequently relapsing NS, and steroid-dependent NS; the latter two were grouped as steroid sensitive (SS).

Results: Of 67 patients, 87% were steroid-sensitive (SS) within four weeks of therapy. The transitional B-cell proportion was lower, and the total B-cell proportion was higher in patients at baseline than 35 healthy controls. The baseline naïve B-cell proportion was lower, and the memory B-cell proportion was higher in steroid-resistant (SR) patients than in steroid-sensitive (SS) patients (Table). The naïve B-cell proportion decreased at the second visit and was followed by a plateau at the third visit (p=0.005). Memory B-cell proportion increased at the second visit, followed by a plateau at the third visit (p=0.005).

Conclusions: The transitional B-cell proportion remained similar across all three visits (p=0.18).
Conclusions: Memory B-cell proportion was higher, and naïve B-cell proportion was lower in SR patients than in NC patients. While naïve B cells decreased, memory B cells increased initially during prednisone treatment in the white blood cell. Funding: Government Support - Non-U.S.

Baseline B-cell percentage

<table>
<thead>
<tr>
<th>IFNAR-1(N%)</th>
<th>IFNAR-2(N%)</th>
<th>TNFRS(N%)</th>
<th>TNFRS(v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total B-cells</td>
<td>% of total lymphocytes</td>
<td>18.2 (12.2±3.1)</td>
<td>18.2 (12.2±3.1)</td>
</tr>
<tr>
<td>Naive B-cells</td>
<td>% of total B-cells</td>
<td>85 (76.6±9.7)</td>
<td>87 (79.1±9.9)</td>
</tr>
<tr>
<td>Memory B-cells</td>
<td>% of total B-cells</td>
<td>15 (13.3±5.9)</td>
<td>19 (10.9±5.3)</td>
</tr>
<tr>
<td>Transitional B-cells</td>
<td>% of total B-cells</td>
<td>3.8 (3.8±2.4)</td>
<td>4.6 (4.2±1.6)</td>
</tr>
</tbody>
</table>

IFNRS: infrequently relapsing nephrotic syndrome, SDNS: steroid-dependent nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome

SA-P0982

Cooperative Elicitation of Complement-Dependent Cytotoxicity by Anti-PLA2R Autoantibodies in Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (pMN) is an autoimmune disease causing abnormalities in the glomerular basement membrane and podocytes, leading to proteinuria. These changes relate to autoantibodies and accumulated complement components proteins on the glomerulus. Autoantibodies, primarily against phospholipase a2 receptor 1 (PLA2R) bind to the urinary podocytes and activate the complement system and contribute to pMN. Surprisingly, the predominant PL2AR autoantibodies in pMN patients are IgG4, which doesn’t activate the complement, while the complement-activating IgG1 and IgG3 are less common, questioning the role of PLA2R autoantibodies in pMN pathogenesis.

Methods: We isolated monoclonal anti-PLA2R antibodies (mAbs) from pMN patients' PBMC using single B cell sorting, then amplified the IgG4 clone for cloning into Lentiviral vector for expression. Using a CDC assay on PLA2R-overexpressing podocytes, we discovered that the combination of CTLD1 with another mAb significantly boosted CDC activation. After modifying the mAbs to IgG4, we found that a single IgG1 mAb was critical for CDC activation, but IgG4 could enhance it. Intriguingly, polyclonal IgGs from pMN patients, not from healthy volunteers, induced CDC. Furthermore, some patients with only CysR, IgG3 showed increased CDC activation with added CTLD1-IgG1 mAb.

Conclusions: These results identify an essential role of complement-reactive IgGs, presumably IgG1 and IgG3 synergies between single-domain epitopes CysR and CTLD1, which underlie pMN.

Funding: Government Support - Non-U.S.

SA-P0983

Apol1 in Podocyte-Derived Urinary Microparticles

John C. Edwards, Rebecca L. Winkler, Saint Louis University, Saint Louis, MO.

Background: Apol1 variants contribute to the high risk of progressive kidney disease in people with high risk genotypes; ability to assess podocyte Apol1 expression in vivo could be useful. Microparticles are 100-1000 nm vesicles that represent a sample of the plasma membrane of their cells of origin, and hence may reflect the level of expression of proteins such as Apol1. We isolated monoclonal anti-PLA2R antibodies (mAbs) from pMN patients' PBMC using single B cell sorting, then amplified the IgG4 clone for cloning into Lentiviral vector for expression. Using a CDC assay on PLA2R-overexpressing podocytes, we discovered that the combination of CTLD1 with another mAb significantly boosted CDC activation. After modifying the mAbs to IgG4, we found that a single IgG1 mAb was critical for CDC activation, but IgG4 could enhance it. Intriguingly, polyclonal IgGs from pMN patients, not from healthy volunteers, induced CDC. Furthermore, some patients with only CysR, IgG3 showed increased CDC activation with added CTLD1-IgG1 mAb.

Conclusions: These results identify an essential role of complement-reactive IgGs, presumably IgG1 and IgG3 synergies between single-domain epitopes CysR and CTLD1, which underlie pMN.

Funding: Government Support - Non-U.S.

SA-P0984

Topology of Membrane-Inserted Apol1

John C. Edwards, Jonathan M. Bruno. Saint Louis University, Saint Louis, MO.

Background: Apol1 inserts into membranes at low pH where it functions as an anion permease. Titration of the cis compartment to neutral suppresses the anion permease and activates a cation channel activity. pH 6.0 is optimal for membrane association that leads to cation channel after titration; pH 5 is optimal for the anion permease activity. As pH is lowered from 6 to 5, the total amount of protein associated with membranes increases along with the anion permease, but the potential for cation permease after titration is suppressed. We hypothesize that the structure of the membrane inserted Apol1 is altered by the pH at which it encounters the membrane.

Methods: Single cysteine mutants were generated at position 40, 80, 89, 149, 168, 178, 204, 226, 247, 263, 300, 314, 330, and 365, expressed in bacteria for sepharose 4B chromatography. Membrane associated protein was separated by SDS PAGE. AF-Mal modification was detected by in-gel fluorescence, total protein by western blot.

Results: Protein associated at pH 6 was accessible to trans-modification at positions 300, 314 and 330 only, and was unchanged by subsequent titration to pH 5. Protein associated at pH 5 was accessible to trans-modification at the same sites, plus at 365.

Conclusions: Apol1 associated with vesicles at pH 6 only has one trans-accessible segment detected by these methods, minimally including positions 300 through 330 and we detect no change in topology with transition to conditions that activate the cation channel, consistent with a previously published model (Schaub et al., JBC (2021) 297: 101009). However, association at pH 5 leads to a larger portion of the molecule accessible from the trans compartment, consistent with the entire C-terminal region from 330 to the end being translocated across the membrane. This additional translocation would eliminate the transmembrane segment that has been proposed to form the cation selective pore and would explain the decrease in cation channel activity after association at lower pH, additionally predicting different ion permeability activities depending on where along the endocytic pathway Apol1 inserts into membranes.

Funding: NIDDK Support

SA-P0985

APO1 G1-Mediated Cation Transport Inhibits Amino Acid Transport and Increases Endoplasmic Reticulum Calcium Release, Causing Podocytopathy

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Background: How two coding variants of APO1 gene (G1 and G2) cause kidney disease is poorly understood. While experimental models have shown that these APO1 renal risk variants induce cytotoxicity, the causal mechanism underlying these effects is unknown. Previously, we reported that RvR's form cation pores that transport Na+ and K+ across the plasma membrane of mammalian cells.

Methods: We blocked APO1 G1-cation channel function with a new small molecule inhibitor, VX-147 in inducible HEK293 cells and human-derived podocytes and measured cytotoxic phenotypes. We used Real-time cation sensors including genetically-encoded Ca2+ sensor to measure levels of cations in the cytoplasm and the endoplasmic reticulum (ER). We used inhibitor of IP3R and CRISPR-Cas9-mediated IP3R knockout to determine the impact of IP3R on APO1-G1-induced increases in cytoplasmic Ca2+ and cell viability. Finally, using metabolomics and related methods, we measured APO1-G1-mediated changes in amino acid transport, protein synthesis and ATP production, in the presence and absence of VX-147 treatment.

Results: We demonstrate for the first time that APO1 G1-mediated transport of Na+ and K+ induces Ca2+ release from the ER via IP3R and ryanodine receptor (RyR), and that the liberated Ca2+ triggers a sequence of downstream cytotoxic events including cell death, disruption of protein synthesis via AMPK-TSC2-mTORC1 and eIF2a signaling. We also discovered for the first time that APO1 G1 cation function impeds amino acid uptake in kidney cells. All observed cytotoxic phenotypes are rescued by VX-147.

Conclusions: These findings established APO1-mediated Na+/K+ transport as the proximal driver of podocyte injury, and that Ca2+ signaling and protein synthesis are potential therapeutic targets for APO1 nephropathy.

Funding: Other NIH Support - NH I Common Fund; NIMHD
SA-PO986

Characterizing Roles of Reference and Haplotype FAT10 in APOL1-Related Kidney Diseases in Human Podocyte
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Background: FAT10 is a ubiquitin-like modifier, which can covalently link to target proteins or non-covalently interact with proteins, thereby altering protein function and/or stability. FAT10 is highly expressed in HIV-associated nephropathy (HIVAN) and is upregulated in glomeruli of nephrotic patients with APOL1 high-risk genotypes. FAT10 was also reported to interact with G0 and to accelerate degradation of APOL1 risk variants in vitro. A FAT10 haplotype with 4 missense mutations, referred to here as FAT10b, has a high allele frequency in persons of African ancestry. However, it is not known whether the FAT10b variant has altered effects on APOL1 compared to the FAT10a (reference) allele. Since expression of APOL1 risk alleles in podocytes promotes glomerular injury, we compared the effects of FAT10 variants upon APOL1 G0 and G1 proteins in human podocytes.

Methods: APOL1G0/G0 (G0) and APOL1G1/G1 (G1) podocytes were transfected with GFP-FAT10 variants using a Neon Transfection System. Immunoprecipitation (IP) was performed using anti-GFP antibody to pull down GFP-FAT10 and western blotting was performed to detect FAT10 and APOL1. Proteasome inhibitor MG132 (5 µM) was added 4 hours before IP.

Results: FAT10a increased endogenous APOL1-G0 and -G1 protein abundance, whereas FAT10b suppressed them. Both APOL1-G0 and G1 co-immunoprecipitated with FAT10a and FAT10b. 70kD and 110kD bands were observed only in APOL1G1/G1 podocytes transfected with FAT10b, likely representing novel covalent FAT10 conjugates but western blotting revealed these FAT10 conjugates did not contain APOL1.

Conclusions: FAT10a and FAT10b interacted with APOL1-G0 and -G1, but FAT10a increased APOL1-G0 and G1 expression whereas FAT10b increased APOL1 degradation. The emergence of high molecular weight FAT10 covalent conjugates only in podocytes co-expressing APOL1 G1 and FAT10b may indicate important new targets that contribute to podocyte injury in persons with high risk APOL1 and FAT10 genotypes. These data support the importance of further studies to elucidate mechanisms by which FAT10 variants modify APOL1-mediated kidney injury.

SA-PO987

RNAomics of APOL1 Risk and Non-Risk Allele Expressing Podocytes in HIV Milieu
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Background: African Americans (AAs) develop chronic kidney diseases (CKD) at 4-5 folds higher rates than European Americans (EAs), and this disparity is over 10 folds in the case of HIV-associated nephropathy (HIVAN), which is predominantly related to two risk alleles (G1 and G2) in APOL1 gene in AAs. To explore the underlying molecular mechanisms, we evaluated the gene expression profiles in podocytes expressing APOL1-G0 (wild-type), G1, and G2 in the HIV milieu.

Methods: Stably expressing APOL1-G0, G1, or G2 cell lines were transduced with HIV, followed by the extraction of RNAs and RNA-seq analysis.

Results: All cells expressed comparable RNA (Figure A) and protein expression of APOL1 (Figure B), but G1- and G2-podocytes displayed downing of podocyte nephrin expression in HIV milieu. RNA-seq analysis showed that G1- and G2-podocyte expression profiles were disparate from that in G0-podocytes (Figure C). KEGG pathway enrichment analysis revealed that compared with APOL1-G0, the risk alleles G1 and G2 mainly altered inflammation regulating signaling pathways (Figure D).

Conclusions: These findings suggest that AAs may suffer from a higher occurrence of CKD due to enhanced inflammatory milieu in podocytes caused by APOL1 risk alleles. Our study provides insights into the underlying molecular mechanisms in developing APOL1-associated nephropathy.

Funding: NIDDK Support

SA-PO988

Microvesicular Passage of APOL1
Prabhjot K. Johal,1 Vinod Kumar,1 Ashwani Malhotra,1 Karl Skorecki,2 Pravin C. Singhal,3 Post Graduate Institute of Medical Education and Research, Chandigarh, India; 2Bar-Ilan University, Ramat Gan, Israel; 3Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY; 1New York City Health and Hospitals Jacobi, Bronx, NY.

Background: Podocyte-APOL1 (APOL1) carry a signal peptide, but its secretion and paracrine/endocrine role are controversial. We propose that APOL1 secretion in podocytes use microvesicles (MVs) to get out of cells rather than direct secretion to the medium.

Methods: APOL1 (wild-type, G0) and its risk variants (G1 or G2) were over-expressed in human podocytes. After 48hr of incubation, the culture medium was collected and processed for MVs isolation by ultracentrifugation and MVs isolation kit. Isolated MVs were characterized by HSP70, CD81, and CD63 and the absence of Calnexin by Western Blot (WB) and FACS. The size was measured using the Nanosite system and Scanning Electron Microscopy (SEM). APOL1 was detected in the culture medium and lysed MVs using ELISA & WB. The isolated MVs were further incubated with non-APOL1 expressing Human Embryonic Kidney (HEK) cells, and after 48hr, HEK cell lysate was analyzed for APOL1 presence by WB.

Results: Nanoset & SEM measured the size of isolated MVs between 90-125nm. These MVs stained positive for the expression of CD63, CD81, and HSP70 but were negative for the expression of calnexin. Therefore confirming that there was no cytosolic contamination. We observed the presence of APOL1 protein only in the lysed MVs. However, the level of APOL1-G0 (intensity: 1.92±0.01) is much higher compared to Vector (0.11±0.01) G1 (0.12±0.01) and G2 (0.17±0.02) as shown in the figure.

Conclusions: This preliminary study shows that podocyte and HEK cells secrete APOL1 through the MVs pathway.

Funding: NIDDK Support

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

1006
SA-PO989

HIV-Associated Nephropathy (HIVAN) Phenotype Is a Consequence of Compromised Parietal Epithelial Trans-Differentiation in the APOL1 Renal Risk Milieu

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1Post Graduate Institute of Medical Education and Research, Chandigarh, India; 2Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY; 3Bar-Ilan University, Ramat Gan, Israel.

Background: HIV-infected patients with African ancestry carrying APOL1 variants (ARRVs G1 and G2) have a several-fold higher risk of developing HIVAN than patients with APOL1 wild-type (G0). HIV enhances APOL1 expression in parietal epithelial cells (PECs). We hypothesized that HIV-mediated PECs' proliferation and transition are compromised in the ARRV milieu & result in PECs' accumulation in Bowman's space, manifesting HIVAN phenotype (a collapsing variant).

Methods: The cultured human parietal epithelial cells (PECs) were transduced with vector, G0, G1 & G2 & analyzed for their proliferative, fibrotic, & podocyte (PD)-specific differentiation phenotype (transition markers) using western blotting (WB). For phenotype-specific proliferative, profibrotic, and transition markers under the HIV milieu, V/G0/G1-G2-PECs were transduced with HIV (NL4-3) for 48h (r=4) & analyzed by WB. The expression of mTOR signaling and PECs' transition markers was measured using Western blotting and miR193a expression by RT-PCR to evaluate the involved mechanisms. Renal tissues from control & Tg26 (a HIV model) mice were analyzed for mTOR expression & mTOR expression by FISH & IHC in PECs.

Results: In vitro studies, G1/G2-PECs displayed an increased expression of profibrotic (CD44, PERK, α-SMA, Fibronectin, Vimentin, MMP9, SNAIL) but an attenuated expression of transition markers in control and HIV milieu when compared to G0-PECs; in contrast, G0-PECs showed attenuated expression of profibrotic but an increased accumulation of transition markers in HIV milieu. These findings indicate that PEC transition is compromised in G1/G2-PECs in the control and HIV milieu. G1/G2-PECs also displayed increased expression of p-mTOR, p-70S6K, & p-eEF, indicating the activation of mTOR signaling. Renal cortical sections of Tg26 mice showed an increased accumulation of PECs in their Bowman’s space & increased miR193a & mTOR expression by PECs compared to control mice.

Conclusions: HIVAN phenotype (collapsing variant) results from the compromised transition in profibrotic PECs to podocytes in APOL1 renal risk (G1/G2) milieu in HIV-infected patients.

Funding: NIDDK Support

SA-PO991

FSGS Recurrence Modeling Using Induced Pluripotent Stem Cell (iPSC)-Derived Podocytes in Patients with Idiopathic Nephrotic Syndrome

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Background: Clinical outcome is highly variable, often resulting in renal failure, in patients with idiopathic Nephrotic syndrome and disease returns after transplantation (Tx) in about 50% of patients. Proposed circulating permeability factors (CPF) are as of yet few and unvalidated in larger cohorts. In vitro assays to detect podocyte damage result in heterogeneous outcomes. Taken together, there are potential patient- and donor-specific characteristics that influence disease outcome after Tx. Here, we modelled FSGS recurrence using iPSC-derived podocytes.

Methods: We included 5 patient-donor couples with known outcomes of FSGS recurrence after Tx (3x recurrence, 2x non-recurrence) and generated iPSCs out of PBMNCs. We subsequently exposed iPSC-derived podocytes to suspected CFP-containing plasmas and measured podocyte damage using various previously published in vitro damage assays.

Results: Using an optimized hybrid directed differentiation protocol, we successfully created iPSC-derived podocytes showing podocytes-specific markers. We were able to model primary FSGS using patients' iPSC-derived podocytes exposed to pre-Tx plasma (patient-specifically) mimicking the in vivo situation. We also modelled FSGS recurrence using donor iPSC-derived podocytes exposed to post-Tx plasma (patient-specifically) (Figure 1) again according to the in vivo situation. Differences in damage response between iPSC-derived podocyte celllines suggest we found proof for donor-specific characteristics that may influence disease recurrence after Tx using a crossmatching experiment.

Conclusions: iPSC-derived podocytes can be used to model primary FSGS and FSGS recurrence. Data suggests that currently unknown donor-specific characteristics may influence disease outcome after Tx in patients with idiopathic Nephrotic syndrome. We aim to further study these potential donor-specific characteristics.

Funding: Government Support - Non-U.S.
Modeling Podocyte Pathologies in Human Kidney Organoids

Jamil El Saqir, C. Berthier, Moritz Lassé, Matthew Fischer, Akiko Minakawa, V. Vega-Warner, Rajasree Menon, Markus M. Rinschen, Matthias Kretzler, Jennifer L. Harder. MiKTMC. University of Michigan Medicine, Ann Arbor, MI; Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.

**Background:** Podocyte pathologies include multiple kidney diseases such as Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD) in which podocyte injury results in albuminuria. Kidney organoids (KOrgs) derived from human pluripotent stem cells generate 3D architecture with multiple cell types seen in native kidneys more reflective of the human in vivo podocyte environment. The aim of this study was to assess KOrg podocyte (KOrg-podos) response to inflammatory stressors and hypoxia to evaluate their ability to capture pathways relevant to human podocyte pathologies.

**Methods:** KOrgs were treated with recombinant TNFs α or β interferon (IFN) or subjected to 1% O2 environment for 24 and 48h. Assessment of gene/protein expression in pluripotent stem cells (iPSCs) using the well-established such as AEPC, are well established causes of SRNS and focal segmental glomerulosclerosis. Organoids stressor-specific gene signatures were generated from bulk RNA-seq and/or proteomics data and used to assess summary gene expression in proteinuric human kidney tissue (NEPTUNE cohort).

**Results:** Proteinomics analysis showed that baseline KOrgs expressed >90% proteins detected in human glomeruli; IF imaging confirmed anticipated localization of silh diaphragm proteins SYNPO and CD2AP in KOrg-podos. Further, NicheNet analysis confirmed that KOrg-podos responded to a host of ligands expressed by other cell types. Following treatment with TNFs α or β interferon, SC transcriptional profiling revealed that KOrg-podos lose expression of key podocyte markers (NPHS1, PODXL) and increase expression of genes observed in early glomerular epithelial cells (LYPD1, CDH6) as well as pathways associated with inflammatory response (NFkB) and mitochondrial stress. KOrgs stressor-specific gene signature expression segregated subgroups of individuals in a podocyte-centric cohort.

**Conclusions:** Our multi-platform integrative analysis of KOrgs demonstrates that KOrg-podos functionally respond to multiple stimuli thought to contribute to podocyte pathologies. Further, KOrgs stressor-specific gene activity identified individuals with poor outcome in proteinuric kidney disease. These results confirm the relevance of KOrgs to studies of molecular mechanisms of podocyteopathies.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences (NCATS), Commercial Support - Eli Lilly, Private Foundation Support

**SA-PO994**

Abstract Withdrawn

**SA-PO994**

Studying Organoid Phenotypes in CoQ10-Deficient Glomerulopathy

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**Background:** Monogenic causes of steroid resistant nephritic syndrome (SRNS) account for 11-30% of childhood. Genes involved in coenzymes Q10 (CoQ10) biosynthesis, such as PIS22, COQ2, COQ6 and ADCK4, are well established causes of SRNS and focal segmental glomerulosclerosis (FSGS) and Minimal Change Disease (MCD) in which podocyte injury results in albuminuria. CoQ10 is a component of the mitochondrial inner membrane which plays an important role in supporting electron transport of oxidative phosphorylation and protection from oxidative stress. ADCK4-deficient glomerulopathy can be partially treated by CoQ10 supplementation, but the therapeutic efficacy of this treatment is variable and has limitations. We here established a robust in vitro model system of CoQ10-deficient glomerulopathies to study the therapeutic effects of drugs using elaborate manipulations, and to better understand the disease and thereby develop more effective treatment.

**Methods:** We generated CoQ10-deficient kidney organoids from human induced pluripotent stem cells (iPSCs) using the well-established in vitro induction protocol (Takahashi et al. 2007). To establish CoQ10-deficient human iPSCs, gRNAs targeting PIS22, COQ2, COQ6 or ADCK4 were used with Cas9 protein individually. We performed immunostaining and light microscopy analysis to evaluate the extent of their differentiation and further test the mitochondrial dysfunction to observe the phenotypic characteristics due to CoQ10-deficiency.

**Results:** Gene ablation of the four genes in iPSCs was confirmed by sanger sequencing. CoQ10-deficiency did not lead to failure of induction to nephron progenitors in organoids. CoQ10-deficient kidney organoids were positive for NPHS1 (a podocyte marker), LTL (a proximal tubule marker), and ECAD (a distal tubule marker) expression, and no difference was observed when compared with control organoids. Further, studies will assess mitochondrial dysfunction and ROS levels to quantify pathogenic characteristics.

**Conclusions:** In conclusion, we have developed a modeling system of CoQ10-deficient glomerulopathy that can be used to further evaluate the efficacy of potential drugs for this disease.

Funding: Government Support - Non-U.S.

**SA-PO995**

Podocyteopathy in Diabetic Nephropathy

Divya Rawi, Mohammad AL Wahadneh, Wajid M. Choudhry, Rochester Regional Health, Rochester, NY.

**Introduction:** Minimal change disease constitutes 15% of adult idiopathic nephrotic syndrome. The exact mechanism is unknown but is postulated to be due to T cell dysfunction and the production of glomerular permeability factor. With an underlying immune mechanism involved, minimal change disease responds to steroids and steroid-sparing agents. We present a case of diabetic kidney disease with overlying podopctopathy.

**Case Description:** A 47-year-old female with a past medical history of hypertension, and poorly controlled diabetes presented with complaints of worsening swelling of legs along with abdominal distension and reported weight gain of 40 pounds over a few weeks. She reported no improvement with oral furosemide 40 mg daily which she was prescribed for her edema and was not using her insulin for the past 9 months before admission. Her creatinine at presentation was 0.9. 24-hour urine protein revealed 6.4 g/day. Autoimmune workup was negative. The patient was started on IV diuretics. She underwent a kidney biopsy which revealed moderate chronic kidney disease with podocyte foot effacement suggestive of minimal change disease. CT imaging was done to assess for any lymphoproliferative disease which found mildly enlarged inguinal lymph nodes. Oncology was consulted for the possibility of lymphoproliferative disease and believed that malignancy was unlikely. The patient was offered a steroid course versus immunosuppressive medications like mycophenolate mofetil. The patient chose to start mycophenolate mofetil to avoid steroids and their effect on diabetes. Proteinuria decreased and patient was discharged on mycophenolate mofetil 1000 mg twice daily with outpatient follow-up.

**Discussion:** Minimal change disease is often an idiopathic disease but has also been known to be associated with the use of certain drugs, infections, and hematological malignancies. The mainstay of diagnosis remains to be a kidney biopsy. In our patient, the most likely diagnosis at presentation was diabetic kidney disease from poorly controlled diabetes, the kidney biopsy proved vital in the assessment of the coexisting minimal change disease. Few case reports have been listed where patients with diabetes presented with sudden onset nephrotic syndrome and were found to have minimal change disease.

**Funding:**** NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences (NCATS), Commercial Support - Eli Lilly, Private Foundation Support

**SA-PO996**

DLBS3233 Reduces Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Increases Peroxisome Proliferator-Activated Receptor Gamma and Nephrin in Diabetic Rat Podocytes

Chandra I. Mohani, Universitas Brawijaya, Malang, Indonesia.

**Background:** DLBS3233 is a standardized extract derived from Cinnamomum burmanii and Lagerstroemia speciosa, has shown antidiabetic effects. Here, we sought to explore the potential of DLBS3233 to regulate insulin signaling in renal podocytes, cell represented by HOMA-IR, as well as podocytes PPAR gamma and Nephrin in diabetic rats with insulin resistance.

**Methods:** Thirty adult male Wistar rats were randomly divided into six groups (n=5 per group): nondiabetic rat group as a negative control (group I); untreated diabetic rats (group II), diabetic rats treated with DLBS3233 4.5mg/kgBB (group III); 9mg/kgBB (group IV); 18mg/kgBB (group V), and diabetic rats treated with pioglitazone (group VI). We checked HOMA-IR to confirm the occurrence of insulin resistance before and after administration of DLBS3233 in a group of rats with diabetes. Convocal examination was performed to examine the expression of PPARγ and Nephrin. The data were analyzed using paired t-test and ANOVA for pre and post DLBS3233 for HOMA IR.

**Results:** Administration of DLBS3233 showed work on improving insulin resistance from a significant decrease in HOMA-IR compared to the control group (p<0.05). Increased expression of PPARγ and Nephrin also confirmed the effect of a significant improvement in insulin resistance (p<0.05).

**Conclusions:** DLBS3233 was able to improve insulin sensitivity in diabetic rats with insulin resistance. The insulin sensitizing effect was projected from the reduction of HOMA-IR, increase of PPAR gamma and nephrin expression in renal podocytes. So further studies are needed to clinically test the efficacy of DLBS3233.
Extracellular Vesicles of Podocytes Impact Intraglomerular Signaling and Parietal Epithelial Cell (PEC) Activation

Alexander Pausch,1 Annika Gathmann,1 Kilian Teicher,1 Inka C. Homeyer,1 Milagros N. Wong,1 Anja Obser,1 Kian Deheshwar,2 Kelly A. Dryden,3 Hetty N. Wong,4 Nicola Wunner,5 Maja Lindenmeyer,6 Lawrence B. Horsman,7 Catherine Meyers,7 René von Wurmb,8 Franz J. Rickels,1 Ut A. Erdbrügge,9 Victor G. Puells,9 Tobias B. Huber,9 Fabian Braun,9
1Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; 2University of Pennsylvania, Philadelphia, PA; 3University of Virginia, Charlottesville, VA.

Background: Extracellular vesicles (EVs) have the ability to impact basic pathological processes such as malignant, metabolic and autoimmune diseases through intercellular signaling. However, we lack a concise knowledge about their role in kidney health and disease. Our study aims to characterize the intraglomerular signaling promoted by medium sized (mEVs) and small EVs (sEVs) shed by podocytes.

Methods: Using differential (ultra-)centrifugation we separated mEVs and sEVs from cell culture supernatants, kidney tissue and urine samples. Using Western Blot, immunofluorescence microscopy as well as image flow cytometry and ecyro electron microscopy we investigated the release dynamics of podocyte-specific EVs in different models of murine podocyte damage in vitro and in vivo. Life microscopy and cross culture experiments were used to determine the effect of podocyte-specific EVs on parietal epithelial cells (PECs). To determine potential signaling factors we performed proteomic analysis of EV content.

Results: Podocytes shed medium-sized and small EVs detectable in culture supernatant, murine kidney tissue as well as the urine of healthy human volunteers. Upon podocyte damage in vitro, we detected an increase in EV release as a unified response with differences in certain conditions revealed in Cryo-EM. Surprisingly, podocyte-specific EVs exerted different effects on the migratory behavior and proliferation of PECs depending on EV size and the initial insult to the podocyte. Proteomics revealed limited differences in the EV proteome in different stress conditions, with first candidate proteins potentiating the effect on PECs in vivo, decreased EV release by podocytes resulting in reduced PEC activation and limited recruitment of macrophages in a model of crescentic nephritis.

Conclusions: Our study yields essential insights on podocyte-specific release of different classes of extracellular vesicles, their protein contents and functional implications in health and upon podocyte damage. Ongoing experiments focus on further elucidating the impact of podocyte-specific release in vivo and the impact of knocking-out identified EV candidate proteins.

Extracellular Vesicles of Podocytes Impact Intraglomerular Signaling and Parietal Epithelial Cell (PEC) Activation

SA-PO997

PIK3CA Activation in Extracapillary Glomerulonephritis


Background: Extracapillary glomerulonephritis are severe kidney disorders frequently associated with end stage kidney disease. Therapeutic options for these diseases are limited especially due to insufficient understanding of their pathophysiology.

Methods: Following the identification of a somatic PIK3CA gain-of-function mutation in podocytes of a patient, we used multiple genetically engineered mouse models, single cell RNA sequencing and spatial transcriptionomics to unveil the role of PI3K-Akt mTOR pathway in podocyte biology of proliferative glomerulonephritis. Alpelisib, a pharmacological PI3Ka inhibitor, was used to inhibit the pathway.

Results: Podocyte-specific PIK3CA overactivation in mice developed progressive focal segmental glomerulosclerosis with podocyte proliferation, dedifferentiation and inflammation. Alpelisib treatment improved glomerular lesions and kidney function in different models of collapsing glomerulopathy and lupus nephritis by targeting podocytes. In addition, even more importantly and unexpectedly, we uncover that pharmacological inhibition of PIK3Ka affects B and T lymphocyte population in lupus nephritis mouse models with reduction in proinflammatory cytokine and auto antibodies production, immunoglobulin and complement deposition. These findings were further confirmed in Human lymphocytes isolated from patients with lupus nephritis.

Conclusions: We demonstrate the crucial role played by PI3Ka for proliferative glomerular diseases and showed for the first time that alpelisib represents a promising therapeutic acting on both, podocytes and immune compartment. These findings were further confirmed in models with reduction in proinflammatory cytokine and auto antibodies production, inhibition of PI3Ka affects B and T lymphocyte population in lupus nephritis mouse models, single cell RNA sequencing and spatial transcriptomics to unveil the role of different models of murine podocyte damage in vitro and in vivo. Life microscopy and cross culture experiments were used to determine the effect of podocyte-specific EVs on parietal epithelial cells (PECs). To determine potential signaling factors we performed proteomic analysis of EV content.

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Extracellular Vesicles of Podocytes Impact Intraglomerular Signaling and Parietal Epithelial Cell (PEC) Activation

SA-PO998

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Conclusions: We demonstrate the crucial role played by PI3Ka for proliferative glomerular diseases and showed for the first time that alpelisib represents a promising therapeutic acting on both, podocytes and immune compartment.

Extracellular Vesicles of Podocytes Impact Intraglomerular Signaling and Parietal Epithelial Cell (PEC) Activation

SA-PO999

Podocyte and Endothelial Infolding in Focal Segmental Glomerulosclerosis with INF2 Mutation

Tingting Yang, Jianhua Zhu. Chengdu First People’s Hospital, Chengdu, China.

Introduction: Podocyte infolding glomerulopathy (PIG) is characterized by podocyte cell invading into the GBM and intra-GBM spherules with around 40 reports only. The invaginations of endothelial cells to the GBM were generally not described. We report the specific ultrastructure of endothelial cells evidently invading into the GBM besides podocytes of a 25-year-old woman with the inverted form-2 (INF2) mutation.

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

Underline represents presenting author.

1009

Glucoma Diseases: Podocyte Biology - II

Poster/Saturday
Conclusions: Laminin α2-mediated activation of integrin α3β1 and α-dystroglycan receptor is a major contributor to podocyte damage and glomerular disease progression in Alport mice.

Funding: Other NIH Support - NIDCD

SA-PO1001

EPAC1-Mediated cAMP Signaling Promotes Cellular Energy Adaptations and Glycolytic Metabolic Shift in Podocytes to Protect from Glomerulonephritis

Lilia Abbad,1 Maximin Detrait,2 Panagiota Kavvdas,1 Lisa Melis,1 Frank Lezoualch2; Christos Chatziantoniou.1 1Inserm U1153, Paris, France; 2Inserm U1297, Toulouse, France.

Background: Many efforts are made to identify new therapeutic targets to slow down, prevent Chronic Kidney Disease (CKD) progression. One of the therapeutic approaches is activating cAMP pathway. The exchange factor directly activated by cAMP 1 (EPAC1) has been identified as a novel, PKA-independent, mediator of cAMP signalling. EPAC1 is a guanine exchange factor that regulates important cellular functions. Here we aim to determine the role of EPAC1 in CKD progression.

Methods: An immunostaining of EPAC1 is performed on biopsies of patients with glomerulonephritis. Nephrotic serum glomerulonephritis (NGS-GN) is induced in genetically modified mice with total and conditional EPAC1 deletion in podocytes. Then isolated glomeruli from the conditional mice are analysed by RNA-sequencing. The main metabolic energy pathways are studied in podocytes in vitro under oxidative stress exposure in the presence/absence of an EPAC1 agonist.

Results: EPAC1 is expressed in different GN disease and localized in glomeruli. Following the induction of NTS-GN, mice with genetic deletion of EPAC1 show aggravated renal disease, characterized by increased proteinuria, tissue inflammation and fibrosis compared to control mice. Conversely, pharmacological activation of EPAC1, with the agonist 8-cPT-2-OME-cAMP, delays NTS-GN progression. In human and mouse kidney tissues we observe EPAC1 expression in podocytes, mice with conditional deletion of EPAC1 are protected. Similar to the whole-kidney knockout, conditional mice show worsened disease progression compared to control mice. RNA-sequencing analysis of glomeruli isolated from these mice show that gene expression of proteins linked to the pathway of glycolysis are abolished in early stage of NTS-GN. EPAC1 activation of oxidative stress in podocytes in vitro promotes glycolysis with cellular energy production independently from mitochondrial respiration. The EPAC1-mediated glycolysis protected podocytes by increasing cell viability.

Conclusions: Podocytes-derived EPAC1 plays a protective role against the development of GN through cellular energetic adaptations based on metabolic shift to glycolysis. Activating the cAMP-EPAC1 signalling axis could represent a therapeutic option to delay CKD.

Funding: Government Support - Non-U.S.

SA-PO1002

Preliminary Renal Biopsy Registry: Dominican Republic

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Background: The rising incidence of renal diseases and the need to enhance their prevention, diagnosis, and treatment has prompted the establishment of national renal biopsy registries. These registries provide essential information about the epidemiology of renal diseases and can inform the design of clinical trials and the development of therapeutic strategies. With this premise, the Preliminary Renal Biopsy Registry was implemented in the Dominican Republic, aiming to compile and analyze renal biopsy data nationwide. This registry provides a valuable data source for studying renal diseases and developing therapeutic strategies. With this premise, the Preliminary Renal Biopsy Registry was implemented in the Dominican Republic, aiming to compile and analyze renal biopsy data nationwide. This registry provides a valuable data source for studying renal diseases and developing therapeutic strategies.

Methods: A retrospective database analysis was conducted, collecting national renal biopsy data. A call was made to nephrologists performing renal biopsies through the national society. Biopsies from 2002 to 2022 were included.

Results: A total of 929 biopsy were included of this study. Consisting of 814 (87.7%) non-transplant patients. 455 (55.9%) were female, 604 (74.2%) were biopsies performed in northern part of the country and just 32 patients (3.9%) were re-biopsied. The five more common primary biopsy diagnosis in non-transplanted patient were the following: focal segmental glomerulosclerosis 174 (21.4%), lupus nephritis (14.3%), minimal change disease (10.3%), membranous nephropathy 73 (9%) and Alport syndrome/thin membrane disease 66 (8.1%). In transplanted patients however, the five more common were: acute rejection 45 (39.1%), no rejection 25 (21.7%), chronic rejection 22 (19.1%), acute tubular necrosis 5 (4.3%) and focal segmental glomerulosclerosis 4 (3.5%).

Conclusions: According to our study, FSGS was the most common type of glomerulonephritis in our population. Also, this study showed a high frequency of Lupic nephritis, ranking second among all the glomerulonephritis diagnoses, followed by minimal change disease. This pattern is similar to other studies in Latin America, revealing a high prevalence of lupus nephritis compared to European and American countries. This information is essential to realize and emphasize kidney diseases’ importance, especially autoimmune glomerular disorders in Latin America.

SA-PO1003

Mechanisms of TMEM30A/NLRP3 Inflammammasome Pathway-Mediated Podocyte Pyroposis in FSGS

Yanpei Hou, Yi Li, Li Wang, Guisien Li. 1Sichuan Provincial People’s Hospital, University of Electronic Science and Technology of China, Chengdu, China.

Background: Primary Focal and Segmental Glomerulosclerosis (FSGS) is a renal histological disease characterized by podocyte injury. Transmembrane Protein 30A (TMEM30A) is involved in FSGS podocyte injury, but the underlying mechanism remains unclear.

Methods: Bioinformatics techniques were used to screen datasets related to FSGS in GEO database and search for key genes. 20 FSGS patients and 20 normal control renal tissue were collected, and multispectral fluorescence staining was used to detect the expression levels of TMEM30A, Nephrin and NLRP3 in renal podocytes. In vivo study, adriamycin (ADR)-induced podocyte injury mice were constructed, and the expression levels of TMEM30A, Nephrin and NLRP3 were observed by multispectral fluorescence staining. Meanwhile, Podocyte specific Tmem30a knockout mice were constructed, and the expression levels of Nephrin and NLRP3 in renal podocytes were detected by multispectral fluorescence staining. In vitro study, ADR was used to induce mouse podocytes and Tmem30a knockdown mouse podocytes were constructed to observe the expression levels of podocyte protective marker and pyroposis related proteins. After the intervention of NLRP3 inhibitor, the changes of podocyte marker protein and pyroposis related protein were observed.

Results: In kidney tissues of FSGS patients and ADR-induced mice, We found that the expression of TMEM30A, Nephrin and NLRP3 was significantly increased. The level of NLRP3 significantly increased with obvious colocalization. In addition, multi-spectral fluorescence staining showed that NLRP3 was significantly increased in the kidney tissue of podocyte-specific Tmem30a knockout mice, colocalized with podocyte-related protein Nephalin. In vitro study, we successfully constructed Adriamycin induce mouse podocytes and Tmem30a knockout mouse podocytes with decreased podocyte marker WT1 and Nephrin. Then, We further found the expressions of pyroposis-related proteins NLRP3, Caspase 1 and GSDMD were significantly increased. The NLRP3 inhibitor MCC950 could alleviate the podocyte pyroposis and improve podocyte injury.

Conclusions: TMEM30A could inhibit the activation of NLRP3 inflammasome, prevent the production of active Caspase 1 and the cleavage of GSDMD, reduce the podocytes pyroposis, weaken the damage of podocytes, and improve FSGS.

SA-PO1004

Deletion of IRE1α Exacerbates Diabetic Nephropathy in Mice

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Background: Protein misfolding in the endoplasmic reticulum (ER) of podocytes is an important contributor to the pathogenesis of glomerular diseases. ER protein misfolding activates a compensatory signaling network called the unfolded protein response (UPR). Deletion of the UPR transducer, inositol-requiring enzyme 1α (IRE1α) in mouse podocytes leads to podocyte injury and albuminuria in aging, and exacerbates injury in glomerulonephritis. This study addresses the role of the UPR and IRE1α in diabetic nephropathy.

Methods: We studied mice with podocyte-specific deletion/knockout (KO) of IRE1α. Hyperglycemia was induced in male mice (age 3-4 months) with streptozotocin.

Results: Streptozotocin-treated control and IRE1α KO mice developed comparable hyperglycemia (diabetes). Diabetes caused progressive albuminuria in control mice (3.7 mg/mg creatinine at 6 months) that was exacerbated in IRE1α KO mice (8.5 mg/mg creatinine; P<0.01). Albuminuria was ~1 mg/mg creatinine in non-diabetic groups (4-13 mice/group). Compared to diabetic controls, diabetic IRE1α KO mice showed a reduction in podocytes (WT1-positive cells; P<0.001) and syndopatin (P<0.001). Both non-diabetic and diabetic IRE1α KO mice showed increased glomerular matrix expansion compared to their respective controls. Glomerular ultrastructure was altered only in diabetic IRE1α KO mice; changes included widening of foot processes and glomerular basement membrane, microvesiculation of podocyte plasma membranes, and markedly dilated ER and mitochondrial architectural damage in podocytes. Activation of the UPR (increased glomerular ER chaperones) and autophagy (increased LC3-II, decreased p62) was evident in diabetic control, but not diabetic IRE1α KO mice. Analysis of human glomerular gene expression in the MCKD (Nephros) database demonstrated activation of pathways and gene ontology categories, as well as induction of genes associated with the ER, UPR and autophagy in diabetic nephropathy.

Conclusions: Mice with podocyte-specific deletion of IRE1α demonstrate more severe diabetic nephropathy. This was associated with an attenuation of the glomerular UPR and autophagy, implying a protective mechanism mediated via IRE1α. These results are consistent with data in human diabetic nephropathy and highlight the potential for therapeutically targeting these pathways.

Funding: Government Support - Non-U.S.
The miR-143/145 cluster-induced reduction in TGF-β targets SMAD4 and inhibition of mammalian target of rapamycin (mTOR) signaling by shRNA efficacy studies with integrin expression in cultured human podocytes. The miR-143/145 cluster expression significantly increased in a time-dependent manner for up to 48 h after exposure to TGF-β1 in cultured human podocytes (13.3 ± 3.7/17.4 ± 0.4 fold at 48 h vs. 0 h). We also observed upregulation of miR-143 in glomeruli of 16-week-old type 2 diabetic db/db obese mice compared to control mice, although miR-145 levels were comparable. Lentiviral ectopic expression of miR-143 and miR-145 in cultured human podocytes suppressed mRNA and protein expression of WT1. We confirmed that in DKD there is a progressive loss and mis-localization of WT1. In summary, in cultured human podocytes, TGF-β1 for 24 h and control podocytes, db/db mice were used as animal models of type-2 diabetic nephropathy.

**Results:** Microarray analysis identified miR-143 as the miR with the greatest increase following exposure to TGF-β1 (2.3 fold increase as 2ΔLMR vs. control, p=0.0000077). We confirmed by reverse transcription-quantitative polymerase chain reaction that the microarray results were validated. 

**Methods:** miR-microarray studies were performed using total RNA extracted from differentiated human podocytes exposed to 5 nM TGF-β1 for 24 h and control podocytes. db/db mice were used as animal models of type-2 diabetic nephropathy.

**Background:** Transforming growth factor (TGF)-β1 contributes to podocyte injury in various glomerular diseases, including diabetic kidney disease (DKD), probably in part by attenuating expression of Wilms’ tumor (WT1). We aim to identify microRNAs associated with TGF-β1-induced podocyte injury.

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Gene Expression and Regulatory Activity Disruptions in Glomerular Disease Patients

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Background: The role of noncoding variants in glomerular disease is not well understood. In this work we use deep learning to analyze contributions of these variants to gene expression and regulatory activity disruptions in the CureGDN cohort, which includes patients with minimal change disease (MCD), membranous nephropathy (MN), IgA nephropathy (IgN) and focal segmental glomerulosclerosis (FSGS).

Methods: To systematically assess the functional impact of the variants, we used deep learning models to predict gene expression changes in primary human cell types and the underlying biochemical disruptions to chromatin regulators across millions of patient variants.

Results: Gene expression changes were predicted for over 3 million variants in 25 kidney cell types. Effects of rare variants were accumulated per gene. We found multiple genes and pathways (Reactome) that were significantly dysregulated across all patients. For example, a gene with significant gene expression disruption was RABGCTB (p-val=1.42e-74), which is prognostically unfavorable in renal cancer. Others include RREBL1 (p-val=1.17e-88) and MAPK7 (p-val=2.73e-220). Top variants from each diagnosis group impacted distinct sets of partially overlapping genes and pathways. In addition to gene expression, we obtained predictions for regulatory activity disruption for over 25 million gene proximal patient variants. Predicted chromatin biochemical disruption was more severe for strongly conserved variants and variants associated with disease-related pathway genes. A subset of genes and pathways were significantly disrupted between and within patient groups. For example, within variants found in MCD patients, genes involved in PCSK9 reactions had stronger chromatin profiling disruptions (p-val=6.36e-05) than the other variants of MCD patients.

Conclusions: Through comprehensive analysis of the non-coding variants in the CureGDN cohort, we discovered variants, genes, and biological pathways disproportionately perturbed across the CureGDN patients. Gene expression predictions provided functional effects, while chromatin profiling predictions offered additional insight into disruption of molecular mechanisms. This analysis provides hypotheses for disease-contributing biologic and an approach for the future experimental follow-up.

Funding: NIDDK Support. Other NIH Support - R01HG005998, U54HL117798, R01GM071966, Private Foundation Support

Podocyte-Specific Deletion of MCP-1 Fails to Protect Against Angiotensin II- or Adrionycin-Induced Nephropathy

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Background: Investigating the role of podocytes in the pathophysiology of proteinuric disease is important to remedy the increasing global burden of chronic kidney disease (CKD). Monocyte chemotactic protein-1 (MCP-1 or CCL2) is a chemokine upregulated in CKD. Since podocytes can express both MCP-1 and its receptor (CCR2), we hypothesized that an autocrine MCP-1/CCR2 loop contributes to proteinuric injuries (Podo-CCR2). We tested this hypothesis by crossing MCP-1 floxed mice with mice harboring Cre recombinase under the transcriptional control of the podocin promoter. Podo-Mcp-1flox/c controlled mice and litter mates were subjected to either angiotensin II (Ang II; 1.5mg/kg/day × 28 days) or Adrionycin (Adr; 18mg/kg) to induce glomerular injury. Weekly spot urines were assessed for albuminuria. After 28 days, sera were collected to assess renal function while kidney tissues were used for histological, immunofluorescence, immuno blot, and quantitative PCR analyses. Unpaired Student’s t-test (two-tailed) was performed for two group comparisons. Log-rank test was used to compare survival distributions. The threshold for significance was P<0.05.

Results: At baseline, there were no between-group differences in body weight, histology, albuminuria, and podocyte markers. After 28 days of injury with either Ang II or Adr, there were no between-group differences in survival, albuminuria, renal function, inflammatory mediators, histopathology, podocyte loss, nephrin expression, and fibrosis.

Conclusions: Due to the lack of protection in the knock-out mice, our findings suggest that podocyte-specific MCP-1 production is not a major contributor to either Ang II- or Adr-induced glomerular injury. MCP-1 signaling must originate from a non-podocyte cell type. Future studies will determine the source cell of MCP-1.

Funding: NIDDK Support, Other NIH Support - National Institutes of Health T32DK061296, Veterans Affairs Support, Private Foundation Support

Effect of Transglutaminase-Induced Stiffening of Glomerular Basement Membrane on Podocyte Function

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Background: Glomerular basement membrane (GBM) and podocytes are important components of the glomerular filtration barrier. Podocytes are terminally differentiated cells that develop an intricate 3D architecture in vivo that is difficult to maintain in vitro. New approaches to maintaining podocyte differentiation may improve in vitro studies. Matrix stiffening is closely related to cellular function and GBM stiffness is altered in chronic kidney disease. How GBM mechanical properties affect molecular permeability and podocyte function is not fully understood. This work aims to investigate podocyte differentiation on native and transglutaminase crosslinked GBM and evaluate its effects on molecular transport.

Methods: Glomeruli were isolated from pig kidneys by sieving. The stiffness of native and transglutaminase (TG) crosslinked glomeruli was evaluated by a customized compression system. Decellularized and lyophilized glomerular matrix was rehydrated in PBS and coated on a 12-well plate. Immortalized human podocytes were plated on sterilized native GBM, TG treated GBM, and Matrigel coated plates. Podocytes were proliferated at 33°C, followed by transferring to 37°C for 14 days differentiation. Podocyte specific markers (nephrin, WT-1, and synaptopodin) and tight junction markers (ZO-1) were evaluated by immunofluorescence. Glomerular matrix was pressure compacted to Transwell membranes under pressure in a stirred cell to evaluate barrier function.

Results: Crosslinking GBM with transglutaminase increases its stiffness. Podocytes express nephrin and WT-1 after 14 days differentiation in culture on native and crosslinked GBM, and Matrigel coated cover slips. There is no synaptopodin expression in undifferentiated podocytes, but it has strong expression in differentiated podocytes. Podocytes cultured on native GBM show clear ZO-1 staining but weak staining on the TG treated GBM. Diffusive permeability measured on GBM with cultured podocytes is significantly reduced after 14 days differentiation compared to 7 days differentiation. This suggests podocyte differentiation contributes to barrier permeability.

Conclusions: We provide an easy method to fabricate biomimetic GBM which can support podocyte differentiation during long-term culture. Stiffening of GBM affects podocyte differentiation and junction marker that may contribute to loss of filtration barrier integrity.

Funding: Other U.S. Government Support, Private Foundation Support

A Novel Mutation in Podocyte-Specific Protease HtrA1 Is Associated with Glomerular Disease Progression

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Background: In kidney allografts, IGF-1 signaling was associated with reduced expression of Integrin A3, a key podocyte adhesion protein, and accelerated podocyte detachment. Insulin-like growth factor binding protein 2 (IGFBP2) and the high-temperature requirement factor A1 (HTRA1) contributed to the observed IGF-1 signaling. Podocyte specificity of HTRAI was affirmed by single-cell RNA sequencing of healthy kidney tissue. The HTRAI encodes a protease and makes bound IGF-1 locally bioavailable [doi:10.1016/s0014-5793(06)01229-x]. Since 99% IGF-1 is bound, functional mutations in the HTRAI gene could therefore perturb local IGF-1 signaling with functional consequences.

Methods: We searched for HTRA1 coding variants in the NEPTUNE cohort (n=620). Six distinct variants passed QC filtering. Each variant was then examined for its association with negative outcome (ESRD or 40% reduction in GFR). Transcriptional consequences on IGF-1 signaling of these mutations were evaluated in glomerular RNA-sequencing data.

Results: One variant was associated with a 2.7-fold increased risk of negative outcome. This relatively rare SNP (rs369149111); allele frequency-0.0248 results in a missense mutation, leading to alanine to valine change within the conserved signaling peptide (Ala20Val) region. Corresponding higher expression of IGF-1R in glomeruli as observed in patients with this variant.

Conclusions: SNP (rs369149111) is associated with glomerular disease progression. This rare allele likely interacts with glomerular IGF-1 signaling that then contributes to podocyte loss observed in glomerular diseases and transplanted kidneys. Further studies are necessary to determine the prevalence and mechanistic implications of this HTRA1 variant.

Funding: NIDDK Support
SA-PO1013

Novel Allosteric Agonists of Integrin α3β1 as Therapeutics for FSGS
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Background: Podocytes form the kidney filter that allows separation of urine and waste from blood. They attach to the extracellular basement membranes via cell surface integrin α2β1. Reduced podocyte adhesion, due to injury or mutations in α3β1, associated membrane proteins (CD151), or the integrin linked cytoskeleton, results in podocyte detachment and loss that weakens the kidney filter, resulting in progressive glomerular disease. Reinforcement of podocyte adhesion, via increased integrin-mediated cell adhesion and strengthened cytoskeleton is protective in various kidney diseases.

Methods: We used a human phage display library to identify α3β1 activating antibodies. K562 cells stably expressing α3β1, differentiated podocytes, and human SKOV cells were used in in vitro assays. K562 cells were used in flow-cytometry assays to characterize α3 agonists. Podocytes were used in High-Content Screening (HCS) based assays to quantify paroxycyn amionucleoside (PAN) induced cell damage and integrin agonist mediated protection. Cells were also utilized in cell adhesion and cell migration based functional assays.

Results: Measurement of F-actin fibers, focal adhesions and active integrin levels in podocytes showed a quantifiable change due to PAN in injury in podocytes, and protection from PAN-injury by b1 integrin agonist VEGF and prynargin as well as by the novel antibodies, α3b1 agonists also increased cell adhesion and reduced cell migration in vitro. Mapping of the antibodies using various integrin chimeras showed that they selectively bound to the α3 heat-domain, away from the ligand binding pocket.

Conclusions: We previously reported that activation of podocyte-expressed integrin α3β1 increases podocyte adhesion to matrix proteins and protects cells from damage. Here, we show that novel, integrin α3β1-directed allosteric agonist antibodies can be used to reinforce podocyte adhesion to the basement membrane. Data from our currently ongoing in vivo efficacy studies will provide further evidence of the therapeutic efficacy of this approach as a novel therapeutic strategy against a variety of glomerular diseases.

Funding: NIDDK, Support, Commercial Support - 1-49 Bio, LLC

SA-PO1014

Expression and Modulation of SGLT2 in Human Podocytes: Not All in Tubule
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Background: Inhibitors of the sodium-glucose cotransporter type 2 (iSGLT2) modify important non-glucortic pathways that lead to the protection of target organs. Its repertoircie pleiotropic effects in CKD, associated or not with diabetes, justifies further studies to elucidate the mechanisms of action (MoA) of these drugs. Although the co-transporter is mostly expressed in the proximal tubule, its location and function in other cells, potential therapeutic targets for inhibitor drugs, has not been well studied. We explored the presence of SGLT2 in human podocyte cells and whether it is modified in different situations of cellular stress.

Methods: Differentiated immortalized human podocytes were cultured under different experimental conditions for 24 or 48 h: Normoxia Control (N); Normoxia + High concentration of glucose (HG); Hypoxia (H); Reoxygenation (H) and the combination H+HG. We also incubated with 0.1uM Dihydrotroestosterone (DHT). SGLT2 gene expression was determined by quantitative PCR and SGLT2 protein was detected by Western Blot (WB) and immunofluorescence (IF).

Results: SGLT2 gene expression was detected with an increase after 24h of exposure to HG. Protein expression by WB showed a non-significant increase after 48h of exposure to HG and hypoxia, which was significant with co-incubation with DHT. The IF measured by intensity of area did not show an increase in the protein expression of the transporter under HG incubation. However, protein expression increased under all hypoxia conditions: Control 50.05±3, Hypoxia 140±16.3 (p<0.005 vs control) and HG+Hypoxia 253±21.29 (p<0.001 vs control).

Conclusions: Our data suggest that podocyte may be one of the therapeutic targets on which the SGLT2 agonist therapy may act. The experimental conditions described did not show differences in the expression of the transporter before the single stimulus of glucose, but they did under hypoxia and the combination Hypoxia-high glucose. In addition, co-incubation with testosterone seems to enhance the expression. Studying the MoA of iSGLT2 will open better comprehension of the kidney pathophysiology, particularly in the podocytocysters, regardless of diabetes.

SA-PO1015

A Case of Steroid Refractory Lupus Podocytopathy: Is Glucocorticoid Monotherapy Sufficient?
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Introduction: Lupus Podocytopathy (LP) is a rare, but clinically impactful, manifestation of Systemic Lupus Erythematosus (SLE). Accepted management of LP, Minimal Change (MC) and FSGS - subtypes alike, utilizes glucocorticoid (GC) monotherapy for proteinuria suppression. We present a case of high-grade podocyte effacement LP with MC subtype refractory to conventional GC management requiring the addition of an immunosuppressive agent.

Case Description: 38 yo female with SLE and no chronic kidney disease presented with nephrotic syndrome and acute kidney injury. Creatine on presentation was 5.7 mg/dL and urine protein:creatinine ratio 11 g. Serologies demonstrated >ANAs >1:640 and >dsDNA. Renal biopsy was performed and suggestive of LP - MC subtype. Electron Microscopy: diffuse (90%) visceral epithelial foot process effacement; no endothelial tubuloreticular inclusions or subendohelial immuneocomplex deposits were noted (Figure 1). Light Microscopy and immunofluorescence were unremarkable for chronicity or proliferative nephritis. High-dose prednisone was initiated at 1mg/kg. No significant change in nephrotic syndrome was observed despite 4 months of prednisone monotherapy. Mycophenolate Mofetil (MMF) was subsequently incorporated achieving complete remission of proteinuria and return to baseline creatinine.

Discussion: Small retrospective studies evaluating LP have suggested GC monotherapy should be successful in achieving clinical remission, especially in MC subtypes. The case presented suggests the addition of a non-glucocorticoid agent may be required to mitigate the proposed pathogenic cytokine and T-cell dysfunctions. Factors such as high-grade podocyte effacement and heavy proteinuria should prompt consideration for empiric dual-agent immunosuppression. Larger-scale randomized studies are needed to demonstrate the clinical and pathologic criteria determining single vs. dual immunosuppressive therapy for LP.
Recognizing new genetic variants will help with developing future therapies and avoiding FSGS with a normal glomerular basement membrane have been reported in the literature.

Mapping the Molecular Atlas of Podocyte Response to Glucocorticoids

SA-PO1018

De Novo Relapsing Podocytopathies Following Novel COVID-19 Infection: A Case Series


Introduction: COVID-19 infection can result in significant multi-system disease, including pneumonia and renal pathologies. Thirty published articles have shown wide yet limited variety of underlying pathologies including collapsing FSGS, minimal change disease, and TMA following infection and vaccination. Our case series reintroduces discussion for unique podocytopathies following COVID-19 infection and vaccination, with relapsing MCD proteinuria, resistant MCD, and TIPS variant FSGS.

Case Description: Our first case is a 22 year old female, with no past medical history, who presented with abdominal pain, nausea, and positive COVID-19 positivity, with a 24 urine protein of 5.3g, and secondary serologies negative. Her renal biopsy showed MCD phenotype. Her proteinuria initially responded to prednisone therapy, but relapsed secondary to a taper, requiring rituximab, with remission over 3 months. For this second case, a 36 year old male with a history of mast cell activation syndrome, thin basement membrane nephropathy, abatopic steroid use, presented with lower extremity edema and proteinuria of microalbumin to creatinine ratio of 4.5g, with kidney biopsy demonstrating TIPS variant FSGS, following COVID-19 infection positivity. Patient initially responded to tocilizumab and prednisone due to adverse drug reactions, pending evaluation for sparsenatan and rituximab. The third case is a 43 year old female with a history of APLS, presented with swelling, proteinuria, following COVID-19 infection, found to have a 24 hr urine protein of 10.7 grams. Patient initially responded to prednisone, however, had flare of proteinuria following taper, and COVID-19 vaccinations. Course unresponsive to cyclophosphamide based treatment, with minimal responsiveness to rituximab, however given anticoagulatio for APLS, repeat biopsy deferred.

Discussion: This case series reinforces an association between COVID-19 infection, vaccination and podocytopathy. However, it also provides groundwork for exploration of resistant and relapsing nephrotic syndromes, and the utility in early biopsies for early treatment. This raises the question whether there are long term effects of COVID-19 on renal health, and if COVID-19 induced nephrotic syndrome deserves its own treatment guidelines over traditional therapies.

SA-PO1019

Nephrotic Syndrome from Primary Amyloidosis Can Be Linked with Multiple Myeloma: A Rare Presentation of a Case

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Introduction: Nephrotic syndrome from primary amyloidosis can co-exist with multiple myeloma on rare occasions. Early diagnosis and Appropriate management is crucial for the prognosis of these patients as the combination can reduce life expectancy.

Case Description: A 61 year-old female with PMH of Type 2 DM, HTN was seen for nephrotic range proteinuria detected by PCP screening. Her DM and HTN have been well-controlled for over 10 years. She had no complaints. Physical examination was unremarkable. She has had microalbuminuria since 2017 but developed significant proteinuria and hypoalbuminuria over the last year. A renal ultrasound was done which showed normal kidneys. Laboratory tests showed normal kidney function. Serum electrophoresis revealed monoclonal gammapathy and urine immunofixation showed monoclonal lambda plus IgG lambda fragments. Renal biopsy showed amyloidosis with randomly elevated fibrillary structure. Bone marrow biopsy showed mildly hypercellular marrow with 30% plasmacytosis. Flow cytometry showed lambda light chain. The patient was diagnosed with asymptomatic multiple myeloma and amyloidosis presenting as nephrotic syndrome. She was treated with daratumumab plus CyBorD, which includes cyclophosphamide, bortezomib, and dexamethasone. Over several months, her serum albumin levels have increased and the lambda light chain has decreased.

Discussion: Multiple myeloma (MM) is a malignant plasma cell disorder characterized by uncontrolled proliferation and infiltration of monoclonal plasma cells to the bone marrow. MM is observed concomitantly with amyloidosis in 12-15% of cases. Primary amyloidosis refers to the deposition of immunoglobulin light chains throughout body tissues. This case highlights a rare but possible scenario of asymptomatic multiple myeloma and amyloidosis that presented as nephrotic syndrome. Diagnosis asymptomatic multiple myeloma and amyloidosis can be challenging, as patients may have no significant symptoms. Further research is needed to investigate which types of patients are at risk. In this case, the patient was diagnosed following routine urine screening for diabetic nephropathy, emphasizing the importance of screening for these conditions. Treatment for asymptomatic multiple myeloma and amyloidosis largely overlaps, focusing on reducing abnormal proteins and managing complications such as renal damage.

SA-PO1020

Novel Anatomic and Macromolecular Models Define Realistic Glomerular Barriers

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Background: The glomerular barrier has been studied extensively using the polyvinylpyrrolidone (dextran) and fluorescein, both modeled as rigid impenetrable spherical particles. Recent glomerular reconstructions reveal that efferent and afferent glomerular arterioles are joined by non-communicating branches; these parallel tubes are combined into a single uniform cylindrical filter composed of the two most restrictive layers of the glomerular capillary wall, basement membrane and visceral epithelial cells joined by slit diaphragm. Methods: The classic matrix formulation is modified for flow dependent solute size because water penetrates partial draining polyanion chains such as dextran, but not non-draining proteins; linear regression yields fiber density from slope and transepithelial shunt. Results: Fiber density was similar to fiber density reported for isolated basement membrane and was essentially the same in controls and patients; epithelial shunts were not affected. Conclusion: Based on these models, we propose that new methods can be used to better understand glomerular function and blood flow through the kidney.
were proportional to total urinary protein excreted, fiber density was not. Effective polysaccharide size decreased when confined by filters in basement membrane and when confined by streamlines in slit pore. Four-fold higher fiber density encountered by small polysaccharides compared to proteins and large polysaccharides reflect the stratified nature of the glomerular basement membrane and define two pathways through the glomerular capillary wall, a selective route direct through lamina densa and slit diaphragm, a non-selective indirect route through more lamina rara externa and infrequent widely spaced epithelial defects. Filtration area was similar to reported anatomic measurements in controls and was decreased in proportion to histologic abnormality in patients.

Conclusions: Dextran and Ficoll are more permeable than similar size proteins such as albumin and IgG because moving water penetrates, rearranges, and aligns chemically similar polysaccharides. In disease the basement membrane is preserved, but the visceral epithelium is not.

SA-PO1021
The Expression Profile of Complements in Human Renal Mesangial Cells, Endothelial Cells, Podocytes, and Proximal Tubular Epithelial Cells
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Background: More and more evidence indicated that the kidney was a notable source of complements. We aimed to explore the expression profile of complements in human renal mesangial cell (HRMC), glomerular endothelial cell (HRGEC), podocyte (HPC), and proximal tubular epithelial cell (PTEC) under physiological conditions.

Methods: Single-cell RNA sequencing (scRNA-seq) by a 10xGenomics Chromium system was used to identify the transcription of 30 complement genes in HRMCs, HRGECs, HPCs, and PTECs. RT-PCR was used to verify the expression of complement genes in cultured primary HRMC and HRGEC, and in HPC and PTEC cell lines. Immunofluorescence was used to confirm the protein expression of several key complements.

Results: By scRNA-seq, the transcription of nearly all complement genes was found in HRMCs, HRGECs, HPCs, and PTECs, and the expression of complement regulatory proteins was highest. RT-PCR confirmed the transcription of C1S, C1R, C4, CFD, MBL2, MASPI, MASPII, C3, C5, CFH, DAFA, CD46, CD59, protein S, and C3AR1 in cultured cells. Immunofluorescence verified the expression of C3, C5, DAFA, C4BBP, and CD59.

Conclusions: Under physiological conditions, HRMCs, HRGECs, HPCs, and PTECs express multiple complements involved in three activation pathways.

Funding: Government Support - Non-U.S.

SA-PO1022
Membranous-Like Glomerulopathy with Masked Monoclonal Deposits in a Patient with Class 5 Lupus Nephritis: A Case Report
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Introduction: Membranous-like glomerulopathy with masked IgG kappa (κ) deposits is a pattern of immune complex deposition characterized by masked deposits that show Igκ K restriction and are subepithelial and mesangial by electron microscopy. We present a case of a patient with SLE and biopsy-proven class 5 lupus nephritis whose repeat biopsy showed MMMD.

Case Description: A 26-year-old Hispanic female was admitted for the evaluation of persistent proteinuria. She was diagnosed with systemic lupus erythematosus (SLE) in 2015 and underwent a kidney biopsy in 2019 for proteinuria >1g that return with positive dsDNA, antinuclear antibody (IgG and IgM), and low C4. Initial biopsy was reported as “Membranous Glomerulonephritis consistent with class 5 Lupus Nephritis. The IgG was Glomerulì with focal segmental trace peripheral granular staining, Igκ was Glomerulì with diffuse and global, peripheral granular staining 3+, IgM was Glomerulì with diffuse, segmental to global, and peripheral granular staining 2+, C3 was Glomerulì with focal and segmental weak peripheral staining, arterioli +, C1q was Glomerulì with diffuse and global, peripheral granular staining 1+ to 2+. She volunteered to participate in a clinical trial for lupus nephritis in mid-2023, her labs were positive for dsDNA, low C4, and proteinuria >1g. FLC ratio indicates that Kappa and Lambda Glomeruli with diffuse and global, peripheral granular staining 3+, tubular protein droplets are positive, the second renal biopsy was done at this visit that reported as Membranous Glomerulonephritis, consistent with Class V Given the new finding of MMMD, a search for monoclonal gammopathy/MGRS, the MMMD was considered secondary to lupus nephritis, a rarely reported renal manifestation of Lupus Nephritis. She is currently on Mycophenolate, Hydroxychloroquine, Lisinopril, and Hydrochlorothiazide, based on recent lab results there is no significant improvement in her proteinuria.

Discussion: In conclusion, patients with SLE can develop Membranous glomerulonephritis with masked monoclonal deposits as a renal manifestation of the SLE in addition to classic class 5 lupus nephritis.

SA-PO1023
The Decrease of the Filtration Slit Density, Not Proteinuria, Is the Early Indication of Filtration Barrier Dysfunction
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Background: Intact podocyte foot processes (FP) are essential for proper slit selective filtration. Changes in FP morphology are thought to be the first event leading to proteinuria, but this has yet to be proven. Since FP are below the optical resolution of a light microscope, changes are studied on ultrathin sections by electron microscopy. Here, we show the relationship between morphology and proteinuria using podocyte exact morphology measurement procedure (PEMP), which is a 3D-SIM-based procedure.

Methods: Mice were treated with NTS and sacrificed 24, 48, and 72 h after injection. 3D-SIM was done on podocin and integrin co-stained standard formalin-fixed and paraffin-embedded kidney sections (3 μm). The filtration slit density (FSD) was measured by PEMP (Siegerist, 2017). Electron microscopic analysis were done on glutaraldehyde fixed tissue and processed using standard procedures. Albumin to creatinine ratios were also analyzed.

Results: We have found, that mice developed moderate proteinuria 48 h after NTS injection. Using PEMP, we found that the FSD was already significantly reduced in NTS-treated mice at 24 h compared to control-injected mice. Transmission electron microscopy analysis confirmed the presence of these structural alterations, indicating that effacement of the podocytes serves as the initial indication, followed by the onset of proteinuria.
Conclusions: PEMP analysis of standard histological sections from NTS-injected and control mice demonstrated that the first event in the functional loss of the size-selectivity of the filtration barrier is the effacement of FP morphology, followed by detectable proteinuria. Therefore, the assessment of the FSD is a promising strategy for early and accurate detection of a loss of filtration barrier integrity, providing opportunities for faster and precise diagnostics.

Funding: Commercial Support - NiPOKA GmbH, Government Support - Non-U.S.

SA-PO1024
Expression Evaluation of CD2AP, ITGA3, and ITGB1 in Podocyte Cell Cultures After Albumin Overload with and Without Puromycin-Expression Evaluation of CD2AP, ITGA3, and ITGB1 in Podocyte Cell Cultures After Albumin Overload with and Without Puromycin

Mara S. Guarrana,1,2 José R. Alves Troleze,1 Jackeline P. da Silva,1 Marcela L. Souza,3 Felipe R. de Oliveira,1,3 Heber Antonio,1 Luana dos Santos,1 Tais N. Mazzola,1 Adriana S. Torsoni,1 Vera Maria S. Belangero,1 Maricilda P. de Mello.1 State University of Campinas, Center for Molecular Biology and Genetic Engineering (CBMGE), Campinas, Brazil;2 Universidade Estadual de Campinas Faculdade de Ciencias Medicas, Campinas, Brazil;3 State University of Campinas, Growth and Development Laboratory, Center for Investigation in Pediatrics (CIPED), School of Medical Sciences, University of Campinas, Sao Paulo, Brazil, Campinas, Brazil; State University of Campinas, Faculty of Applied Sciences, Limeira, Brazil.

Background: Proteinuria is considered a prognostic marker for kidney disease and one of the main symptoms of podocytopenias. Several molecules participate in the maintenance of glomerular filtration barrier, including the CD2-associated protein (CD2AP) present in the slit diaphragm and the eGFR integrin in the basal membrane of podocytes. This study aimed to evaluate the relative expression of CD2AP, ITGA3 and ITGB1 genes after overload of albumin in podocytes in vitro.

Methods: Conditionally immortalized human podocytes were exposed to progressive concentrations of albumin (0, 3, 20 and 40 mg/mL) for 24 hours under two conditions with or without 12 hours of 15 μg/mL of puromycin aminoglycoside (PAN) treatment. We evaluated CD2AP, ITGA3 and ITGB1 genes relative expression through qPCR (n=3). The Friedman test was used to compare the different albumin exposures with and without PAN (p<0.05).

Results: The fold change of CD2AP, ITGA3 and ITGB1 genes are presented in Table 1. No significant difference was found among the albumin exposures, neither with nor without PAN (p>0.05).

Conclusions: In the condition here studied, albumin overload have not modulated CD2AP, ITGA3 and ITGB1 genes.

Funding: Government Support - Non-U.S.

Fold change of CD2AP, ITGA3 and ITGB1 genes

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SA-PO1025
Significance of Single-Point Cystatin C Measurement

Abutaleb A. Eljaz,1,2 Evan I. Fisher,1 Nazli Atefi,1 Zain Haq,1 Taylor R. Moody,1 Stephen L. Seliger,1,3 University of Maryland Baltimore, Baltimore, MD;1 VA Maryland Healthcare System, Baltimore, MD.

Background: Single-point serum Cystatin C in the absence of prior reference points has resulted in difficulties in interpretations in changes in kidney function. We investigated the correlation between Cystatin C and prior year change in creatinine (SCR) based eGFR for which multiple datapoints were available.

Methods: Simultaneously measured SCR and Cystatin C and their respective eGFRs were analyzed.

Results: 33 SCR-Cystatin C pairs were available for analysis. Patient characteristics included: mean age 72.1±8.7 years, 90.9% male gender, 84.8% African American race, prevalence of hypertension 90.9%, diabetes 48.4%, BMI 28.8±6.2, SCR 2.1±0.8 mg/dL, eGFR CKD-EPI 41±14.9 mg/mL/min, Cystatin C 2.1±0.7 mg/dL and Cystatin-C-eGFR 35.6±14.6 mg/mL/min. The mean difference in prior year eGFR was 2.28±0.41 mg/mL. Mean rate of change of prior year eGFR was 2.4±4.1 mL/min/year. SCR-Cystatin C demonstrated good correlation, as did eGFR CKD-EPI and Cystatin-C-eGFR. Although statistically significant, Cystatin C and prior year eGFR CKD-EPI changes demonstrated poor correlation. There were no significant correlations between delta SCR-Cystatin and delta eGFR CKD-EPI – Cystatin eGFR, Cystatin-BMI. Significant inverse correlation was observed between Cystatin C and eGFR CKD-EPI (R²=0.69, p<0.001).

Conclusions: In a small sample of CKD patients, serum Cystatin C, while well correlated with simultaneously measured SCR and GFR, was a poor indicator of prior year change in GFR.

Funding: Veterans Affairs Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
and indirubin (red) pigments, resulting in purple urine color. Risk factors include old age, female gender, alkaline urine, constipation, and the use of plastic urinary bags. The discoloration itself is benign but timely recognition of this uncommon presentation of urinary tract infection is crucial to ensure prompt diagnosis and treatment while avoiding unnecessary investigations.

**SA-PO1028**

**Melanuria: Black Urine as a Presenting Sign of Metastatic Melanoma**


**Introduction:** The worldwide incidence of malignant melanoma has been increasing at an average annual rate of 5%. We describe a case of melanuria as an initial sign of metastatic melanoma in a previously healthy young woman.

**Case Description:** A 24-year-old female with no medical history presented with two weeks of abdominal pain. On admission, she had mild tachycardia. Physical exam was notable for abdominal tenderness and lower extremity edema. Blood work showed creatinine of 1.5 mg/dL, lactate 19mmol/L, LDH 5000 IU/L. Amber urine that turned black upon exposure to air. Urine studies were negative for hemoglobin and bilirubin and was notable for abdominal tenderness and lower extremity edema. Blood work showed metastatic melanoma in a previously healthy young woman.

**Discussion:** Melanuria is the urinary excretion of melanin precursors leading to black discoloration of the urine. It is present in up to 15% of cases of malignant melanoma and typically occurs with diffuse melanosis. Urine sediment may show atypical pigment-laden cells and dark brown casts. Our patient had dark casts with atypical cells suggesting melanin-containing tubular epithelial cells and histiocytes. Although we did not test her urine for melanin precursors, we proposed the melanuria resulted from extensive tumor necrosis causing cytolysis of melanocytes and subsequent excretion in the urine. This case demonstrates that metastatic melanoma should be considered in the differential diagnosis of black urine.

**SA-PO1029**

**No Need for Beef: A New Vegetarian Test to Measure Renal Functional Reserve**

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**Background:** Renal functional reserve (RFR) corresponds to the physiologic increase in glomerular filtration rate (GFR) after a stimulus. It can be measured to evaluate living kidney donor candidates, risk and recovery of AKI in critical care situations and even risk of pre-eclampsia. The most frequently used test to measure RFR is by ingesting an oral load of protein from animal meat. We aimed to develop an alternative test to measure RFR without the need of meat consumption using L-arginine, a precursor of nitric oxide. Herein, we present the results of a pilot study.

**Methods:** A 4-hour creatinine clearance (CrCl) was measured in 7 healthy individuals in whom eGFR by CKD-EPI equation was 103.9 mL/min/1.73m² (range 92.3-113.4) after a day of plant-based diet and normal ingestion of fluids. The next day, at the same hour, a new 4-hour CrCl was measured, this time after the ingestion of 5 grs of L-Arginine 1 hour before the start of urine collection. RFR was calculated as the difference between indexed post-L-Arginine CrCl and indexed basal CrCl.

**Results:** Median basal CrCl was 124.6 mL/min/1.73m² (range 54.7-162). Post-L-Arginine CrCl was significantly augmented to 145.4 mL/min/1.73m² (range 81.1-179.7) (p<0.05). Median RFR was 20.8 mL/min/1.73m² (range -7.6-48.9). No adverse effects were reported.

**Conclusions:** Evaluation of RFR can be safely done using L-Arginine stimulation and could be considered as an alternative to meat consumption in vegetarian population. This preliminary data needs to be confirmed in a larger cohort. The optimal dosing of L-Arginine for this purpose should be determined in larger studies.

**SA-PO1030**

**Augmented CD36 Stimulation by Fatty Acids Promotes Macrophage Activation and Endothelial Injury in ANCA-Associated Vasculitis**

Xiang Zhang, Xiong Z. Ruan, Alan D. Salama. UCL Department of Renal Medicine, Royal Free Hospital, London, United Kingdom.

**Background:** ANCA-associated vasculitis (AAV) is characterised by monocyte/macrophage activation and small blood vessel inflammation leading to organ damage. In some patients, macrophage activation leads to giant cell and granuloma formation, resulting in further tissue damage. CD36 is a transmembrane glycoprotein expressed on various cells, including macrophages and endothelial cells. CD36 is crucial in the modulation of inflammatory processes. However, the role of CD36 in AAV remains understudied.

**Methods:** Cellular expression of CD36 and endothelial cell activation markers was assessed by FACS and immunohistochemistry on tissue sections. ELISA was used to measure soluble(s) CD36 in serum and cell supernatants. Multinucleate Giant cell(MNGC) formation was investigated using established protocols following Palmitic acid (PA) stimulation of cells with or without CD36 knockdown. Macrophage activation markers were examined using qPCR.

**Results:** CD36 expression was found to be increased in AAV kidney biopsies on glomerular and tubular macrophages. Additionally, CD36 expression on classical and intermediate monocytes was significantly increased in AAV patients compared to healthy controls. Serum sCD36 was elevated in AAV patients, specifically in the PR3-ANCA subtype, in both remission and active disease. Stimulation of THP1-derived macrophages with PA resulted in an increase in CD36 expression, increased the expression of e-Myc and ATF-2, and generated M1 polarised macrophages with significant MIF production. In addition, there was an increase in MNGC formation. These findings were all attenuated by CD36 knockdown or MIF antagonism. Similarly, PA stimulation of endothelial cells increased CD36 and VCAM expression and promoted MIF production. Co-culture of endothelial cells and macrophages with PA resulted in increased migration of macrophages towards the activated endothelial cells.
Conclusions: AAV patients demonstrate elevated levels of monocye and sCD36. Stimulation of CD36 by fatty acids promotes inflammatory responses in both macrophages and endothelial cells, potentially contributing to many of the features found in AAV. Targeting CD36 or its downstream effector MIF is a novel therapeutic strategy to be tested in AAV.

Funding: Government Support - Non-U.S.

SA-PO1031
Longitudinal Analysis of Urine Metabolomics of Preterm Infants Based on Ultra-High-Performance Liquid Chromatography-Tandem Mass Spectrometry (UHPLC-MS/MS) Technique
Qian Shen, Hong Xu, Shu Hong. Children's Hospital of Fudan University, Shanghai, China.

Background: To explore the regular urinary metabolic characteristics of preterm infants in the early postnatal period and find the association between early metabolic adaptation and urinary metabolism.

Methods: Between June 1, 2021 and September 31, 2022, 36 preterm infants were recruited from the Children’s Hospital of Fudan University, urine samples were collected on postnatal day 1 (PND1), PND7 and PND14 respectively, for a longitudinal cohort self-control analysis. UHPLC-MS/MS was used to characterize urinary metabolic changes at postnatal week 1 and week 2. Multivariate analyses were used to screen for differential metabolites and metabolic pathway.

Results: Widely targeted metabolic analysis of urine from the first week of postnatal life and find the association between early metabolic adaptation and urinary metabolism. Targeting CD36 or its downstream effector MIF is a novel therapeutic strategy to be tested in AAV.

Funding: Government Support - Non-U.S.

SA-PO1032
Preservation of Slides of Fixed Urinary Sediment for Educational Purposes
Lauren Cohen, Juan Carlos Q. Veléz, Jay R. Seltzer. ‘Ochsner Health, New Orleans, LA; *Missouri Baptist Medical Center, Saint Louis, MO.

Background: Urine sediment slides for microscopy are best inspected promptly, as drying artifact, the result of evaporation, will occur and limit the time the slide is viable for viewing. Although teaching urine microscopy using stored images of cells, casts, and crystals is useful, there is no replacement for real-time microscopic examination of a urine sediment slide. Thus, we aimed to develop a reproducible method of preserving urine sediment slides.

Methods: Urine specimens from patients at Ochsner Medical Center (New Orleans) and Missouri Baptist Medical Center (St Louis) seen by the nephrology department were randomly chosen based on the presence of distinct urine sediment findings. Specimens were centrifuged and the supernatant discarded. Ten drops of 10% buffered formalin were added to resuspended pellets. After 30 minutes, samples were centrifuged for 2 minutes and remaining supernatant was discarded. The new pellet was resuspended in a solution of 1 drop of Sternheimer-Malbin stain, 2 drops of glycerol, and 1 drop of clear Elmer’s® glue. One drop of this mixture was placed on the slide and a coverglass applied. CoverGrip® was painted around the perimeter of the coverglass as a sealant. Slides were examined at regular intervals (24, 48, 96 hours; 1, 2, 4, 8 weeks) and images were captured using ScBaCam®. Slide quality was evaluated for structure retention, stain intensity, and evaporation artifact.

Results: Various cast types (granular, waxy, cellular, vacuolated), amorphous, and crystals were captured in the preserved slides across all specimens (n ~ 12). The integrity of the structures identified on day 1 was preserved up to 8 weeks in all cases. No significant decay in quality was observed over time. Artifacts observed included evaporation artifact, cloudiness, and stain fading. However, none of those factors altered the overall interpretation of the slide. A library of preserved slides was successfully used by the authors in a recent hands-on educational workshop (KidneyCon).

Conclusions: Our novel method of urine sediment slide preservation was effective in preserving the quality and quantity of the findings revealed upon inspection immediately following urine collection. This technique can be implemented in academic centers for educational and clinical purposes. Further studies are required for optimization.

SA-PO1033
New Method of Immunophenotyping of Urinary Cells by Multicolour Flow Cytometry: A Pilot Study
Ivan Rychlik, Peter Habara, Karolina Krátká, Martin Havrda, Renata Lazanska. Nephrology Unit. Univerzitní Karlova 3 lekarska fakulta, Praha, Czechia.

Background: Podocyturia, non-invasive option, was used to diagnose glomerulopathies(GN), namely fibrosis and glomerulosclerosis, previously detected only by renal histology(RB). Urinary sediment analysis after labelling with antibodies against podocalyxin and podocyte-specific transcription factor WT-1 was proven as clinically useful. Determination of mRNA was used, too, but hardly usable due to high instability.

Methods: Patients(pis) who underwent RB for nephrotic syndrome, regardless of its etiology, were examined before RB. First morning urine sample was collected. Urinary cell concentrates were prepared by ultrafiltration using strainers. Conventional staining protocol was used with panel of antibodies: anti-podocalyxin-PE, anti-CD86-FITC, anti-CD87-BV510, anti-CD24-PeCy7, anti-CD10-PerCP, anti-CD133-APC, anti CD45-APC-Cy7. Healthy volunteers and isotype controls were used. The Hoechst33342 DNA dye was applied to identify cells. Gating strategy: only population of cells binding the DNA dye Hoechst33342 was selected to exclude non-nuclear elements, then exclusion of white blood cells, and then immunophenotypically specific rare cell populations could be observed in scatter plots.

Results: 13 pts with histology: DKD 5x, obesity-related glomerulopathy 2x, IgA nephropathy 5x, ANCA associated vasculitis 1x and 5 healthy controls were examined. Population of PCX+/CD10+/CD133+/CD24- cells was detected in varying degrees of abundance, as well as a population of PCX-CD10+/CD133+/CD24- cells. The former population predominated mainly in patients where the histological findings were dominated by degenerative changes (interstitial fibrosis and glomerulosclerosis). In contrast, the latter population was more prevalent in active inflammatory changes, most notably in AAV and IgAN with the presence of fibroepithelial crescents. None of the above cell populations were present in healthy controls, both isotype controls.

Conclusions: The method significantly reduces the autofluorescence background of urine samples to reduce noise that prevented multi-color analysis of urinary cells on flow cytometer and thus capture different rare populations of urine glomerular cells, which no published approach to urine flow cytometry has yet allowed. The method is inexpensive and offers the potential for non-invasive differential diagnosis and monitoring of therapy. Supported by COOPERATIO 34.
MUC1 on Urinary Extracellular Vesicles for Detection of Impaired Renal Function

Keichi Takizawa, Tatsuya Nishimura, Yutaka Harita, Tokyo Daigaku, Bunkyo-ku, Japan.

Background: The nephron’s various cell types produce urinary extracellular vesicles (uEVs), which have the potential as a promising biomarker resource. Aiming to detect chronic kidney disease (CKD) in its early stage, we performed proteome analysis of uEVs from patients with a congenitally reduced number of functional nephrons and found that pediatric CKD can be detected accurately by the expression levels of molecules such as MUC1 in uEVs (Science, 2022). In this study, we validated the diagnostic capacity of an ELISA-based test method analyzing uEVs to separate adult individuals with decreased renal function in a Japanese community cohort of the Tokoku Medical Megabank Project.

Methods: Two hundred eleven samples (male 109, female 102) provided were analyzed. The mean age ± SD was 51.2 ± 14.7 years. The expression levels of MUC1 and CD9, a classical exosomal marker, on the surface of uEVs (uEVs_MUC1 and uEVs_CD9) were measured using ELISA plates that enabled the isolation of uEVs and quantitation of expression of molecules. The correlation between the expression levels and clinical parameters was analyzed.

Results: uEVs_MUC1 showed a positive correlation with uEVs_CD9 but not with urinary albumin. As in pediatric patients with kidney diseases, the expression of uEVs_MUC1 was significantly decreased in adult individuals with reduced renal function (eGFR < 60 ml/min/1.73m2) (P < 0.001). uEVs_MUC1 had an AUC of 0.88 for separating individuals with eGFR < 45 from those with eGFR ≥ 45 and 0.92 for separating those with eGFR < 30 from those with eGFR ≥ 30. When combined with urinary albumin, the diagnostic accuracy was further enhanced. To further apply this ELISA to clinical testing, we generated a high-titer monoclonal antibody against MUC1, and established a protocol to quantify uEVs_MUC1 in clinical samples.

Conclusions: MUC1 expression in uEVs can be a biomarker of renal dysfunction independent from proteinuria, which was validated in childhood and adult cohorts. Future research will focus on elucidating the mechanism and conducting prospective investigations in order to advance the development of the uEVs-based noninvasive test technique robustly diagnostic for CKD.

Funding: Other NIH Support - Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI; grant number JP16K15523 to Y.H.), and by Japan Agency for Medical Research and Development (AMED; grant number JP20lm0203003 and JP21lm0203003, and JP22ym0126063h0001 to Y.H.), and by the University of Tokyo Gap Fund Program fifth period (to Y.H.), Government Support - Non-U.S.

SA-PO1035

Findings in Urinary Sediment Inspected by Microscopy Several Days After Collection

Serenella A. Velez, Lauren Cohen, Jay R. Seltzer, Juan Carlos Q. Velez.

1Ochsner Health, New Orleans, LA; 2Missouri Baptist Medical Center, Saint Louis, MO.

Background: Textbooks and clinical practice manuals recommend inspection of urine sediment specimens immediately or within < 2 hours of collection for the presence for up to 1 week. However, no conclusive evidence supporting that recommendation. Based on anecdotal observations, we hypothesized that adequacy of urinary sediments can be maintained way beyond the 2-hour limit.

Methods: An experimental study was conducted utilizing urinary sediment specimens obtained from patients seen by the nephrology inpatient consultation service due to acute kidney injury. Aliquots of the specimens were stored at both room temperature (RT) and at 4°C. Urine microscopy was performed at the time of collection, 24 hours, 48 hours, and a week post collection, and assessed for presence of granular casts (GC), waxy casts (WC), red blood cell casts (RBCC), acanthocytes, and lipids. Abundance of casts was assessed by an adaptation of the Perauxza score (cast number/low power field).

Results: A total of 16 urine specimens were collected and divided into RT (n=16) and 4°C (n=14). Overall, only 4.6% (3/65 data points) revealed a change in density of casts. By 48 hours, GC, WC, WC, RBCC and RBCC did not change in presence or abundance at either RT or 4°C. By 1 week, 90% (9/10) did not change GC score for both RT and 4°C (3/4) and 80% (4/5) did not change WC score at RT and 4°C respectively, and 83.33% (5/6) and 100% (7/7) did not change RBCC score at RT and 4°C respectively. For samples with acanthocytes, at RT, 2 did not change in abundance for up to 1 week, whereas 1 changed from 40% to 25% at 48 hours. At 4°C, 1 case did not change in acanthocyte abundance for up to 1 week, whereas 1 changed from 40% to 25% at 48 hours. For samples with lipids, 100% (5/5 at RT, 3/3 at 4°C) maintained lipid presence for up to 1 week.

Conclusions: Our findings challenge the traditional knowledge and demonstrate that long-term storage of the urinary sediment, although recommended, is not essential in clinical practice. Collected specimens can be kept for later examination in the event that an expert observer is required for corroboration of findings. Further research is necessary to precisely determine at which point urinary sediment quality begins to decay.

SA-PO1036

Urinary Sediment Podocin mRNA Excretion in Healthy Adults


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Background: We have previously reported that the excretion of urinary sediment podocin mRNA (U-sed Pod mRNA) is a useful biomarker for the early diagnosis and evaluation of various glomerular diseases. However, no study has been conducted on healthy adults. In this study, we investigated the excretion of U-sed Pod mRNA in healthy adults, including the effects of gender and age.

Methods: We studied 294 healthy individuals (48 in their 20s, 52 in their 30s, 58 in their 40s, 49 in their 50s, and 42 in their 60s or older, including 40 in their 60s and 2 in their 70s; a male-to-female ratio of approximately 1:1) who received health checkups from June 2018 to March 2019 and did not have hypertension (>140/90 mmHg), diabetes (fasting blood sugar >126 mg/dL), albuminuria (U-Alb/Cre > 3 mg/gCre), or chronic kidney disease (eGFR > 60 ml/min/1.73m2) and were not receiving medication. We measured the excretion of U-sed Pod mRNA in spot urine samples.

Results: No significant differences in U-sed Pod mRNA normalized to urinary creatinine (U-sed Pod mRNA/Cre) or U-sed Pod mRNA normalized to urinary sediment aquaporin 2 (U-sed AQAP2a mRNA) were observed among the healthy adults less than 60 years of age. In addition, neither marker was significantly different between the genders. However, U-sed Pod mRNA/Cre excretion was significantly lower in subjects over 60 years of age compared to those less than 60 years (1.65 ± 0.15 M/gCre vs. 12.4 ± 4.14 M/gCre; p < 0.001). Furthermore, U-sed Pod mRNA excretion was not detected in approximately 30% of subjects over 60 years of age. U-sed AQAP2a mRNA excretion was also significantly lower in subjects over 60 years of age, similar to U-sed Pod mRNA excretion.

Conclusions: No age or gender differences were detected in U-sed Pod mRNA/Cre or U-sed Pod mRNA/AQAP2a mRNA excretion in healthy adults less than 60 years of age who could be used as normal controls.

Funding: Government Support - Non-U.S.

SA-PO1037

Rapid Diagnosis of Urinary Tract Infection by Flow Cytometry-Based Urine Analyzer

Supasyndh, Patid Tananaboriboon, Thanapat Punchucherd.

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Background: Urinary tract infections (UTIs) are important healthcare problems for hospitalized and community patients. Various bacterial species can cause UTI, the most common of which is the Gram-negative bacilli Escherichia coli. The gold standard for UTI diagnosis remains urine culture, followed by antibiotic sensitivity testing. However, this takes around 48 hours for urine to be reported. Therefore, a rapid screening test for UTI is highly desirable to guide clinical decision-making. The Sysmex UF-5000 is a flow cytometry-based automated urine analyzer capable of providing WBC and bacterial counts and the Gram staining of the causative bacteria that positive impact on the rate of antimicrobial resistance. Our prospective cohort study aims to validate the automated flow cytometric analysis using Sysmex UF-5000 for rapid UTI screening and discrimination of gram-positive and gram-negative bacteria, compared to urine culture and conventional Gram staining.

Methods: Midstream urine samples from patients with suspected UTIs were collected in sterile containers. They were then subjected to analysis by Sysmex UF-5000 automated urine analyzer, conventional Gram staining, and urine culture. The correlation and agreement between the different methods were then determined and ROC curve analysis was performed where appropriate.

Results: A total of 285 urine samples were collected from 285 patients for analysis. An almost equal gender distribution was achieved. Out of the 285 patients included, 163 were outpatient, 104 were inpatient, 14 were wards in the ICU, and 4 presented to the emergency department. In total, 140 of 285 samples (49%) yielded a 105 CFU/ml bacterial growth (73 with Gram-negative bacteria, 36 with Gram-positive bacteria, 27 with mixed cultures, and 4 with yeast). In comparison, 68 samples (23.9%) yielded a 104 CFU/ml bacterial growth on urine cultures. We found that a UF-5000 bacterial count of ≥5×103 CFU/ml predicted a 105 CFU/ml bacterial growth on urine culture with a sensitivity of 86.8% and specificity of 81.1%. The bacterial discrimination performance of the UF-5000 for GN bacteria was superior to that for GP bacteria.
Conclusions: UF-5000 demonstrated a good potential utility for rapid UTI screening. This situation’s clinical advantage of predicting Gram-negative bacterial infection is reasonable despite the need for further evaluation.

Funding: Commercial Support - Sysmex(Thailand) Co.,Ltd., Government Support - Non-U.S.

SA-PO1038

Urine Immune Complex of V-Set Immunoglobulin Domain-Containing 4 as a Novel Biomarker of Lupus Nephritis
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Background: Lupus nephritis (LN) is a devastating chronic kidney disease (CKD) caused by Systemic lupus erythematosus (SLE). However, to monitor disease activity and predict the risk of LN flare is still challenging, and there is an urgent need to identify novel biomarkers of LN that have high diagnostic or predictive values. In our recent study, by using a quantitative proteome immunoarray, V-set Immunoglobulin-domain-containing 4 (VSG4) was found significantly elevated in the serum and kidneys of LN patients compared to healthy controls, and could reflect renal pathology of LN. We were interested to ask if VSG4 was secreted into the urine in LN patients.

Methods: In an initial testing using ELISA, we simultaneously measured the free form, autoantibody, and immune complex levels of VSG4 in the urine and serum samples from the same LN patients (N = 28), compared to other chronic kidney disease controls (CKD, N = 7) and healthy controls (N = 13).

Results: We found that the free form of VSG4 was not detectable in the urine of LN or controls by using commercial sandwich ELISA kits. Interestingly, the urinary immune complex of VSG4(VSG4 ICx) was detectable in LN and controls. Importantly, the urinary VSG4 ICx was significantly elevated in the LN patients, compared CKD controls (P-value = 0.031) and healthy controls (P-value = 3.05E-05). Urinary VSG4 ICx was also significantly increased in the CKD patients compared to healthy controls (P-value = 2.5E-05). In the same patients, the free form of VSG4 was significantly elevated in LN, compared to CKD controls (P-value = 2.6E-05) and healthy controls (P-value = 1.14E-10); both serum autoantibody and serum ICx levels of VSG4 were also significantly elevated in LN compared to healthy controls. By using a Spearman’s paired test, the urinary VSG4 ICx levels were positively correlated with the serum free-form VSG4 levels (r = 0.67, p = 0.001). More interestingly, the urinary VSG4 ICx levels were positively correlated with the following clinical parameters: SLEDAI (Spearman’s Rank Correlation Coefficient r = 0.49, p = 0.007), SLEDAD1 (r = 0.44, p = 0.03), urea protein/creatinine (r = 0.4, p = 0.03), and white blood cell counts (r = 0.49, p = 0.04).

Conclusions: Urinary VSG4 immune complex may be a promising novel biomarker of SLE and LN.

Funding: Other NIH Support - R01AG062987

SA-PO1039

Profiling of Urinary RNA Biomarkers for CKD with Nanopore Sequencing
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Background: There is a need to develop new biomarkers of kidney dysfunction & damage that are more informative than the estimated glomerular filtration rate (eGFR) & urine albumin to creatinine ratio (UACR). While RNAseq is increasingly being used for biomarker discovery, there are few reports of applications of 3rd generation sequencing platforms (Nanopore) to CKD.

Methods: Urinary RNA from participants in the COMPASS study (PMCS830221) with variable kidney function & UACR was isolated to make cDNA libraries with a novel pipeline for Nanopore sequencing (PALS-NS, https://www.biostars.org/content/10.1101/2022.12.16.520507v1). RNA counts were normalized via Analysis of Variance and analyzed via negative binomial mixed effects models (NBEMEM, PMCS499834).

Results: 19 cDNA libraries were made from the initial and follow up (12 mo) samples of 7 pts (6f), aged 54 ± 2.2 yrs with SBP 132 ± 15 mmHg, UACR 48 ± 73 mg/g, eGFR was assessed via the 2021 CKD Epi formulas for Creat (74 ± 35), Beta 2 microglobulin (65.5 ± 30), Creat/Cystatin (86.53 ± 39). Protein coding and long non coding (lncRNA) RNA was the most frequently encountered RNA species (14-20%) and 8-9% respectively. Correlation of the counts between follow up & baseline samples was high (>0.89). NBME estimates of the effects of eGFR on counts were correlated highly with each other, correlated moderately with UACR and not correlated with SBP[fig]. Term analysis mapped the differentially expressed RNAs (>70% lncRNA) to transcriptional factors and the lpsine degradation pathway (including several lysine methyltransferases) that has been recently implicated in the pathogenesis of CKD (PMCS928357) and podocyte injury (PMCS906535).

Conclusions: Nanopore sequencing provides a cheap, portable, platform for novel RNA biomarker discovery & quantification in CKD.

Funding: Other NIH Support - NCATS, ULTR001449, Commercial Support - Dialysis Clinic Inc, 1C-3765

SA-PO1040

Melatonin Increases Survival Through Upregulation of Clock NEAT1 and Enhancer-Associated Histone Modifications in Albumin-Injury Tubular Cells
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Background: Melatonin modulates circadian rhythm via the core clock genes, thereby regulating numerous physiological conditions in kidneys. The melatonin-regulated coding RNA is highly identified, it remains unknown whether long noncoding RNAs (lncRNAs) can be modulated by melatonin and exhibit the diurnal rhythm in renal tissue.

Methods: We identify melatonin-regulated clock lncRNAs including NEAT1, which are upregulated by melatonin and BMAL1/CLOCK heterodimer in human renal tubular epithelial cells (TECs).

Results: NEAT1 oscillations associated nocturnal change of core clock genes and endogenous melatonin in mouse TECs. Clock NEAT1 promote TECs proliferation through increased occupancy of histone 3 lysine 27 acetylation (H3K27ac) and histone 3 lysine 4 mono-methylation (H3K4me1) levels at MKI67 enhancer regions. Molecular studies showed that melatonin enhanced NEAT1 expression via increasing BMAL1 stability and thereby enforce on NEAT1 promoter. Treatment of albumin-injured TECs with melatonin alleviated cell death by transcactivating clock NEAT1 and restore the reduction levels of H3K4me1, H3K27ac, core clock genes and MKI67. Using an experimental membranous nephropathy (MN) model, exogenous melatonin treatment ameliorates the proteinuria and hypoalbuminaemia in experimental MN kidneys associated with the increased levels of core clock genes, H3K27ac, Mks67 and Neat1 in TECs.

Conclusions: Collectively, our results suggest that melatonin enhanced cell proliferation in albumin-injured TECs via upregulation of clock NEAT1 and NEAT1 mediated-changes in histone modifications and MKI67 levels, which has the potential for therapeutic intervention.

Funding: Government Support - Non-U.S.

SA-PO1041

Single-Cell Transcriptome Atlas in C57BL/6 Mice Encodes Morphological Phenotypes in the Aging Kidneys
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Background: C57BL/6 mice are commonly used marine models with the desired genetic background for modification in different research settings. So far, there is still a lack of comprehensive kidney morphology and single-cell transcriptome atlas at various developmental stages of C57BL/6 mice. To provide an interactive set of reference standards for the scientific community, we designed the present study to dissect the kidney from the capillary-loop stage of development till senescence at 30 months of age.

Methods: Eight groups, with five to six mice each, represented embryonic (18.5 days), newborn (1 day), adolescent (1 month), young (3 months), adulthood (6 months), middle-aged (10 months), old (20 months), and senescent (30 months) animals, respectively. Periodic acid-Schiff and silver staining were used to examine the histology of the kidney. The ultrastructure features of the kidney were examined using transmission electron microscopy. Kidney single-cell transcriptome analysis was conducted in three and 30 month-old mice to reveal the gene expression profiles in glomerular cells. Unbiased sampling and quantitation method was used to analyze the glomerular structures.

Results: With age, there was an increase in the glomerular size, the percentage of podocyte foot process effacement, and the extent of mesangial expansion. The number

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author.
of Wilms’ tumor 1 (WT1) positive podocytes remained stable from the young till 20 months old. By age 20 months, the number of WT1 positive podocytes was reduced till 30 months of age. Of note, GMB knobs appeared at three months and became frequent with age. The level of urinary albumin to creatinine ratio (UACR) was increased in the senescent mice compared with the immature and middle-aged mice. Using single-cell transcriptomic data, we assessed cell-type-specific manifestations of different hallmarks of aging, such as changes in the genes of intrinsic renal cells and biological alterations involved with age.

**Conclusions:** In conclusion, the availability of comprehensive kidney morphology and single-cell transcriptome atlas at various developmental stages of C57BL/6 mice would be a new and significant resource for mechanistic investigations and testing of potential therapeutic interventions.

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

SA-PO1042

**Investigation of Temporal Patterns of Biomarker Expression from Different Segments of the Kidneys in Healthy Subjects**

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**Background:** Urinary extracellular vesicles (uEVs) may parallel physiologic and pathologic processes taking place in their kidney cell of origin. Combined with their ease of access, this makes uEVs excellent candidate biomarkers. It is known that kidney function and expression of some proteins follow a circadian pattern. Therefore, the normal daily variation in uEV excretion and the content of specific protein cargos must be understood. The goal of this study is to examine changes over a 24 hour period of uEV markers of glomerular and tubular origin. In addition, we examined TSG101 (Tumor susceptibility gene protein 101) as an EV marker.

**Methods:** Each void during a 24-hour period for 13 healthy individuals (108 samples total) was collected. uEVs from each void was isolated by differential centrifugation at 20,000g, and washed with a low ionic strength buffer to remove uromodulin. uEV count and sizing was performed on each final pellet using Nanoparticle Tracking Analysis (ZetaView; Particle Metrix). Flow Cytometry using SpectralFlow was performed on uEVs stained with an antibody panel including CD35 (CR1), CD26 (DPP4), CD9 (Tetraspanin) and CD10 (Neprilysin). uEV protein lysates were immunoblotted for SLC12A3 and TSG101.

**Results:** TSG101 signal normalized to total protein has a positive linear correlation with creatinine (r=0.62, p<0.001), indicating it may be expressed steadily. Normalizing to creatinine, we observe the expression of SLC12A3 vary over a day in a temporal pattern. The antibody panel of glomerular and tubular markers detected with single flow cytometry did not express a temporal pattern when normalized to TSG101.

**Conclusions:** uEV biomarker expression may be normalized to TSG101 signal as it correlates with creatinine. SLC12A3 has a critical role in kidney function with sodium reabsorption and has shown circadian pattern of expression previously in rodent models. Our results demonstrate a similar temporal pattern of a large range of uEVs carrying SLC12A3 in humans. This temporal variation of uEV markers needs to be further characterized and in heart, kidney and disease. A uEVs characterization of temporal protein expression patterns of uEVs has potential to accelerate uEV biomarker discovery for kidney diseases.

SA-PO1043

**Nicotinamide Adenine Dinucleotide (NAD) Deficiency Contributes to Progressive Kidney Disease in HIV Nephropathy Mice**

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**Background:** HIV disease remains prevalent in the USA and is even more highly prevalent in sub-Saharan Africa. Recent investigations revealed that renal mitochondrial dysfunction contributes to HIV-associated nephropathy (HIVAN) in Tg26 transgenic mice. We hypothesized that nicotinamide adenine dinucleotide (NAD) deficiency contributes to energetic dysfunction and progressive tubular injury.

**Methods:** Tg26 and wild-type (WT) mice were treated with nicotinamide riboside (NR, 500 mg/kg body weight/day in drinking water or the farnesoid-X receptor agonist intestines, and body weight/day in the diet from 6 to 12 weeks of age. We used multi-omic characterization of kidney tissue transcriptomes and metabolomes to investigate metabolic mechanisms of HIVAN tubulopathy and the effects of treatment with NR and INT-747.

**Results:** Treatment with NR and INT-747 ameliorated kidney tubular injury in Tg26 mice, as shown by serum creatinine, urine albumin and the tubular injury marker, urinary neutrophil-associated lipocalin (NGAL). NR levels were significantly lower (2.86 [2.54-3.82, IQR] nmol/mg) in Tg26 kidney compared with WT mouse kidney (6.94 [5.48- 7.87, IQR] nmol/mg) and levels were restored by either NR or INT-747 treatment. We used multi-omic analysis of transcriptomic and metabolomic measurements showed that the NDV salvation pathway was downregulated in Tg26 mouse kidney. Sirtuin3 acetyltransferase activity and mitochondrial oxidative phosphorylation activity were lower in ex vivo proximal tubules from Tg26 kidney compared to those of WT mice. These activities were restored by supplementation with NR and with INT-747.

**Conclusions:** NAD deficiency contributes to HIVAN tubulopathy and mitochondrial dysfunction in Tg26 mice. Restoration of NAD levels in kidney improves these pathologies.

**Funding:** NIDDK Support (A-D) Representative PAS staining images of mouse kidney, (E) NAD signaling pathway map overlaying transcriptomic and metabolomic results comparing Tg26 and WT mice.

SA-PO1044

**Systemic Immune Dysregulation in a Mouse Model of Oxalate Nephropathy**

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**Background:** Chronic kidney disease (CKD) is a leading cause of mortality and morbidity. Crystalline nephropathy induced by high oxalate is an established cause of CKD. CKD and crystal formation were shown to influence immune cell composition and gut microbiota. To investigate the impact of oxalate nephropathy on the immune system and the microbiome, high oxalate-fed mice were analyzed by flow cytometry and 16S sequencing.

**Methods:** To investigate the effects of oxalate we fed single housed C57BL6/N mice (n=7) a high oxalate diet for 10 days. Chow diet fed littermates served as healthy controls. Both groups were analyzed for immune cell composition (flow cytometry) of the spleen, kidney and small intestine (lamina propria immune cells (s/lPL)) and bulk RNA sequencing of the kidney. Microbiota composition was analyzed by 16S sequencing.

**Results:** Mice fed a high oxalate diet demonstrated hyperoxaluria and increased kidney injury as measured by plasma creatinine concentration. Furthermore, we observed a significant reduction in body weight. Bulk RNA sequencing revealed a prominent inflammatory signature of the kidney, including increased classical damage markers (Lcn2, Haver), as well as genes enriched for Th17 differentiation pathway. Flow cytometry analysis identified more than 100 dysregulated immune subpopulations in the kidney. Furthermore, we detected a pronounced inflammatory response in the spleen and the intestine. Interestingly, type 17 T cells (IL-17A+ and ROR+g) within conventional T helper and regulatory T cells were the main and overlapping phenotypic drivers across different organs, namely the kidney, small and large intestine. Compared to the immune system, the microbiome only showed small scale taxonomic shifts (increase of 4 vs. decrease of 9 operational taxonomic units).

**Conclusions:** Our in-depth immune phenotyping uncovers a pronounced inflammatory signature across several organs (intestine, spleen and the kidney). Our study provides a comprehensive description of immune cell alterations and serves as a valuable resource for the scientific community.

SA-PO1045

**Renal Macrophages Play a Pivotal Role in Cleaning off Intratubular Particles**

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**Background:** During the passage of the glomerular filtrate through the renal tubular system, various microscopic sediment particles, including mineral crystals resulting from urine concentration, are generated. Dislodging these particles in the intratubular compartment is critical to ensure free flow of filtrate and the final formation of urine. However, the underlying cellular mechanism for the clearance is unclear.

**Methods:** The interactions of macrophages and segments of renal tubules were analyzed by high-resolution confocal microscopy and scanning electron microscopy. Live movement of renal macrophages was monitored by two-photon microscopy. Bulk RNA-seq was performed to analyze the transcriptomic difference between cortical and medullary macrophages. Hyperoxaluria model was used to induce kidney stone formation.

**Results:** We uncovered that the juxtatumular macrophages in the renal medulla constitutively formed transepithelial protrusions and were “sampling” urine contents. This transepithelial protrusions were formed in a transcellular route instead of between epithelial cells, so that the overall junctional architecture of tubular epithelium was intact. This transepithelial protrusions were constitutively formed transepithelial protrusions and were "sampling" urine contents. The kidney is a small organ but has a large surface area where the glomeruli and the tubules take place. The kidney is responsible for regulating the volume and composition of urine. The kidney is also responsible for removing waste products from the body. The kidney is a vital organ that is essential for maintaining health and well-being.
of renal macrophages were prone to developing various intratubular sediments. Mechanistically, integrin β1-mediated ligation to the tubular epithelium is crucial to the transepithelial behaviors of medullary macrophages.  

Conclusions: This study unveils a previously unappreciated role of renal macrophages in keeping the tubular system unobstructed. In contrast to the traditional view that the renal epithelial cells are the primary barrier to cell passage, we found that these juxtamural macrophages present in the medulla constitutively formed transepithelial protrusions, and the underlying molecular mechanisms were provided as well. In addition, we demonstrated a divergence between medullary and cortical macrophages in transcripts and in behaviors. These findings may pave the way for developing novel therapies for nephrolithiasis as well as renal infection caused by ascending microbes.

Funding: Government Support - Non-U.S.

SA-PO1046

Vascular Injury-Derived Exosomes Trigger Renal Tertiary Lymphoid Structures and Accelerate Lupus Nephritis

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Background: Microvascular damage is an emerging contributing factor to Lupus Nephritis, leading to end stage renal disease. We have demonstrated that apoptotic exosomes derived from vascular injury (ApoExo) trigger the production of SLE-associated antibodies in wild-type mice. ApoExo infusion induces autobody production and tertiary lymphoid structure (TLS) formation in a murine vascular allograft rejection model. We hypothesize that ApoExo induce an autoimmune response that accelerates the development of lupus nephritis.

Methods: 20 weeks old NZB/WF1 mice were infused with ApoExo or vehicle every second day for 3 weeks. Circulating anti-LG3 and ApoExo levels were measured by ELISA and Bs-FCM respectively. Kidneys were collected and renal histology and 3D in vivo micro-computed tomography (MicroCT) analyses were performed.

Results: NZB/WF1 mice infused with ApoExo show higher levels of circulating anti-LG3 compared with the vehicle group (p=0.0034). MicroCT data suggest microvascular involution associated with LN development. In addition, ApoExo infused NZB/WF1 mice demonstrate significant renal inflammatory infiltration compared to mice infused with vehicle. ApoExo triggered the recruitment to the renal interstitium of CD3+, CD20+, and AID+ lymphocytes into nodules reminiscent of TLS (p=0.0342) associated with increased Ly6G+ and Ly6C+ expression and multiple myeloma transgenic. Finally, heightened renal tubular damage (p=0.05), blood urea nitrogen levels (p<0.05) and decreased survival (p=0.0055) were observed in ApoExo infused NZB/WF1 mice compared to the ones infused with vehicle.

Conclusions: ApoExo infusion increases renal nodular lymphocyte infiltration, autobody production increase renal damage in lupus prone mice. This project is, to our knowledge, the first to evaluate the contribution of vascular injury derived extracellular vesicles to LN.

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

SA-PO1047

Extracellular DNA Traps Are Induced by Medullary Range NaCl, but Not Urea, and Protect Against Bacterial Pyelonephritis In Vivo

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Background: Excessive NaCl and urea concentration can characterize the kidney medulla. Their effects on innate immune cell death, namely extracellular DNA trap (ET) formation, have never been examined.

Methods: ET formation in individual cardiomyocytes were revealed by distinguishing cardiomyocytes between healthy and hypertrophied cardiomyocytes.

Results: Medullary-range NaCl concentrations and pharmacologic modulations of different cell death pathways. ET were defined.

Conclusions: Our data demonstrate that renal medullary range NaCl concentrations are novel inducers of programmed myeloid cell death, namely ET formation. PAD4-dependent extracellular DNA traps promote antibacterial host response in the kidney.

Funding: Government Support - Non-U.S.

SA-PO1048

Gadolinium Retention Is Modulated by Prior Magnetic Resonance Imaging Contrast Agent Exposures

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Background: Complexes of magnetic resonance imaging (MRI) contrast agents include crippling systemic fibrosis, kidney injury, and fatal gadolinium encephalopathy. Gadolinium, a rare earth metal in the periodical table’s lanthanide series, has been extensively used in modern diagnostic medicine to enhance MRI procedures. Gadolinium-based contrast agents (GBCAs) are grouped into two categories: linear (OmniScan) or macrocyclic (Dotarem). Patients are often exposed to multiple brands of contrast agents. The impact of this practice on gadolinium retention and pathology has never been examined.

Methods: In our study, 21 male mice were randomized to five experimental groups: (1) saline-treated controls; gadolinium-based contrast agent-treated (2) OmniScan (OMN), (3) Dotarem (DOT), or in combination (4) OMN (1 week) followed by DOT administration for 3 weeks or (5) DOT (1 week) followed by OMN treatment for 3 weeks. Saline or contrast agents were administered via intraperitoneal injections 5 days a week for 4 weeks according to our established protocols. Tissues were excised and snap-frozen in liquid nitrogen. On average, 15 mg of tissue were digested in nitric acid, and gadolinium concentrations were quantified using PerkinElmer NexION 300D inductively coupled plasma mass spectrometry (ICP/MS) with a detection limit of 0.01 ppb.

Results: Regardless of the mode of exposure, 4-week treatment of OMN or DOT only or in combination (OMN-DOT or DOT-OMN) resulted in a significant accumulation of gadolinium in the tested organs. Gadolinium accumulation in the liver was lower in animals treated with DOT alone or in combination with OMN (OMN-DOT) than in animals administered with OMN alone or with DOT (DOT-OMN). In the kidney, the lowest gadolinium accumulation was observed in the OMN-DOT group in comparison model. GBCA-treated groups. GBCA treatments did not influence calcium levels in the kidneys or livers.

Conclusions: Our data indicate that prior GBCA exposures influence gadolinium retention in the kidney or liver. Future studies are needed to determine if this factor is influential in the pathophysiology of NSF in humans.

SA-PO1049

Semiautomated Pipeline for Quantitative Analysis of Uremic Cardiomyopathy

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Background: Cardiac remodeling in patients with chronic kidney disease, also called uremic cardiomyopathy, is a leading cause of high mortality in these patients. The biologic changes include thinning and rarefaction of microvasculature. We have developed a semiautomated pipeline for quantification of the size of cardiomyocytes.

Methods: We generated macros in ImageJ, a broadly used, open-source, java-based software. We have used modified Gomori silver staining, which is easy to perform and digitize in high throughput, or Fluorescein-labeled lectin staining. The latter can be easily combined with other stainings, allowing additional quantitative analysis, e.g., of nuclei, capillary density, or single-cardiomyocyte protein expression. We validated the pipeline in a mouse model of cardiac hypertrophy induced by transverse aortic constriction, and in autopsy samples of patients with and without aortic stenosis.

Results: In both animals and humans, ImageJ-based histology quantification revealed a significant hypertrophy of cardiomyocytes and enabled the analysis of protein expression in individual cardiomyocytes. The analysis also revealed that murine and human cardiomyocytes had similar diameters in health and extent of hypertrophy in disease. The number of capillaries relative to the size of the cardiomyocytes indicates a reduction of microvasculature.

Conclusions: The pipeline enables a rapid analysis not feasible by manual methods and facilitates quantitative histology analyses in preclinical and clinical samples. The software requires few hardware requirements and is freely available.

Funding: Government Support - Non-U.S.
SA-PO1050

DQB1 Mismatch in Living Donor Kidney Transplantation

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Background: Several studies have reported an association between HLA-DQ mismatch, and formation of ddDNA and ABMR. Given the notable linkage in inheritance of HLA-DR and -DQ, we sought to determine what additional benefit can be gained by adding DQB1 allele matching to predicting allograft outcome.

Methods: We included living donor kidney transplant recipients (N=3886) transplanted between 2010-2022. Clinical, demographic, and outcome data were obtained from SRTR. HLA DQ81 allele typing and DR antigen was provided by each center. Using multivariable Cox-proportional hazards models we evaluated the hazard (aHR) of graft failure with level of DR and DQB1 mismatching. We used AIC to evaluate which model provide the best fit.

Results: In an unadjusted model, DQB1 allele mismatching was not associated with an increased hazard of death-censored graft failure (DCGF). In adjusted models, both DQB1 and DR were independently associated with increased hazard of DCGF aHR per mismatch 1.2 (1.01, 1.44) and 1.21 (1.02, 1.45), respectively. When both DR and DQB1 are in the model, neither is statistically significant. The model with DQ+DR provided best fit, although the difference was not statistically significant (delta-AIC<2).

Conclusions: Despite a strong association between DQB1 mismatching and ddDNA/ABMR, its addition to matching algorithms in living donor recipients when considering ABMR, its’ addition to matching algorithms in living donor recipients when considering ABMR.

SA-PO1051

Noninvasive Monitoring for Rejection: Need of the Hour, an In-Center Experience with Donor-Derived Cell-Free DNA (dd-cf-dNA) and Its Association with Antibody-Mediated Rejection (ABMR)

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Background: Conventional modalities for detecting allograft rejection predominantly revolve around serial measurements of serum creatinine, and proteinuria. Serum creatinine, is a poor marker for detection of rejection as it lags considerably, and histologic analysis can be non-specific and operator dependent. Allograft biopsy remains the gold standard for detecting allograft rejection however biopsy is an expensive and invasive procedure by itself with risk of multiple complications. The quest for non-invasive tests for early rejection has been elusive. Recent advancements have shifted this paradigm towards newer diagnostic tests that independently provide an estimate into the injury state of the allograft kidney. Of these newer diagnostic modalities, dd-cf-dNA and gene expression, can be done regularly and can be used to complement traditional histological analysis.

Methods: We undertook a retrospective observational study in our renal transplant recipients to assess an association of dd-cf-dNA, gene expression, molecular tissue markers and histological analysis. We looked at the correlation of these variables with presence of antibody mediated rejection (ABMR) that was validated via protocol biopsy and molecular tissue marker analysis.

Results: We observed that dd-cf-dNA > 0.58% correlated with histological and molecular tissue marker proven antibody mediated rejection (ABMR). Furthermore, cf-dNA did not correlate with TCMR nor gene expression had any association with ABMR. With this study we report that a dd-cf-dNA of more than 0.58% is suggestive of ABMR which in the future can be used as a sole noninvasive test to diagnose ABMR and thereby avoiding the need for protocol biopsy.

Conclusions: Noninvasive monitoring for rejection is a need of the hour. Available literature along with our study supports the notion that cf-dNA is valuable in detecting ABMR.

Blood Gene Expression Profile and dd-cfDNA for Diagnosis of Persistent Rejection

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Background: Persistent rejection (PRx) after treatment of BPAR is increasingly recognized and associated with worse outcomes. Repeat biopsies in the absence of clinical concern are rare.

Methods: This was a post hoc analysis performed on subjects with BPAR from the CTOT-08 study that had repeat biopsies available within 270 days after BPAR, and subanalysis of those within 90 days.

Results: Overall, 64 “index” BPAR with repeat biopsies were identified and 61% had PRx within 270 days. Rejection types are shown in Figure 2. Biomarker test characteristics for F/U biopsies within 270 days and 90 days are shown in Figure 1. PRx was associated with worse outcomes. GEP and dd-cfDNA may be tools to identify those in need of a F/U biopsy even when no clinical alterations are present (2/3 of subjects had stable function). The overlap of biomarker results shows that the 2 tests identify different rejections.

Funding: Other NIH Support - U01 AI084146, 3 U01 AI063594-07S1, uUo1AI086835, 2U19 AI063603, R34 AI118493, Commercial Support - Transplant Genomics, Inc.
Results: Absolute and relative dd-cfDNA were lower in recurrent IgAN than in ABMR (median: 11 cp/mL [IQR 7 - 13] vs. 76 cp/mL [IQR 57 - 103], p=0.001; median 0.32% [IQR 0.24 - 0.41] vs. 1.68% [IQR 1.1 - 2.7], p<0.001), but did not differ between recurrent IgAN and no rejection (median 11 cp/mL [IQR 7 - 13] vs. 12 cp/mL [IQR 7 - 16], p=0.995; median 0.32 % [IQR 0.24 - 0.41] vs. 0.30 % [IQR 0.26 - 0.54], p=0.983) (Fig. S1). Mycophenolate (n = 9) followed by Prednisone and Everolimus (n = 2). Mean levels even if immune quiescent, as prior AlloMap studies primarily included patients treated with tacrolimus-based immunosuppression. Higher cutoffs may be necessary for patients on Belatacept-based immunosuppression regimen have a higher baseline AlloMap expression profiling (AlloMap) threshold of 11.5 has shown to discriminate rejection from immune quiescence. We aimed to investigate their utility in weaning to Belatacept monotherapy immunosuppression.

Methods: Between December 2022 and April 2023, we enrolled adult kidney transplant recipients on Belatacept immunosuppression with stable renal function (eGFR > 40 mL/min/1.73 m2) and negative Donor-Specific Antibodies (DSA) into a prospective, single-center, observational pilot study. Patients with acute rejection episodes were excluded. AlloSure, AlloMap, serum creatinine, urine protein, and DSA were measured at monthly Belatacept infusion visits. Patients deemed immune quiescent underwent immunosuppression tapering. Outcomes were: 1) Incidence of biopsy-proven acute rejection and 2) allograft and patient survival, change in eGFR, development of donor-specific antibody, and DSA.

Results: We analyzed the first 11 patients who completed 6 months of follow-up. Subjects were predominantly male (n=7), with a mean age of 57 years, mean eGFR of 65.1 mL/min/1.73 m2 ± 14.7 SD on enrollment, and 67 mL/min/1.73m2 ± 15.0 SD at the 6 months follow up. The most common agents used with Belatacept were Prednisone and Mycophenolate (n = 9) followed by Prednisone and Everolimus (n = 2). Mean AlloSure and AlloMap values throughout follow up were 0.20% ± 0.05 and 11.5 ± 1.4 respectively. 5 patients (45%) were weaned off steroids; no subjects were weaned entirely off mycophenolate or everolimus due to an AlloMap over the threshold. There was 100% patient and graft survival, with no cases of biopsy-proven rejection, proteinuria or de-novo DSA.

Conclusions: Despite having AlloSure <1%, the mean AlloMap score was above the reported threshold shown to discriminate rejection from quiescence. We hypothesize that patients on Belatacept-based immunosuppression regimen may have a higher baseline AlloMap levels even if immune quiescent, as prior AlloMap studies primarily included patients treated with tacrolimus-based immunosuppression. Higher cutoffs may be necessary for these patients. Investigation is ongoing to assess this hypothesis in our cohort.

Funding: Commercial Support - Oncoocyte

SA-PO1054
Use of Donor-Derived Cell-Free DNA and Gene Expression Profiling to Facilitate Belatacept Monotherapy in Kidney Transplant Recipients
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Background: Studies have demonstrated that a donor-derived cell free DNA (dd-cfDNA; AlloSure) >1.0% can be used as a biomarker of allograft rejection. A gene expression profiling (AlloMap) threshold of 1.5 has shown to discriminate rejection from immune quiescence. We aimed to investigate their utility in weaning to Belatacept monotherapy immunosuppression.

Methods: Between December 2022 and April 2023, we enrolled adult kidney recipients on Belatacept immunosuppression with stable renal function (eGFR > 40 mL/min/1.73 m2) and negative Donor-Specific Antibodies (DSA) into a prospective, single-center, observational pilot study. Patients with acute rejection episodes were excluded. AlloSure, AlloMap, serum creatinine, urine protein, and DSA were measured at monthly Belatacept infusion visits. Patients deemed immune quiescent underwent immunosuppression tapering. Outcomes were: 1) Incidence of biopsy-proven acute rejection and 2) allograft and patient survival, change in eGFR, development of proteinuria or de-novo DSA.

Results: We analyzed the first 11 patients who completed 6 months of follow-up. Subjects were predominantly male (n=7), with a mean age of 57 years, mean eGFR of 65.1 mL/min/1.73 m2 ± 14.7 SD on enrollment, and 67 mL/min/1.73m2 ± 15.0 SD at the 6 months follow up. The most common agents used with Belatacept were Prednisone and Mycophenolate (n = 9) followed by Prednisone and Everolimus (n = 2). Mean AlloSure and AlloMap values throughout follow up were 0.20% ± 0.05 and 11.5 ± 1.4 respectively. 5 patients (45%) were weaned off steroids; no subjects were weaned entirely off mycophenolate or everolimus due to an AlloMap over the threshold. There was 100% patient and graft survival, with no cases of biopsy-proven rejection, proteinuria or de-novo DSA.

Conclusions: Despite having AlloSure <1%, the mean AlloMap score was above the reported threshold shown to discriminate rejection from quiescence. We hypothesize that patients on Belatacept-based immunosuppression regimen may have a higher baseline AlloMap levels even if immune quiescent, as prior AlloMap studies primarily included patients treated with tacrolimus-based immunosuppression. Higher cutoffs may be necessary for these patients. Investigation is ongoing to assess this hypothesis in our cohort.

Funding: Commercial Support - CareDs

SA-PO1053
Donor-Derived Cell-Free DNA in Biopsy-Proven Antibody-Mediated Rejection (ABMR) vs. Recurrent IgA Nephropathy After Kidney Transplantation
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Background: Antibody-mediated rejection (ABMR) and recurrent IgA nephropathy (IgAN) are major causes of graft loss and show comparable clinical features such as decline in renal function, proteinuria or worsening hypertension. Since ABMR and recurrent IgAN are indistinguishable using eGFR and urine albumin-creatinine-ratio (uACR) alone, we evaluated the ability of donor-derived cell-free DNA (dd-cfDNA) to discriminate both entities in consecutive cases from an ongoing prospective, observational trial.

Methods: At the time of clinically indicated biopsies, we collected venous blood samples and measured absolute (cp/mL) and relative (%) dd-cfDNA. We included 57 biopsy-matched biopsies, and assigned them to 3 groups based on histopathology: (1) active or chronic active ABMR (n=21), (2) recurrent IgAN (n=15), (3) no signs of rejection, infection or glomerulonephritis (n=21).

Results: Absolute and relative dd-cfDNA were lower in recurrent IgAN than in ABMR (median: 11 cp/mL [IQR 7 - 13] vs. 76 cp/mL [IQR 57 - 103], p=0.001; median 0.32% [IQR 0.24 - 0.41] vs. 1.68% [IQR 1.1 - 2.7], p<0.001), but did not differ between recurrent IgAN and no rejection (median 11 cp/mL [IQR 7 - 13] vs. 12 cp/mL [IQR 7 - 16], p=0.995; median 0.32 % [IQR 0.24 - 0.41] vs. 0.30 % [IQR 0.26 - 0.54], p=0.983) (Fig. S1). Mycophenolate (n = 9) followed by Prednisone and Everolimus (n = 2). Mean levels even if immune quiescent, as prior AlloMap studies primarily included patients treated with tacrolimus-based immunosuppression. Higher cutoffs may be necessary for patients on Belatacept-based immunosuppression regimen have a higher baseline AlloMap expression profiling (AlloMap) threshold of 11.5 has shown to discriminate rejection from immune quiescence. We aimed to investigate their utility in weaning to Belatacept monotherapy immunosuppression.

Methods: Between December 2022 and April 2023, we enrolled adult kidney recipients on Belatacept immunosuppression with stable renal function (eGFR > 40 mL/min/1.73 m2) and negative Donor-Specific Antibodies (DSA) into a prospective, single-center, observational pilot study. Patients with acute rejection episodes were excluded. AlloSure, AlloMap, serum creatinine, urine protein, and DSA were measured at monthly Belatacept infusion visits. Patients deemed immune quiescent underwent immunosuppression tapering. Outcomes were: 1) Incidence of biopsy-proven acute rejection and 2) allograft and patient survival, change in eGFR, development of proteinuria or de-novo DSA.

Results: We analyzed the first 11 patients who completed 6 months of follow-up. Subjects were predominantly male (n=7), with a mean age of 57 years, mean eGFR of 65.1 mL/min/1.73 m2 ± 14.7 SD on enrollment, and 67 mL/min/1.73m2 ± 15.0 SD at the 6 months follow up. The most common agents used with Belatacept were Prednisone and Mycophenolate (n = 9) followed by Prednisone and Everolimus (n = 2). Mean AlloSure and AlloMap values throughout follow up were 0.20% ± 0.05 and 11.5 ± 1.4 respectively. 5 patients (45%) were weaned off steroids; no subjects were weaned entirely off mycophenolate or everolimus due to an AlloMap over the threshold. There was 100% patient and graft survival, with no cases of biopsy-proven rejection, proteinuria or DSA.

Conclusions: Despite having AlloSure <1%, the mean AlloMap score was above the reported threshold shown to discriminate rejection from quiescence. We hypothesize that patients on Belatacept-based immunosuppression regimen may have a higher baseline AlloMap levels even if immune quiescent, as prior AlloMap studies primarily included patients treated with tacrolimus-based immunosuppression. Higher cutoffs may be necessary for these patients. Investigation is ongoing to assess this hypothesis in our cohort.

Funding: Commercial Support - Oncoocyte
Transplantation: Clinical - II

SA-PO1055

Early Detection of Microvascular Injury in Renal Allografts Utilizing Donor-Derived Cell-Free DNA (cfDNA)
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Background: Early detection of allograft injury is critical in improving long-term allograft outcomes. Standard tests of renal function are insensitive, while renal biopsies are invasive and expensive. cfDNA allows sensitive surveillance of allograft injury. We present a series of patients where we identified microvascular injury (MVI) without evidence of alloantibody (DSA or donor directed non-HLA Ab) or C4d on biopsy based on elevated cDNA.

Methods: We followed universal surveillance with cfDNA at month 1, 2, 3, then quarterly till 24 months. A biopsy was triggered if their surveillance value of cfDNA was >1%. Isolated MVI was diagnosed if their glomerulitis (g+) peritubular capillaris (ptc) score of >2 and C4d was negative. There were no other histopathological indicators of AMAR or CMR or infection based on Banff 2017 criteria. DSA and non-HLA antibodies (anti-ATIR, Anti-MICA) were negative.

Results: We followed 120 consecutive patients from 2/2022 till 2/2023. 5 patients with isolated MVI biopsied solely on elevated cDNA signature. Their renal function was normal. C4d, DSA and non-HLA antibody panels were negative. None of these biopsies satisfied the Banff 2017 criteria for AMAR. Patients were treated based on individual physician prerogative. Patients 1 & 2 received steroids only. Patients 3, 4 & 5 received steroids as well as 5 sessions of Plasmapharesis and IVIG. All five patients maintained renal function and showed decreased allograft injury based on reduced cDNA signature (Table 1).

Conclusions: 1. Surveillance with cfDNA is an important tool to detect allograft injury. 2. Early detection of MVI by cfDNA provides an opportunity to treat it before allograft dysfunction becomes apparent 3. The exact nature of isolated MVI remains unclear, however, it can be postulated as an alarming response or allograft injury due to missing self class I antigens. 4. The exact treatment regimen remains unclear. In our series, there was stabilization in injury based on cDNA signature by increasing immunosuppression.

Patient ID Baseline (MFI) Post-treatment (MFI)
1 1.3 1.8
2 0.14 1.7
3 0.79 0.76
4 2.9 6.6
5 3.9 5.4

SA-PO1056

Prospective Assessment of the Need, Discrepancies, and Added Value of Molecular Diagnostics of Kidney Allograft Biopsies: An Evaluation in Clinical Practice
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Background: The Molecular Microscope Diagnostic System (MMDx) may resolve inconclusive histology findings, as preserved biopsy material can be examined after histology findings have been obtained. The extent to which this proposed approach can be implemented remains uncertain as an open question or allograft injury due to missing self class I antigens. The exact treatment regimen remains unclear. In our series, there was stabilization in injury based on cDNA signature by increasing immunosuppression.

Methods: We prospectively analyzed 102 consecutive indication kidney allograft biopsies by histology and MMDx at the University Hospital Zurich from April to September 2022. Pathologists and clinicians with experience in MMDx assessed the need for MMDx in renal biopsies depending on the real-time availability and clinical necessity in treatment. Clinicians subsequently assessed the discrepancy rate and assumed added value by questionnaire when the MMDx report was available.

Results: The need for MMDx was most frequently assessed for suspected ABMR (12/20), followed by suspected early TCMR (9/18) and late TCMR (5/11), TCMR/borderline (1/6), DSA only (1/20), and no ABMR/TCMR (3/28). Discrepancies were observed most frequently in cases with proven/suspected rejection (36/55) but rarely in the absence of histologic rejection (1/47). Clinicians considered an added value of molecular diagnostics mostly in suspected ABMR (3/20), mixed ABMR/TCMR (7/18), and TCMR/borderline (3/6). Classification into molecular ABMR occurred in 9 of 32 cases with suspected ABMR. However, classification into molecular TCMR was not observed in any of the 17 cases with suspected TCMR.

Conclusions: The need for MMDx in clinical practice goes beyond the recommendation for suspected ABMR. While discrepancies appear to be limited to cases with histologic rejection, an added value of MMDx is particularly suspected along the ABMR continuum. Because MMDx aims to overcome the inter-observer variability of histology, the potential added value of MMDx must be determined for each center individually.

Funding: Private Foundation Support

SA-PO1057

The Molecular Microscope Diagnostics System (MMDx) Does Not Identify Early Molecular Antibody-Mediated Rejection (ABMR) in the Presence of Donor-Specific Antibodies (DSA), but Absence of Microvascular Inflammation

Background: The development of de novo donor-specific antibodies (DSA) or an increase in MFI values of preformed DSA are common indications for kidney allograft biopsies. But changes in transcript patterns analyzed by the Molecular Microscope Diagnostic System (MMDx) may precede histological antibody-mediated changes and identify early antibody-mediated rejection (ABMR), however, remains uncertain.

Methods: In this single-center cohort of 326 kidney transplant biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 138 cases with no glomerulitis (g0) and no ABMR (not meeting Banff 2019 ABMR criteria 1 and 2) concerning the presence (n=49) and absence (n=89) of DSA.

Results: Kidney allograft biopsies in the presence of DSA were performed later post-transplantation (median 37 months (IQR 5-170) compared to biopsies in the absence of DSA (median 13 months (IQR 3-95); p=0.03). Molecular ABMR was observed in 0/49 cases (0%) in the presence of DSA and 2/89 cases (2%) in the absence of DSA (2 cases of mixed molecular ABMR/TCMR with histological TCMR). 17/49 cases (35%) in the presence of DSA showed an all ABMR rejection phenotype score (sum of R4, R5, and R6) ≥0.20 compared to 22/89 cases (25%) in the absence of DSA (p=0.116). 13/49 cases (26%) with transplant glomerulopathy (gg) showed an all ABMR rejection phenotype score ≥0.20 compared to 26/89 cases (29%) without gg (p=0.41). Among cases with gg, the all ABMR rejection phenotype score did not differ between cases with DSA compared to cases without DSA (p=0.294). 1/4 cases with isolated C4d positivity ≥0.20 in the presence of DSA showed an all ABMR rejection phenotype score ≥0.20.

Conclusions: MMDx does not differentiate early molecular ABMR in the presence of DSA and/or transplant glomerulopathy but in the absence of histological antibody-mediated changes. If minor molecular changes are meaningful, at least in a subgroup of cases, needs to be assessed in the context of follow-up biopsies.

Funding: Private Foundation Support

SA-PO1058

Isolated Glomerulitis Is Associated with the Absence of Molecular Antibody-Mediated Rejection (ABMR) in Cases with Histologically Suspected and Confirmed ABMR

Background: According to the 2018 Banff classification, the Molecular Microscope Diagnostic System (MMDx) is indicated in cases when histology is insufficient to diagnose antibody-mediated rejection (ABMR) due to an absence of histological criteria groups 2 (antibody interaction with tissue) and/or 3 (DSA and equivalents). The impact of the molecular diagnostic system on the likelihood of molecular ABMR appears critical to the implementation of this new biomarker.

Methods: We analyzed 326 kidney allograft biopsies by histology and MMDx at the University Hospital Zurich. Histologic findings were classified into: (1) 30 cases with suspected ABMR: isolated mild glomerulitis (g1), DSA, (2) 32 cases with suspected ABMR: isolated mild glomerulitis (g1), DSA, (3) 33 cases with suspected ABMR: isolated mild glomerulitis (g1), DSA+, (4) 60 cases with confirmed ABMR: MVI (g+ptc+), DSA+. Results: MMDx diagnosed ABMR in 5/30 cases (17%) with isolated g1 without DSA; 12/32 cases (38%) with isolated g1 with DSA; 18/33 cases (55%) with MVI with DSA, and 30/60 cases (50%) with histologically proven ABMR. While only 17/65 cases (26%) with molecular ABMR showed isolated glomerulitis, 64/90 cases (71%) without molecular ABMR showed isolated glomerulitis (p=0.001). Among cases with isolated glomerulitis, molecular ABMR was detected more frequently in cases with proteinuria (p=0.011), the presence of DSA (p=0.033), and transplant glomerulopathy (gg; p=0.014).

Conclusions: MMDx confirms ABMR in a relevant proportion of cases with isolated glomerulitis. However, isolated glomerulitis is associated with the absence of molecular ABMR in cases with suspected and confirmed ABMR. Proteinuria, DSA, and transplant glomerulopathy are associated with molecular ABMR among cases with isolated glomerulitis.

Funding: Private Foundation Support

SA-PO1059

Impact of Donor-Specific Antibodies (DSA) with Low Median Fluorescent Intensity (MFI) on Allograft Outcomes in Kidney Transplant Recipients
Koraksa, Kitpermkiat, Punlop López, Suvana Khamchunvong, Mahidol University Faculty of Medicine Ramathibodi Hospital, Bangkok, Thailand.

Background: Many factors are associated with allograft failure in kidney transplantation patients (KTs). Immune-mediated rejection is one of the most common causes of allograft failure. Many studies demonstrated that high level of donor specific antibody (DSA) correlated with complement binding capability and more severe tissue injury in KT patients.

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

Underline represents presenting author.
injury. However, data on DSA with low MFI are scarce. We compared allograft outcomes in KT patients with low-MFI DSA in this study.

Methods: Post kidney transplant patients who were tested for DSA at Ramathibodi Hospital from January 2007 to December 2021 and had DSA with MFI <1,000, reported as negative, were evaluated. KTIs were separated into two groups: those with very low DSA (VLL) (MFI 1-500) and those with low DSA (LL) (MFI <a href="tel:501-1000">501-1000</a>) (P = 0.21). At 5 years, the median serum creatinine level among ABMR was significantly higher than in non-ABMR KTIs (2.25 [2.00-2.98] mg/dl vs. 1.41 [1.11-1.87] mg/dl) (P = 0.03). Univariate and multivariate analyses were used to analyze factors associated with rejection.

Results: Thirty-six KTIs were identified (VLL n = 27, LL n = 11). Demographic characteristics were similar between the 2 groups except slightly higher use of ATG for induction in LL group. The LL group had significantly higher T-cell-mediated rejection (TCMR) than the VLL group (45% vs. 12%, P = 0.04). Ten patients developed ABMR. Rate of ABMR, 5 years allograft survival and patient survival were comparable between groups. There was a trend toward higher MFI in KTIs with ABMR than without ABMR (MFI 442 [74-684] vs. 198 [33-475]; P = 0.21). At 5 years, the median serum creatinine level among ABMR was significantly higher than in non-ABMR KTIs (2.25 [2.00-2.98] mg/dl vs. 1.41 [1.11-1.87] mg/dl) (P = 0.03). Univariate and multivariate analyses revealed that LL was a risk factor for rejection.

Conclusions: DSA with low MFI is associated with higher incidence of rejection. DSA with low MFI should not be reported as negative and overlooked. All DSA should be reported regardless of MFI. These group of KTIs should be monitored closely and have their immunosuppression intensified to reduce the incidence of rejection.

Funding: Government Support - Non-U.S.

SA-PO1060
Torque Teno Virus Load to Monitor Changes in Immunosuppression in Kidney Transplant Recipients with Indication Biopsy
Marvin Reineke,1 Claudius Speer,1 Julian Klein,2 Christian Nussnag, Florian Kärle, Christoph F. Mahler,1 Martin G. Zeier,1 Ralf Bartenschlager,1 Paul Schnitzler,1 Christian Morath,1 Louise Benning,1 Department of Nephrology, University Hospital Heidelberg, Heidelberg, Germany; 2Department of Infectious Diseases, Virology, Heidelberg, Germany; 3Heidelberg University Medical Faculty Heidelberg, Heidelberg, Germany, Department of Infectious Diseases, Virology, Heidelberg, Germany, Heidelberg, Germany.

Background: Torque teno virus (TTV) is a potential surrogate parameter to monitor immunocompetence in kidney transplant recipients (KTR) early after transplantation. However, its use in monitoring changes in immunosuppression in KTR late after transplantation with different graft-associated pathologies requires further investigation.

Methods: In this study, we quantified TTV load in sera of 108 KTR with indication biopsy. TTV loads of 34 KTR with biopsy-proven acute rejection (BPAR) and 74 KTR with other pathologies, including 15 KTR with BKV-associated nephropathy (BKVAN), were quantified the day of biopsy, as well as 7, 30 and 90 days post-biopsy to identify changes in viral load related to adjustments in immunosuppressive therapy.

Results: In KTR with no BPAR or BKVAN, TTV load increased in the first month following transplantation and was highest in patients who received a ganciclovir biopsy between 1-12 months post-transplantation. Subsequently, with a reduction in immunosuppression, there was a gradual decline in TTV load across patients (Figure 1A). Patients with BKVAN had significantly higher TTV loads than patients with BPAR or other pathology (P<0.01 for both; Figure 1B). When converted from mycophenolic acid (MPA) to mTOR-inhibitors because of BKVAN, TTV loads decreased significantly in these patients (P=0.01, Figure 1C). In KTR with BPAR who received high-dose corticosteroid pulse therapy, a significant increase in TTV loads was observed between biopsy to 30d and 90d (P=0.05 and P=0.01, respectively; Figure 1D).

Conclusions: TTV load reflects changes in immunosuppressive therapy. Individual changes of TTV load appear to be of greater significance than universally defined cut-off values as TTV load varies depending on the time after transplantation.

SA-PO1061
Valacyclovir for Prevention of Cytomegalovirus Infection After Kidney Transplantation
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Background: Cytomegalovirus (CMV) infection is a frequent and devastating complication after kidney transplantation (KT). Although guidelines recommend antiviral prophylaxis with ganciclovir or valganciclovir, there is a demand for alternative regimens for CMV prevention. We investigated the effects of valacyclovir-based prophylaxis for 3 months on CMV infection and clinical outcomes in KT recipients using a nationwide cohort.

Methods: 2,584 KT recipients from 20 transplant centers registered with the Korean Organ Transplantation Registry were analyzed in this study. The recipients were divided into two groups according to valacyclovir prophylaxis (valacyclovir prophylaxis group and non-prophylaxis group). The impact of valacyclovir-based prophylaxis on CMV infection and disease, and clinical outcomes including rejection, graft loss, cardiac events, and all-cause mortality were investigated. Risk factors for the development of CMV infection were also analyzed.

Results: Valacyclovir prophylaxis group showed significantly lower incidence of CMV infection and rejection compared to non-prophylaxis group (3.64 vs. 10.25 events per 100 person-years and 1.85 vs. 7.27 events per 100 person-years, respectively). The risk of CMV infection and rejection was significantly decreased in valacyclovir prophylaxis group compared to non-prophylaxis group. Valacyclovir prophylaxis, donor age, whether deceased donor or not, length of hospitalization after KT, anti-thymocyte globulin usage, and CMV serological mismatch between the donor and the recipient (donor+ and recipient−) were independent risk factors for the development of CMV infection.

Conclusions: Valacyclovir prophylaxis after KT significantly reduced CMV infection and rejection. Valacyclovir could be considered as an alternative strategy for CMV prophylaxis after KT. Well-designed randomized controlled trials with large sample size are needed.

SA-PO1062
Plasma Fibroblast Growth Factor 21 (FGF21) Concentration in Patients After Kidney Transplantation
Marcin Adamczak, Magdalena Bartmanska, Andrzej Wiecek. Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland.

Background: Fibroblast growth factor 21 (FGF21) is a protein hormone involved in regulation of metabolism and energy expenditure. Results of clinical studies suggest that plasma FGF21 concentration increases with the progression of chronic kidney disease (CKD). The aim of the present clinical study was to analyze the effect of successful kidney transplantation (KTx) on plasma FGF21 concentration and to study the factors related to plasma FGF21 concentration in patients long-term after KTx.

Methods: The first part of the study, i.e. the 6 months prospective observation, included 40 CKD patients directly before KTx [26 women and 14 men aged 47.0 (39.2–54.0) years]. In the second part of the study 184 patients long-term after KTx [72 women and 112 men aged 52.0 (48.0–56.0) years] and 50 healthy subjects (HS) [28 women and 22 men aged 52.0 (48.0–58.0) years] were enrolled. FGF21 plasma concentration was measured using Human FGF-21 ELISA (BioVendor R&D). Results were presented as median and 95% CI.

Results: In CKD patients directly before KTx plasma FGF21 concentration was significantly higher than in HS [1013.0 (689.6–1635.8) pg/ml vs 239.5 (219.0–294.5) pg/ml respectively; p<0.001]. At 14, 30 days and 6 months after KTx, a significant decrease of plasma FGF21 was observed [322.5 (197.3–579.6) pg/ml vs 355.0 (268.5–547.0) pg/ml, 344.0 (264.1–405.0) pg/ml vs (p<0.001), respectively]. In patients long-term after KTx, a negative correlation was found between plasma FGF21 concentration and estimated glomerular filtration rate and a positive correlations between plasma FGF21 concentration and BMI and serum concentration of triglycerides, insulin, interleukin 6, CRP and cystatin C.

Conclusions: 1. In CKD patients plasma FGF21 concentration measured directly before KTx was significantly higher than in HS. Successful KTx leads to a significant decrease of plasma FGF21 concentration. 2. Plasma FGF21 concentration in patients long-term after KTx is related to the degree of graft function impairment and several metabolic abnormalities of these patients.

Funding: Government Support - Non-U.S.

SA-PO1063
Is Metabolic Acidosis a Risk Factor for Worse Long-Term Prognosis in Patients After Kidney Transplantation?
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Background: Metabolic acidosis (MA) frequently occurs in patients after kidney transplantation (KTx). Results of both experimental and clinical studies suggest that MA may contribute to faster progression of chronic kidney disease. Data on such relationship
in KTx patients is very limited. The aim of this clinical, single center, retrospective, observational study was to examine the relationship between MA and both mortality and renal outcomes in patients after KTx.

**Methods:** Blood bicarbonate concentration was measured in 486 patients (290 male; 196 female) aged 48.2 ± 12.0 years at least one year after KTx and subsequently all patients were observed during 11 years. MA was defined as the blood bicarbonate concentration lower than 22 mmo/L. The endpoints in Kaplan-Meier survival curves analysis were death, initiation of dialysis therapy or retransplantation as well as cumulative endpoint of the study i.e. death or initiation of dialysis therapy. Differences in survival curves were analyzed with log-rank test and were considered as significant when p<0.05. Relative risks (RR) were presented with 95% CI.

**Results:** Metabolic acidosis was diagnosed in 57 (12%) patients being long-term after KTx. The Kaplan-Meier curves analysis have shown that patients with MA reach endpoints of follow-up earlier (log-rank p=0.002 for death and p<0.001 for dialysis or retransplantation and for cumulative endpoint p<0.001). In patients with MA the risks of starting dialysis therapy or retransplantation was significantly higher than in patients without MA [RR=2.00 (1.42-2.82), p<0.001]. In patients with MA the risks of death was significantly higher than in patients without MA [RR=1.61 (1.01-2.55), p=0.04]. Risk of cumulative endpoint of the study (death and initiation of dialysis therapy or retransplantation) was also higher in patients with MA [RR=1.83 (1.49-2.23), p<0.001].

**Conclusions:** 1. Metabolic acidosis is an important risk factor for increased mortality and progression of graft failure in kidney transplant patients. 2. The prospective interventional studies with correction of MA in patients prone to allograft nephropathy progression will provide information whether treatment of MA improves the survival of both patients and transplanted kidneys.

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

**SA-PO1064**

**Application of Machine Learning for Repertoire Analysis in Antibody-Mediated Rejection (ABMR) of Kidney Transplantation**

**John J. Yang, Korea University Guro Hospital, Seoul, Republic of Korea.**

**Background:** The adaptive immune receptor repertoire (AIRR)-sequencing analyzes the individual repertoire at sequence level. Here we compare AIRRs of kidney transplant recipients using repertoire analyses and machine learning, regarding ABMR.

**Methods:** Total of 30 repertoires (9 ABMR and 21 No rejection) were analyzed. Bulk gDNA (2μg) was sequenced at 500,000 target read-depth (equivalent of 10,000 B lymphocytes). The MiXCR tool (v4.3.2) was used for preprocessing and normalization. Repertoire analysis using the immunarch R package (v1.0.0) included clonality, diversity and V(D)J gene usage analyses. Machine learning by ImmuneML (v2.2.4) used four algorithms of KNN, SVM, RF and logistic regression. Using 3-mer aminoacids encoding and ABMR status as classifiers, the performances of ML algorithms were assessed by AUC.

**Results:** From repertoire analyses, decreased number of clonotypes (P=0.008) and decreased diversity (P=0.02) were seen in ABMR. There were differences in V gene utilization, from which IGHV1-2 and IGHV1-8 were decreased in ABMR group, while IGHV3-30 usage was higher (P=0.026, 0.014 and 0.018). The AUC of ML algorithms KNN, LR, RF and SVM were 0.77±0.11, 0.8±0.09, 0.81±0.11 and 0.75±0.06. Analysis of 3mer correlated V gene usages, from which NEI, TEC, WAK and WAR were statistically significant 3mers after Bonferroni correction (P<0.000000625).

**Conclusions:** Reproducible and clinically applicable AIRR-seq workflow was implemented using DVD product. Repertoire analysis was capable of demonstrating differences from kidney transplant recipients. ML models using different algorithms generated overall favorable performances in classifying ABMR status, indicating that direct interpretation of AIRR-seq data is possible.

**Diffences in number of clonotypes (A), diversity (B) between ABMR and No rejection groups. The performances of ML algorithms (C).**

**SA-PO1065**

**Sodium Restriction Is Associated with Decreased Kidney Function Through TonEBP Downregulation in Calcineurin Inhibitor (CNI)-Treated Kidney Transplant Recipients**

**Satoru Sanada, Saki Katano, Mitsuhiro Sato. Japan Community Health Care Organization Sendai Hospital, Sendai, Japan.**

**Background:** Toxicity responsive enhancer binding protein (TonEBP) protects kidney tubular cells against hypertonicity by adapting the osmolar gap across the membrane. Under hypertonic conditions, TonEBP shifts from the cytoplasm to the nucleus for the transactivation of toxicity responsive genes. Calcineurin inhibitors (CNI) are known to suppress TonEBP by hampering its nuclear translocation. We examined whether CNI induced nephrotoxicity in transplant recipients could be due to impaired TonEBP activity.

**Methods:** A total of 385 kidney transplant recipients at JCHO Sendai Hospital between 2000 to 2022 were enrolled. Data for these patients were extracted from medical records. TonEBP immunohistochemistry was performed by biopsy specimens from 144 patients. The decline of eGFR were described using Kaplan-Meier methods.

**Results:** By immunohistochemistry, TonEBP was predominantly located in the cytoplasm among CNI nephrotoxicity compared to nuclear-cytoplasmic staining in rejections, suggesting that TonEBP transactivation was restricted in CNI nephrotoxicity. Cytoplasmic TonEBP staining was observed regardless of acute or chronic CNI induced kidney injury. Next, we examined sodium intake, which is the primary TonEBP activator of the kidney. Patients diagnosed as CNI nephrotoxicity revealed significantly lower sodium chloride intake compared to rejections (7.5 vs 10.8g/day, p=0.05). A 10% decline of eGFR among transplant recipients without any history of rejection (nor pre/post renal injury events) was significantly faster in the low sodium intake group (<8g/day) compared to the higher intake group (≥8g/day) (Median follow up: 10 years, Log-Rank P=0.03).

**Conclusions:** 1) TonEBP transactivation of renal tubular cells could be impaired in CNI nephrotoxicity and sodium restriction may exacerbate its activity, which could fail the TonEBP-mediated cell protection from the hypertonicity. 2) Sodium intake of kidney transplant recipients should be reevaluated from the view of preventing CNI nephrotoxicity.
Recipient Obesity on Deceased Donor Kidney Transplant (DDKT) Outcomes: Overlooked Threats to Allograft Dysfunction and Delayed Graft Function (DGF)

Seunyeong Hong, 1,2 Byung ha Chung, 1,2 Chul Woo Yang, 1,2 Woo Yeong Park. 1Uijeongbu St Mary's Hospital, Uijeongbu, Gyeonggi-do, Republic of Korea; 2Catholic Medical University of Korea, Seoul, Republic of Korea; 3Seoul St Mary's Hospital, Seocho-gu, Seoul, Republic of Korea; 4Keimyung University Dongsan Medical Center, Daegu, Republic of Korea.

Background: As the prevalence of obesity increases globally, appreciating the effect of recipient obesity on graft outcomes is of increasing importance. However, the impact of recipient body mass index (BMI) on kidney transplant outcomes has been controversial. This study is designed to investigate the effect of recipient BMI on short and long-term outcomes of patients undergoing DDKT.

Methods: A total of 743 patients receiving deceased donor KT between 2005 and 2019 among 3 multi-centers were included in the study. Patients were divided according to their body mass index (BMI) into underweight (BMI<18.5), normal weight (BMI18.5-25) and obese (BMI>25kg/m2, N=488) groups. Their clinicopathological characteristics, graft functions, graft survival rates and delayed graft function (DGF) were analyzed retrospectively.

Results: Obesity was associated with deterioration of allograft function. Kidney function was significantly lower in obese group compared with underweight and normal BMI groups after 3 months to 3 years follow up after DDKT. Though statistically insignificant, the death-censored graft survival rate tends to be negatively associated with recipients’ BMI level.

Conclusions: In conclusion, recipients’ obesity increases the risk of allograft dysfunction and it is found to be statistically significant prognostic factor for DGF. Therefore, appropriate risk-adapted information concerning BMI should be provided to patients and efforts to improve recipients’ obesity should be taken in advance to DDKT.

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SA-PO1067

Long-Term Evaluation of Coronary Calcifications in Kidney-Transplanted Patients: A Single Center Follow-Up of 15 Years

Carlo Alfieri, 1,2 Alessandro Perna, 1 Laura Forzenigo, 1 Giorgia Schiraldi, 1 Anna Regalia, 1 Paolo Molinari, 1,2 Giuseppe Castellano, 1 Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milan, Italy; 1Università degli Studi di Milano, Milano, Italy; 2Università degli Studi della Campania Luigi Vanvitelli, Caserta, Italy.

Background: Few data are available on the long term behavior of coronary artery calcifications (CAC) in kidney transplantation (KTx). In a previous paper (Alfieri C et al. Sci Rep, 2019), we evaluated the factors implicated with CAC progression after 5 years of KTx. Here we present the preliminary data about CAC follow-up of the same population after 15 years of KTx (T15).

Methods: Previously 67 KTxps (2007-2008) were studied. At the present time, 19 of them were lost from the follow up: 8 died, 4 because of major cardiovascular event (MACE), 11 had a graft loss and 20 did not adhere to the control. Then, we evaluated 28 KTxps (M=18; age 60±9 yr). Clinical, blood and urinary data were recorded for 15 years, and comparing the means values in the analyses. At baseline and T15, using coronary TC, Agatson score was evaluated and patients were accordingly categorized in 4 groups: 1)0-10, 2)10-100, 3)100-400, 4)400+.

The CAC progression was used testing the modification in CAC category (Cat-Prog+T15) and the formula proposed by (Provenzale et al. JACC, 2004). During the 15 years of KTx 25% of KTxps had a MACE. No impact for CACs was found in MACE.

Conclusions: To the best of our knowledge, our study is the first one to evaluate CACs in KTxps for such a long time. According to the preliminary data obtained: 1) the prevalence of CAC in KTxps is high, and is related to age, 2) CAC worsening was observed in a consistent part of the cohort and was related to different parameters, especially to Ca levels. Future researches, possibly involving a higher number of KTxps could explain better these findings and explore more deeply the relation of CACs with MACE in the long term.

SA-PO1068

Association Between Pretransplant Dialysis Modality and Long-Term Graft Outcomes

Young Kyeong Soo, Taechee Kim, Yunmi Kim, Hyuk Huh, Yeong Hoon Kim. Inje University Busan Paik Hospital, Busan, Republic of Korea.

Background: previous systemic reviews have shown that peritoneal dialysis (PD) is associated with substantial improvements in patient survival and delayed graft function compared with hemodialysis (HD) treatment as a pretransplant modality, the association between pretransplant dialysis modalities and posttransplant outcomes remains controversial.

Methods: We retrospectively collected records from 773 kidney transplant recipients between January 2008 and October 2021 in 2 transplant centers. We excluded recipients under the age of 18, 2nd or 3rd transplant recipients, and preemptive recipients. The final analysis included 558 kidney transplant recipients(fig1). We examined graft survival across pretransplant modality.

Results: 558 kidney transplant recipient were 47.5 years old and included 42% females and 28% diabetes. 407 recipients underwent HD, and 151 recipients underwent PD before transplantation. The overall graft survival between pretransplant HD and PD showed no statistical difference (P=0.197)(Fig. 2). pretransplant HD seemed to be favorable for graft survival over a long-term follow-up period of over 10 years.

Conclusions: Pretransplant modalities during the transition to a kidney transplant are not associated with graft survival.

Table 1. baseline characteristics of 558 KT recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HD</th>
<th>PD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47 (31-58)</td>
<td>49 (39-63)</td>
<td>0.122</td>
</tr>
<tr>
<td>Female</td>
<td>326 (62%)</td>
<td>131 (87%)</td>
<td>2.4 (2.2-2.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>15.6 (14.2-17.2)</td>
<td>157 (145-174)</td>
<td>1.02 (0.9-1.1)</td>
</tr>
<tr>
<td>SBP</td>
<td>82 (58-105)</td>
<td>90 (70-115)</td>
<td>0.14</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>6 (5-10)</td>
<td>8 (6-12)</td>
<td>0.114</td>
</tr>
<tr>
<td>DMi</td>
<td>157 (28%)</td>
<td>155 (28%)</td>
<td>0.927</td>
</tr>
<tr>
<td>Hyperparasitosis</td>
<td>82 (15%)</td>
<td>99 (17%)</td>
<td>0.25</td>
</tr>
<tr>
<td>ON</td>
<td>156 (28%)</td>
<td>91 (22%)</td>
<td>0.43 (0.3-0.5)</td>
</tr>
<tr>
<td>PVDs</td>
<td>24 (4%)</td>
<td>25 (5%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Others</td>
<td>5 (1%)</td>
<td>11 (7%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Unknown</td>
<td>104 (29%)</td>
<td>116 (29%)</td>
<td>0.056</td>
</tr>
<tr>
<td>HD</td>
<td>187 (75%)</td>
<td>141 (57%)</td>
<td>0.013</td>
</tr>
<tr>
<td>PD</td>
<td>193 (85%)</td>
<td>246 (93%)</td>
<td>0.013</td>
</tr>
<tr>
<td>Peritoneal</td>
<td>18 (2%)</td>
<td>10 (7%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Waiting time [yr]</td>
<td>4.5 (3.1-5.7)</td>
<td>4.4 (3.1-5.7)</td>
<td>0.001 (0.0-0.1)</td>
</tr>
</tbody>
</table>

LD, living donor; DD, deceased donor

SA-PO1069

The Effect of Kidney Transplantation on Biventricular Structure and Function Evaluated by Transhoracic Echocardiography

Claudia A. Navarrete, 1 Luis E. Morales-Buenrostro, 1 Jorge A. Joya Harrison, 2 Lluvia A. Marino-Vazquez, 1 Arturo A. Martinez-Ibarra, 1 Luis Bazca Herrera, 1 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; 2 Tecnologico de Monterrey, Monterrey, Mexico.

Background: Kidney transplant (KT) recipients experience a higher risk of cardiovascular disease outcomes when compared with the general population. Due to the increasing number of patients requiring a transplant, better identification of cardiac risk is required to prevent premature death with a functioning graft.

For present analysis, 100 KT recipients were included in the study; the mean age was 56 years, 62% were male, and 48% had diabetes. The average follow-up time was 36 months. The main echocardiographic findings are presented in the table below.

Table 1. Echocardiographic findings in KT recipients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HD</th>
<th>PD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular mass (g/m²)</td>
<td>75 (48-120)</td>
<td>90 (50-130)</td>
<td>0.012</td>
</tr>
<tr>
<td>Left atrial size (mm)</td>
<td>4 (3-5)</td>
<td>4 (3-5)</td>
<td>0.013</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%):</td>
<td>55 (50-60)</td>
<td>55 (50-60)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

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

Underline represents presenting author.

1028
Methods: We performed a single-center prospective and longitudinal study that included all transplant-eligible patients (living or deceased donors) from January-May 2022. The candidates underwent pre-transplant thoracic echocardiography (TE) as per institutional protocol and a second one a year later. We excluded patients who were lost to follow-up or suffered a cardiovascular event during the study period. The most representative cardiovascular structure and function values were evaluated.

Results: Seventeen patients were included a mean age of 50 years and 64.7% were men. The median time spent on dialysis was 2.6 years, 64.7% were on hemodialysis and 29.4% on peritoneal dialysis. Reverse remodeling of the left ventricular was observed following the KT as the LV mass decreased from 101 to 82 g (p = 0.011). End-diastolic volume decreased from 124 to 100 ml (p<0.002), end-systolic volume from 52 to 30 ml (p<0.001), and ejection fraction increased from 57% to 61% (p=0.06). E/e' did not significantly change (9 vs 7.65 p= 0.14). Additionally, there were no statistically significant differences in left and right ventricle strain (18.5 vs 19.4 p=0.191 and 24 vs 24 p=0.55).

Conclusions: Reverse cardiac remodeling following the KT was observed as a reduction in left ventricular mass and improvement in ejection fraction, left and right ventricle strain did not change. Further description and understanding of cardiovascular function modification before and after KT is needed to improve graft and overall survival.

SA-PO1071

The Impact of Recipient’s Pre-Transplant Viral Status on Acute Kidney Transplant Rejection in the United States: A Retrospective Study

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Background: Acute graft rejection is a feared complication of kidney transplant and some studies have suggested that certain viral infections could be a contributor to this feared outcome. This study therefore set out to identify the impact of some viruses on acute kidney transplant rejection in the United States.

Methods: This study used the 2010-2022 data from the Scientific Registry of Transplant Recipients. This data system includes data on all donors, waitlisted candidates and transplant recipients in the US submitted by the members of the Organ Procurement and Transplantation Network. The study included patients aged 18 years or older who had kidney transplants in the United States. Independent variables include age group of recipients, recipient’s gender, recipient’s race, donor gender, donor race, donor type, previous transplant in recipient, viral detection (HBV, HCV, HIV) in recipient at transplant time, number of HLA mismatches and pre-transplant malignancy. The dependent variable was acute rejection between transplant and discharge. Univariate, bivariate (Chi-square and t-test) and multivariable logistic regression (stepwise selection with P-value for entry and stay of a variable put at <=0.05) analyses were done using SAS 9.4.

Results: There were 207,732 kidney transplants. On multivariable logistic regression that adjusted for significant variables on bivariate analysis (age group of recipients, recipient’s race, previous transplant in recipient, number of HLA mismatches prior to transplant), transplant patients who were positive for HBV surface antigen had 57% (AOR: 95% CI 1.21-2.02) higher odds of developing acute rejection compared to those negative for the antigen. Those who had HCV detected at transplant time had 27% (AOR: 95% CI 1.07-1.49) higher odds of acute rejection compared to those who had no HCV detected. HIV positive patients had 107% (AOR: 95% CI 1.61-2.66) higher odds of developing acute rejection compared to those negative for HIV.

Conclusions: Our study has shown that viral infections (HBV, HCV, HIV) increase the risk of acute rejection in kidney transplants. These findings suggest that treating these viruses to non-detectable levels prior to transplant could reduce the risk of acute graft rejection.

SA-PO1072

Successful Kidney Donation After Gastric Bypass Surgery Using Individualized Stone Risk Assessment

Sambhavi Krishnamoorthy, Anna L. Zisman. University of Chicago Division of the Biological Sciences, Chicago, IL.

Background: The effects of increased prevalence of morbid obesity in the general population is reflected in the population presenting for living kidney donation as well. Bariatric surgery is the most successful and longest-lasting treatment for morbid obesity. Some centers may exclude donors who have undergone Roux en Y gastric bypass due to the risk of hyperoxaluria and risk of stone events post donor nephrectomy. We describe four living donor candidates who underwent evaluation at our kidney stone prevention program that allowed an individualized risk assessment to assess the candidacy of donors.

Methods: Retrospective review of electronic medical records was used to identify four living kidney donor (LKD) candidates with history of Roux en Y gastric bypass between 2012 and 2022. Patients submitted paired 24 hour blood and urine samples for metabolic evaluation. We compared the characteristics of the LKDs who went on to donate and the ones who were declined.

Results: Table 1a and 1b summarize the demographics and urinary metabolic parameters. Patient 1 went on to donate kidney as she did not have any hyperoxaluria. Patient 2 had hyperoxaluria on her initial testing, which normalized on repeat testing after counseling (Table 1c). She went on to successfully donate. Both patients 3 and 4 were declined as candidates for living kidney donation due to significant hyperoxaluria. The patients who were approved for donation were 10 years and 14 years out from previous transplant in recipient, viral detection (HBV, HCV, HIV) in recipient at transplant time, number of HLA mismatches and pre-transplant malignancy. The dependent variable was acute rejection between transplant and discharge. Univariate, bivariate (Chi-square and t-test) and multivariable logistic regression (stepwise selection with P-value for entry and stay of a variable put at <=0.05) analyses were done using SAS 9.4.

Conclusions: Successful living kidney donation after bariatric surgery is possible with careful individualized evaluation of metabolic stone risk parameters at an experienced stone center prior to approving their candidacy.

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SA-PO1073

The Efficacy and Safety of SGLT2 Inhibitors and GLP1 Receptor Agonists in Kidney Transplant Recipients

Vikas Sridhar,1 Maïté Zelderlo,2 Yanhong Li,1 David Cherney,1 Sunita K. Singh,1 University Health Network, Toronto, ON, Canada; 2Katholieke Universiteit Leuven, Leuven, Belgium.

Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) decrease adverse cardiac outcomes in the general population. We aimed to evaluate the efficacy and safety of SGLT2i and GLP1RA monotherapy and combination therapy in kidney transplant recipients (KTR).

Methods: This was a retrospective cohort study of all adult KTR started on SGLT2i and/or GLP1RA between January 1, 2000 and December 31, 2021. Baseline characteristics, drug safety/tolerability, estimated glomerular filtration rate (eGFR), and cardioareal outcomes were collected.

Results: Of 227 patients analyzed, 78 were on SGLT2i, 79 on GLP1RA and 70 on combination therapy. 120 patients had pretransplant diabetes (DM) (53.6%) and 103 had post-transplant DM (46.0%). Compared to the period before drug initiation, there were no differences in rates of CV events and graft failure with either monotherapy or combination therapy. After one month, SGLT2 inhibition resulted in a median eGFR decline of 6 ml/min/1.73m² (interquartile range -11 to 3.5) (Figure 1). Drug discontinuation was high, with 19% of SGLT2i users, 28.7% of GLP1RA and 41.4% on combination therapy stopping treatment – ‘hospitalization’ with SGLT2i and ‘intolerance’ with GLP1RA and combination therapy were the most frequent causes of discontinuation. However, compared to the period before drug initiation, rates of urinary tract infections, ketoacidosis, acute kidney injury and hepato-pancreato-biliary complications were not significantly different.

Conclusions: SGLT2i, GLP1-RA and combination therapy appear to be safe in KTR, though drug discontinuation is relatively common. The acute eGFR ‘dip’ observed with SGLT2 inhibition suggests tubular-glomerular mechanisms are intact in this unique population.

SA-PO1074

A Systematic Investigation on the Impact of Invasive Kidney Allograft Biopsy on Urinary Cell mRNA Profiles

Thalia Salinas, Carol Y. Li, Sheavonnie Wright, Perola Lambda, Mamikka Suthanthiran. Weill Cornell Medicine, New York, NY.

Background: Liquid biopsies offer an unprecedent window into intragraft events. It is preferred that biospecimens are collected prior to biopsy since mechanical injury from this invasive procedure may alter circulating levels of biomarkers of interest, (Kyoo Y et al. Transplantation Direct 2021). In the Clinical Trials in Organ Transplantation (CTOT)-04 study consisting of 485 kidney transplant recipients (KTR), 298 biopsy-matched urine specimens were used to develop and validate a urinary cell 3-gene signature consisting of 18S rRNA normalized CD3ε mRNA and CXCL10 mRNA (CTOT-04 signature) and all but 10 specimens were collected at the time of biopsy or ≤3 days prior (Suthanthiran M et al. N Engl J Med 2013). There were no paired pre and post biopsy specimens to investigate the impact of kidney allograft biopsy on absolute copy numbers of the transcripts or CTOT-04 signature. The current study was designed to fill this gap in knowledge.

Methods: We collected urine from KTR before and after kidney allograft biopsy, both ≥6 hours of biopsy. We used the Weill Cornell Hybrid Protocol consisting of urine filtration to collect eueate with stable RNA and mRNA enrichment during RNA isolation using a silica-membrane-based cartridge (Salinas T et al. Immunol Methods 2022). We measured absolute copy numbers of CD3ε mRNA, CXCL10 mRNA, and 18S rRNA (CTOT-04 signature), and mRNAs for TGFβ1, FOXP3, and BKV VP1 in urine samples collected pre and post kidney allograft biopsy.

Results: Box and whisker plots show that the various urinary cell mRNA levels and CTOT-04 signature score are not different between urine samples collected before and urine samples collected after kidney allograft biopsy (Fig. 1 A-G). All P values >0.05, Wilcoxon matched pairs signed-rank test).

Conclusions: Urinary cell mRNA levels and CTOT-04 signature score are not impacted by the kidney allograft biopsy and yield indistinguishable results irrespective of whether the urine was collected prior to or after the invasive kidney allograft biopsy procedure.

Funding: Other NIH Support - NIH/NCATS Grant #2KL2TR2385

SA-PO1075

Effect of Different Treatment Regimens on Kidney Graft Function and Mortality in Patients with a Diagnosis of Antibody-Mediated Rejection

Laura E. Díaz González,1 Ana C. Hernandez Pugh,1 Jose Ignacio Cerrillos,2 Jorge Andrade-Sierra,2,3 Enrique Rojas-Campos,3 Luis Alberto Evangelista-Carrillo,1 Basilio Jalomo martinez,1 Miguel Medina Perez.1
1Instituto Mexicano del Seguro Social, Guadalajara, Mexico; 2Universidad de Guadalajara Centro Universitario de Ciencias de la Salud, Guadalajara, Mexico.

Background: The optimal treatment for Antibody mediated rejection (AMR) remains uncertain, and its presence causes up to 60% of kidney grafts loss.

Methods: A retrospective cohort from May-2016 to June 2022, that included 176 patients a18 years old, hospitalized with graft dysfunction and histopathological diagnosis of AMR to receive treatment. Were categorized into 3 groups; 1. Plasmapheresis (PF) + Intravenous immunoglobulin (IVIG), 2. IVIG + Rituximab (RTX) 3. Steroids and immunosuppression treatment optimization.

Results: On average, 63% of patients were men, and a majority were transplanted with a living donor kidney (89%), showing a median of age 32 ± 9; baseline serum creatinine (CrS) was 1.15 and during the rejection, 2.75 mg/dL; timing of biopsy 6 ± 5 years; C4d positive (68%) measuring groups of treatments there were no significant difference by CrS at the end of the follow up, episodes of infections was 27%, 20% and 10% (P=0.61), mortality was 6.8%, 2.5% and 5.8% each group (P=0.47).

Conclusions: There was no significant difference in graft function and mortality between treatment groups, but in a logistic regression analysis, predictive variables of poor graft prognosis were: CrS greater than 2.5 mg/dL at the beginning of treatment, using steroids and immunosuppression optimization treatment; greater chronicity and being younger at the time of diagnosis.

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SA-PO1076

Relationship of Serum Procalcitonin (PCT) Levels with Kidney Graft Function in the Immediate Post-transplantation Period in Kidney Transplant Recipients

Beatriz R. Cerezo Samperio,1,2 Ana C. Acosta Peña,1 Abel Humberto V. Compean,1 Claudia B. López,1 Pedro Morales Molina,1 Julio C. Nieto,1 Juan D. Díaz García,1 Irving G. Ramírez,1 Jose H. Cano Cervantes.1

1 Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico; 2 Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico.

Background: Renal function is one of the major determinants of PCT levels, which is why its relationship as a marker of acute kidney injury not associated with sepsis has previously been described. In kidney transplantation (KT) the persistently high levels of PCT seem to show a relationship with the function of the kidney graft because its levels increase after the elevation of other inflammatory cytokines in events of exaggerated inflammatory response and it is poorly cleared in patients with delayed graft function. This study seeks to find the relationship of serum PCT levels as well as their association with kidney graft function in the immediate period.

Methods: We conducted a retrospective cohort study from February 2016 to May 2022 of Nephrology and Transplant patients. A number of 82 KT recipient patients with kidney graft function in the immediate period.

Results: They were classified as normal graft function (NGF), slow graft function (SGF) and delayed graft function (DGF). Within the baseline characteristics, no statistically significant differences were found for age, type of transplant, leukocytes, and hemoglobin at admission. Finding that a level > 3 ng/dl of procalcitonin conferred a statistically significant difference in renal function at admission.

Conclusions: Procalcitonin is an early marker to identify patients who develop delayed kidney graft function.

Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>NGF</th>
<th>DGF</th>
<th>SGF</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57±12</td>
<td>43±12</td>
<td>46±16</td>
<td>0.153</td>
</tr>
<tr>
<td>Male (%)</td>
<td>60</td>
<td>35</td>
<td>56</td>
<td>13</td>
</tr>
<tr>
<td>Diabetic Diabetics (%)</td>
<td>16</td>
<td>12</td>
<td>22</td>
<td>3</td>
</tr>
<tr>
<td>Cold ischemia (h)</td>
<td>11.5±14.25</td>
<td>16±12.65</td>
<td>12.23±10.25</td>
<td>0.164</td>
</tr>
<tr>
<td>Leukocytes (cells/µl)</td>
<td>7.8±5.6±6.04</td>
<td>7.6±5.6±6.73</td>
<td>6.6±4.17±13.17</td>
<td>0.962</td>
</tr>
<tr>
<td>Procalcitin (mg/ml)</td>
<td>1.84±0.23±3.97</td>
<td>5.0±0.76±29.25</td>
<td>2.52±0.37±6.87</td>
<td>0.0224</td>
</tr>
</tbody>
</table>

NGF: Normal Graft Function; DGF: Delayed Graft Function; SGF: Slow Graft Function; Hrs: Hours; Min: Minutes.

SA-PO1077

Characteristics of Renal Allograft Survivors of More than 15 Years: A Single-Center Experience

Amgad E. El Agroudy. Arabian Gulf University, Manama, Bahrain.

Background: We studied the characteristics and the predictors of graft and patient survival in Bahraini renal transplant recipients with an allograft that functioned for more than 15 years.

Methods: Out of 185, underwent renal transplantation between 1982 and 2007, 52 patients (28.1%) maintained functioning allografts for more than 15 years (range 15-41 years). Characteristics of the surviving patients, data on graft survival, and determinants of outcome were obtained by reviewing all medical records.

Results: The mean age at time of renal transplantation was 43.1±11.3 years and 75% were males. The cause of end-stage renal disease was diabetic nephropathy in 28.5% and 86% received dialysis therapy before transplantation. The source of the graft in 39 (75%) recipients was from living related donors with a mean age of 31.7±6.6 years, and it was the first graft in 50 recipients. The primary immunosuppression regimen was cyclosporine (CaA) in 29 patients (29.1%), tacrolimus (Tac) based in 21 patients (40.4%) while three patients (5.6%) received steroids and azathioprine only. Induction therapy was administered to 58 patients. Acute rejection episodes occurred in 10 patients (19.2%), of whom two experienced two episodes. During the last follow-up, the mean serum creatinine was 123±36 umol/L. Two patient were successfully treated for Covid-19 viral infection. A history of hypertension was encountered in 66% and posttransplant diabetes mellitus in 21%. We compared the graft functioning group with the graft failure group and found that the independent determinants of long-term graft survival included age of the recipient, time of late acute rejection episodes, use of induction therapy, histopathologic findings of chronic allograft damage, and serum creatinine at one year.

Conclusions: We conclude that renal transplantation in its earliest years and despite the associated numerous complications has provided a fifteen-year or more of near-normal life to patients with end-stage renal disease.

SA-PO1078

Navigating the Crossroads: Cytomegalovirus (CMV), Neutropenia, and Kidney Transplant Survival in High-Risk Patients


Background: Cytomegalovirus (CMV) infections constitute a significant condition in kidney transplant (KT) recipients with a major impact on morbidity, mortality and graft survival, with CMV negative recipients (R-) transplanted from a CMV positive donor (D+) at highest risk. The prevention of CMV disease in KT recipients mainly relies on antiviral prophylaxis and preemptive therapy with virostatics, e.g., valganciclovir (VGCV). Although these strategies proved to be efficient, their use is limited due to substance related toxicities. This study aims to evaluate the effects of VGCV administration on the development of neutropenia and graft survival in CMV high risk KT.

Methods: A retrospective data analysis was used to analyze KT recipients with CMV high risk constellation received a KT, including 437 (78.6%) and 119 (22.4%) with and without prophylactic VGCV administration, respectively. The likelihood of developing (severe) neutropenia was elevated in KT recipients with VGCV prophylaxis during day 0-200.

Results: 556 patients with CMV high risk constellation received a KT, including 437 (78.6%) and 119 (22.4%) with and without prophylactic VGCV administration, respectively. The likelihood of developing (severe) neutropenia was elevated in KT recipients with VGCV prophylaxis during day 0-200.

Conclusions: Our results show that VGCV prophylaxis in CMV high-risk KT recipients is linked to an increased likelihood of developing neutropenia. However, the timing of the onset of neutropenia is not significantly altered by VGCV. Given the potential negative impact of neutropenia on KT outcomes, it is crucially to closely monitor neutropenic KT recipients. Further research may elucidate if targeting neutropenia could improve KT outcomes.

Funding: Commercial Support - MSD
SA-PO1079

Time-to-Transplantation Prediction in Kidney Transplant Recipients

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Background: Several predictions models have been proposed which estimate graft failure in kidney transplant recipients (KTR). However, the risk resulting from the model is challenging to interpret. Therefore, this study aims to propose a machine learning model which predicts time to kidney graft loss.

Methods: Data were derived from the transplant registry of the University Medical Center Groningen, including KTR transplanted after 1-1-1995. Data for model training was obtained 1 year after transplantation. KTR with missing data <5 years after transplantation were excluded. Graft loss was defined as death or graft failure. To predict the time to graft loss, extreme gradient boosting (XGBoost) with the accelerated failure time objective was utilized. The model was trained using a bootstrap aggregating (bagging) approach. Variables included in the model were selected by feature selection. The performance of the machine learning model was internally evaluated using the C-index on 20% of the dataset which was not used for training.

Results: From 2195 included patients (age 52 [41-61] years, 42% female), 1225 (56%) developed graft loss during median follow-up of 8.1 [5-13.0] years. The model was trained using 45 commonly determined clinical variables, including eGFR, hemoglobin, age, and several feature-engineered variables. Feature engineered variables are new variables created from existing ones to improve the performance of the model. Hematocrit, eGFR, and GA were identified as the most important variables driving time to kidney graft loss. Internal validation showed a C-index of 0.74.

Conclusions: The machine learning model developed predicts time to graft loss with a reasonable accuracy.

SA-PO1080

Association Between Early State of Volume Overload with Delayed Graft Function in Kidney Transplantation

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Background: Delayed graft function (DGF) following kidney transplantation (KT) is a common problem and has been associated with decreased graft survival and increased risk of acute rejection. One of the factors that has been poorly studied so far is the state of volume overload as a risk factor for DGF. The aim is to associate the state of volume overload estimated by the daily accumulated fluid balance and measured through bioimpedance vectors, ultrasonographic parameters, serum B-type natriuretic peptide (sBNP), and Ca-125 with the development of DGF.

Methods: All patients over 18 years undergoing KT were included. Fluid balance was recorded, sBNP and Ca-125 were measured. Electrical bioimpedance and ultrasound measurements were also performed such as diameter of the inferior vena cava (IVC) and the portal vein pulsatility fraction (PVPF). Measurements were taken before KT and then every 24 hours for 3 days after KT. The primary outcome was the development of DGF, defined as need for renal replacement therapy within the first 7 days post-transplantation.

Results: A total of 34 patients with KT were included, with an average age of 31 (26- 42) years, and the main type of renal transplant was deceased donor (68%). Eight patients (23.5%) developed DGF. Analysis of the volume status revealed that the accumulated balance at 72 h was -7.9 mL (-3648 to -1875 mL) in the non-DGF group and 5590 mL (5126 to 7232 mL) in those who developed DGF (p<0.001). Pretransplant sBNP levels were 100.1 pg/mL (38-248) without DGF vs 525 pg/mL (74-1815) with DGF; p = 0.045. Pretransplant Ca-125 levels were 12.1 U/mL (7.9-19) without DGF vs 10.1 U/mL (9-13) with DGF; p = 0.66. The intragroup difference of the trough levels was not significant in both groups. The average questionnaire scores of GI symptoms were comparable between groups. The vital signs and allograft function at 3 months was not significant in both groups. The adherence to the study medication was 100% in both groups. A total of 62 KTRs were randomized to either P-CAB (Tegoprazan ®) or PPI group. A smart clinical trial platform monitored the enrolled patients with remote monitoring and safety management systems. Remote monitoring system transmitted data about adherence to the study drug, blood pressure, body temperature, and electrocardiogram. Questionnaires for general and gastrointestinal (GI) symptoms were surveyed using a self-developed app installed on the patient’s phone. One non-face-to-face visit was scheduled during the study period. Trough levels of tacrolimus and mycophenolate were checked monthly for 3 months.

Results: Baseline characteristics including trough levels did not differ between groups. The adherence to the study medication was 100% in both groups. A total of 3.7% biometric information and 5,031 questionnaire answers were collected. We conducted 5,704 feedback messages and 56 non-face-to-face video visits. Mean trough levels of tacrolimus and mycophenolate did not differ between P-CAB and PPI groups at 3 months (5.2 ± 2.5 vs. 5.8 ± 2.7 ng/dL, P = 0.50 and 2.7 ± 2.0 vs. 2.6 ± 2.0 ng/dL, P = 0.66, respectively). The intragroup difference of the trough levels between baseline and 3 months was not significant in both groups. The average questionnaire scores of GI symptoms were comparable between groups. The vital signs and allograft function maintained stably without significant difference during the study period.

Conclusions: P-CAB does not affect the serum trough levels of tacrolimus and mycophenolate in KTRs. P-CAB showed a similar effect on the patient-reported GI symptoms compared to PPI. Our smart clinical trial system with non-face-to-face video visits demonstrated the efficacy and safety in performing randomized trials.

SA-PO1082

Use of an LCP Tacrolimus (LCPT) in Kidney Transplantation: A Delphi Consensus Survey of Expert Clinicians

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Background: LCPT (Envarsus XR®) is a common once-daily, extended-release oral tacrolimus formulation used in kidney transplantation. Variations in real-world use mean uncertainty remains on how best to use LCPT in kidney transplantation in de novo and conversion populations. The objective of this study was to address the gaps in published data by developing consensus statements on the use of LCPT in kidney transplantation using the Delphi process with a panel of expert clinicians.

Methods: A panel of 12 clinicians with expertise in nephrology and kidney transplantation reviewed available clinical evidence on LCPT. The Delphi panel survey consisted of three rounds of an online survey. Consensus was achieved when ≥75% agreed strongly or with reservation to a statement.

Results: Twenty-three statements were evaluated: 14 on de novo and nine on general or conversion use. After two rounds, consensus was achieved for 20 statements (Figure 1). De novo, LCPT was recognized as a first-line option based on its safety and efficacy compared to immediate-release tacrolimus. In a conversion setting, full consensus was achieved for converting to LCPT to address neurological side effects related to immediate-release tacrolimus and for the time required (~7 days) for steady state LCPT trough levels to be reached.

Conclusions: The consensus statements generated in this study provide a real-world guide to using LCPT in kidney transplantation, especially in a de novo setting, for which guidance is currently lacking.

Funding: Commercial Support - Veloxis, Inc.
SA-PO1083

Effect of Prolonged-Release vs. Immediate-Release Tacrolimus on Neurocognition in Kidney Transplant Recipients: A Pilot Randomized Controlled Trial (RCT)

Hadija Lala Gul, Macey Sockolow, Amanpreet Occhipinti, Sarah A. Howes. UC Davis Health, Sacramento, CA

Background: Tacrolimus is known to cause neurological side effects and elderly individuals seem particularly vulnerable. It is unknown if the prolonged-release (PR) tacrolimus (Envarsus XR) formulation minimizes neurocognitive side effects compared to immediate release (IR) tacrolimus due to lower peak serum levels. We aimed to compare the neurocognitive side effects of PR and IR tacrolimus in elderly kidney transplant recipients within the first months post-transplantation.

Methods: In this single center, prospective, open-label, randomized trial, 64 kidney transplant recipients aged 60 or above were randomized to PR tacrolimus or IR tacrolimus (Envarsus XR) formulation. Envarsus XR was titrated to twice daily dosing. Envarsus XR should be initiated on the morning of POD1 for all kidney transplant recipients, regardless of donor kidney function. In the de novo setting, the initial dosing of Envarsus XR XII can be after the third dose although steady state is not attained until after 7 days at 60% of steady state.

In the de novo setting, the Envarsus XR dosing should begin with 0.34 mg/kg/day and should be calculated for ideal body weight or the setting of obesity, except in the following scenarios:

- The initial dosing of Envarsus XR may be reduced in the setting of diabetes mellitus or when using induction therapy.
- The dose may be increased in known rapid metabolizers.
- The dose may be adjusted in the presence of known drug interactions that influence tacrolimus metabolism.

In the de novo setting, ideal body weight should be used as the preferred initial dosing weight for Envarsus XR or obese recipients.

In the de novo setting, Envarsus XR should be initiated on the morning of POD1 for all kidney transplant recipients, regardless of donor kidney function. In the de novo setting, the initial dosing of Envarsus XR may be adjusted in patients for whom the risk of subtherapeutic levels (i.e., ≥ 10 ng/ml) outweighs the benefit of risk avoidance of therapeutic levels.

During the first week post-transplant the dose of Envarsus XR may be adjusted in circumstances of a subtherapeutic level or in circumstances of a significantly subtherapeutic level (i.e., ≥ 1 ng/ml) through 3 times a day (i.e., tacrolimus) or post-transplant.

Consequence on Envarsus XR: Excessive use of Envarsus XR may induce the use of Envarsus XR in clinical practice.

Further evidence of clinical long-term outcomes (gastrointestinal symptoms) may help support the use of Envarsus XR in clinical practice.

Conclusions: Patients should consult their treating medical doctor about Envarsus XR therapy, even if they are no longer at risk for medical conditions.

SA-PO1084

The Association Between 25-Hydroxyvitamin D and Recurrence of Glomerulonephritis in Kidney Transplant Recipients

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Background: Disease recurrence contributes significantly to allograft failure in kidney transplant recipients (KTR) with kidney failure due to glomerulonephritis (GN). Accumulating evidence has revealed a role of vitamin D in innate and adaptive immunity. While vitamin D deficiency is common among KTRs, the association between 25-hydroxyvitamin D (25(OH)D) and GN recurrence in KTRs remains unclear.

Methods: Data from KTRs with GN (i.e., focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, membranoproliferative GN, or lupus nephritis) transplanted at our center from 2000-2019 were analyzed. All post-transplant serum 25(OH)D measurements were included as a time-varying covariate. Disease recurrence was identified via allograft biopsy following abnormal clinical signs or laboratory measures. Survival models considered other causes of allograft loss, including death, as competing risk events. Disease recurrence within one year after each 25(OH)D measurement was considered as the event of interest. Models were adjusted for age at transplant, sex, race, donor status, prior transplant, and time of 25(OH)D measurement.

Results: A total of 63 cases of GN recurrence (median: 4.6 years) were identified in 823 KTRs followed for a median of 7.6 years after transplant. Each 1 ng/ml lower serum 25(OH)D was associated with a 3.04-fold (aHR = 3.04; 95% CI, 1.60-5.78) higher incidence of recurrence compared with vitamin D sufficiency (< 20 ng/ml) was associated with a 5% higher incidence of recurrence (adjusted hazard ratio [aHR] = 1.05; 95% CI, 1.02-1.07). Vitamin D deficiency (< 20 ng/ml) was associated with a 3.04-fold (aHR = 3.04; 95% CI, 1.60-5.78) higher incidence of recurrence compared with vitamin D sufficiency (< 20 ng/ml).

Conclusions: Vitamin D deficiency is associated with a higher incidence of GN recurrence in KTRs independently of proteinuria. Additional research is needed to explore the utility of vitamin D surveillance and management in KTRs with GN.

Table 1. Association between serum 25(OH)D and GN recurrence.

<table>
<thead>
<tr>
<th>25(OH)D (ng/ml)</th>
<th>GN Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;20</td>
<td>100</td>
</tr>
<tr>
<td>20-30</td>
<td>100</td>
</tr>
<tr>
<td>10-20</td>
<td>100</td>
</tr>
<tr>
<td>&lt;10</td>
<td>100</td>
</tr>
</tbody>
</table>

Vitamin D deficiency is associated with a higher incidence of GN recurrence in KTRs independently of proteinuria. Additional research is needed to explore the utility of vitamin D surveillance and management in KTRs with GN.

### Table 1. Neurocognitive Testing and Tremor Results

<table>
<thead>
<tr>
<th>Test</th>
<th>IR Tacrolimus arm</th>
<th>PR Tacrolimus arm</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOCA</td>
<td>23 (9)</td>
<td>22 (8)</td>
<td>0.15</td>
</tr>
<tr>
<td>DSST</td>
<td>24 (7)</td>
<td>23 (6)</td>
<td>0.15</td>
</tr>
<tr>
<td>QUEST</td>
<td>23 (9)</td>
<td>22 (8)</td>
<td>0.15</td>
</tr>
<tr>
<td>OTSWI</td>
<td>20 (9)</td>
<td>19 (8)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Results: 32 patients were randomized to the IR tacrolimus arm and 31 into the PR tacrolimus arm. Mean age was 69 in both arms and 37% were women. Table 1 shows the assessment scores for the primary and secondary outcomes. There was no statistically significant difference between groups in the change in MOCA or DSST scores from baseline to 6 weeks or in tremor or quality of life measures.

Conclusions: Although prior studies indicated improvement in neurological side effects as assessed by the MOCA or DSST tests in this cohort.

Funding: Commercial Support - Veloxis Pharmaceuticals, Inc

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
SA-PO1085
Cryptococcosis in Kidney Transplant Recipients
Laurène Tardiez,1 Gillian Divard,2 Laurent Mesnard,3 Jean-philippe Rerolle,4 Marie Frimat,5 Cecile M. Vigneau,6 Gabriel Choukroun,7 Matthias Buchler,8 Renaud Shannoudi,9 Valérie Moal,9 Moglie Lequentin-Donnette,9 Hannah Kaminski,5 Cedric Rafat,1 Centre Hospitalier Regional Universitaire de Montpellier, Montpellier, France; 1Hopital Universitaire Necker-Enfants Malades, Paris, France; 2Hopital Tenon, Paris, France; 3CHU Dupuytren 2, Limoges, France; 4Centre Hospitalier Universitaire de Lille, Lille, France; 5Hopital Pontchaillou, Rennes, France; 6Centre Hospitalier Universitaire Amiens-Picardie, Amiens, France; 7Hopital Bretonneau, Tours, France; 8Hopital Bicetre, Le Kremlin-Bicetre, France; 9Assistance Publique Hopitaux de Marseille, Marseille, France; 10Universite de Bordeaux, Talence, France.

Background: Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients. Clinical management and disease prognosis have already been previously scrutinized in this setting but had yet to be investigated specifically in kidney transplant recipients(KTr).

Methods: We carried out a cohort study of patients diagnosed with cryptococcosis after KT in France. Cases were matched with controls derived from a multicenter KT database. Our main objective was to describe course of graft function and patient survival. Secondary endpoints consisted in investigating practices pertaining to immunosuppressive treatment adjustments, identifying risk factors. Multivariable analysis was performed using conditional logistic regression to identify risk factors for cryptococcosis.

Results: Eighty-eight patients were included, matched with 79 controls. During induction treatment of cryptococcosis, 37.5% of patients presented with acute kidney injury (AKI) with 13.3% warranting renal replacement therapy. 35.5% of AKI were caused by drug toxicity. 34% of the patients experienced i side effect amphotericin B-related nephrotoxicity predominated (39%) and was characterized by AKI in every case. All surviving patients were exposed to azole treatment. Of these, 41.8% experienced an overdose of tacrolimus, half of which were complicated by AKI. Twelve months after diagnosis of cryptococcosis or equivalent period for controls, 22.4% of KTr experienced loss of graft function compared with 1.4% for control KT (p<0.001). In 61.4% of patients on mycophenolate mofetil, drug was stopped whereas it was continued at unchanged doses in 12.3%. Dose of calciuminhibitors was not modified in 42.4% and reduced in 37.9% upon multivariable analysis, patient’s age (OR 1.04 p=0.004) and history of rejection (OR 2.32 p=0.04) were significantly associated with the development of cryptococcosis.

Conclusions: Cryptococcosis is associated with a highly impact on overall and kidney graft survival in KTr. Risk of acute graft dysfunction followed a threefold temporal sequence characterized by amphotericin-related tubular injury, tacrolimus overdose due to fluconazole/tacrolimus interaction through CYP competition and acute graft rejection in the setting of immunosuppression tapering.

Funding: Clinical Revenue Support

SA-PO1086
Chronic Lymphocytic Leukemia in Solid-Organ Transplant Recipients: A Single-Center Experience
Liza Cholin, Todd E. Pesavento, Priyamvada Singh. The Ohio State University, Columbus, OH.

Background: To date, only two case series on chronic lymphocytic leukemia (CLL) in solid-organ transplants (SOT) has been published which showed an increased risk for severe infections and mortality. The aim of our study was to add to the limited literature on this topic, by evaluating the overall safety of transplanting such patients.

Methods: A 10 year retrospective chart review was performed to identify patients with a diagnosis of CLL who had undergone SOT at a large transplant center. Post-transplant outcomes including infectious complications, graft loss, and mortality were reviewed.

Results: A total of 10 CLL patients were studied: 5 had a diagnosis pre-SOT, and 5 were diagnosed with CLL post-SOT (table 1). All kidney transplant recipients received anti-thymocyte globulin for induction, while liver transplant recipients received either Basiliximab or steroids. Maintenance immunosuppression (IS) therapy among the patients was similar, with 8 out of 10 patients receiving a calcineurin-inhibitor and mycophenolate derivative. Average follow up for pre-SOT CLL patients was 2.9 years (min 1, max 6) with 1 out of 2 deaths attributed to an infectious complication (COVID). Post-SOT CLL patients had a mean of 9 years between transplantation and CLL diagnosis. On an average follow up of 2.8 (min 0.5, max 7) years after CLL diagnosis, 3 out of 5 post-SOT CLL patients had died as an outcome.

Conclusions: Short-term outcomes in SOT recipients with a diagnosis of CLL prior to transplantation appear acceptable. However, SOT recipients who developed CLL post-transplantation seem to have an increased mortality risk. Infectious complications are a known cause for increased morbidity and mortality in CLL patients. As such, reduction in maintenance IS therapy in patients who are years out from transplantation may allow for improved outcomes.

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

SA-PO1087
Donor-Derived Large B-Cell Lymphoma After SPK
Akshay Athreya, Gaurav Gupta, Ambsreen Azhar, Layla Kamal, Selvaraj Muthusamy, Muhammad J. Saeed, Aamir Khan. Virginia Commonwealth University, Richmond, VA.

Introduction: Absolute risk of lymphoma transmission with SOT is unknown. In this unique case, DLBCL was detected after SPK with delayed renal allograft dysfunction with functional pancreas & mate kidney.

Case Description: Recipient was nonsensitized 42-year-old EBV IgG+ type 1 diabetic male. Donor was 39-year-old female with paraplegia due to multiple sclerosis at time of death, no leukocytosis & preprocurement CT abdomen/brain was normal. Cause of death was cerebellar bleeding. Donor was EBV IgG+, KFDI 31% with negative XM. Before implantation, a core needle biopsy was performed. LM showed CD20+ atypical lymphocytic infiltrate. The recipient received rATG induction & maintenance FK, MMF & steroids per protocol. A creatinine rise prompted biopsy 2 weeks post transplant. It showed diffuse mononuclear inflammatory tubulointerstitial infiltrate with clusters of atypical cells in interstitium & peritubular capillaries staining diffusely for CD20, Ki67(>50%) & variably for BCL2 & MUM1 indicating DLBCL. Atypical cells in procurement biopsy showed similar pattern. Simultaneous tissue gene expression testing (MMdx) showed AbMR, possibly indicating host vs tumor response. Immunosuppression was withdrawn except steroids. PET scan & peripheral flow cytometry were negative. Patient underwent allograft pancreatectomy & nephrectomy. Explant pathology showed DLBCL invasion of renal graft & portion of small bowel. Due to risk of microinvasion of tumor, rituximab (weekly *4) was given with serial PET scans & R-CHOP. No other donor derived lymphomas were reported to UNOS from heart, liver, lungs & mate kidney from this donor.

Discussion: Early allograft removal, immunosuppression withdrawal & cancer therapy was offered to the patient to maximize treatment efficacy & confer the best chance of survival in this high risk disease.
SA-PO1088

Post-Transplant Lymphoproliferative Disorders in Kidney Transplant Recipients: A Retrospective Single-Center Cohort Analysis

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Background: To characterize the posttransplant lymphoproliferative disorders (PTLD) including the Epstein-Barr virus (EBV) status, histological subgroups, site of occurrence and the clinical outcomes of kidney transplant recipients at our institution.

Methods: A retrospective cohort study of all kidney transplant recipients who developed PTLD and were followed up at our transplant centers from 1999 through 2021.

Results: 44 patients developed PTLD, with majority 86.4% being kidney-alone transplants, while 13.6% were kidney-pancreas recipients. Heme- Oncology were primarily responsible for the treatments which was tailored to their individual type and stage and site of PTLD. Immunosuppression was lowered on an individualized basis. We describe a large series of PTLD cases, with their outcomes with reasonable outcomes. The time-line to PTLD was not limited to early post-transplant course as seen in other series, and EBV-ve PTLD was more common. Careful adjustment of immunosuppression, early detection, and aggressive treatment can lead to acceptable outcomes.

Conclusions: Our study has shown that EBV has the potential to be utilized as a non-invasive tool for quantitative measurement of fibrosis in renal allografts with correlation with histopathology. MRE technology has the potential of detecting IFTA in patients with kidney transplant.

Funding: NIDDK Support

SA-PO1089

Kidney MR Elastography on Controls and Patients with Kidney Transplant

Suraj D. Sen,1,2 Hansel J. Otero,1,2 Laura S. Finn,1 Tricia Bhatti,1 Bernarda Viteri,1,2 1The Children’s Hospital of Philadelphia, Philadelphia, PA; 2University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.

Background: To compare the diagnostic performance of MR elastography in controls and in pediatric patients with transplant kidneys.

Methods: A prospective study of pediatric kidney transplants undergoing clinically indicated biopsy & healthy controls, was performed. MRE was performed on a 3T MRI scanner equipped with MRE hardware consisting of an active-passive driver system. A 2D & 3D spin-echo planar MRE sequence were used to acquire coronal wave images and mean kidney stiffness (in kPa) were measured. For each patient, one to three needle biopsy cores of the lower pole were obtained and fixed in formalin. Three micron sections and mean kidney stiffness (in kPa) were measured. Significantly higher mean baseline stiffness was observed in adult controls as compared to children. 12 kidney transplant recipients were enrolled (Median age: 15.5 years). Mean stiffness measured was 5.3 kPa. We found the mean stiffness of kidneys in children with allografts was significantly higher than controls. MRE showed significant differences among the allograft groups when evaluating IFTA.

Conclusions: Our study has shown that MRE has the potential to be utilized as a non-invasive tool for quantitative measurement of fibrosis in renal allografts with correlation with histopathology. MRE technology has the potential of detecting IFTA in patients with kidney transplant.

Funding: NIDDK Support

SA-PO1090

Noninvasive Evaluation of Renal Allograft Fibrosis Using Magnetization Transfer Imaging


Background: Fibrosis negatively affects kidney allograft survival, but the options for early noninvasive diagnosis are limited. Magnetic transfer imaging (MTI) magnetic resonance imaging (MRI) assesses tissue macromolecule accumulation (like collagen), a characteristic of fibrosis. We tested the hypothesis that MTI non-invasively detects allograft fibrosis in patients with KT.

Methods: Multiparametric MRI was performed in 13 (M9/F4) KT recipients with stable kidney function prior to the protocol allograft biopsy (Table 1). Cortical and medullary magnetization transfer ratio (MTI) at 1.5T MRI, oxygenation (blood oxygen level-dependent MRI), perfusion (arterial spin labeling), and microstructure (diffusion-weighted imaging) were compared with interstitial fibrosis (IF) on the kidney biopsy (trichrome staining) and with albumin-to-creatinine ratio (ACR). Glomerular filtration rate (GFR) was measured using iothalamate clearance.

Results: MTR correlated directly with both cortical and medullary histological IF and with ACR (Figure-1) but not with GFR. No other imaging-derived index correlated with any renal parameter.

Conclusions: Both the % of IF on kidney biopsy and ACR correlated significantly with MTR-MDI but not with any other MRI indices. Hence, MTR may provide a noninvasive tool for the detection and assessment of IF in renal allografts, pending confirmation in a larger number of patients.

Funding: NIDDK Support, Other NIH Support - AG62104 (National Institute on Aging) and DK122734 (NIDDK)

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

Underline represents presenting author.
Patient demographics (mean±standard deviation or median (min, max))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-transplant, Yrs.</td>
<td>4 (4-7)</td>
</tr>
<tr>
<td>Age, Yrs.</td>
<td>59 ± 12</td>
</tr>
<tr>
<td>MRI-kidney biopsy interval, days</td>
<td>1 (3-4)</td>
</tr>
<tr>
<td>Creatinine (g/dL)</td>
<td>9.9 (3.6,18)</td>
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<tr>
<td>Medullary fibrosis (%)</td>
<td>17 ± 9.7</td>
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<tr>
<td>Mean arterial pressure, mmHg</td>
<td>100 ± 12</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl</td>
<td>2 ± 1</td>
</tr>
<tr>
<td>Iohexolual clearance, ml/min/BVA</td>
<td>53 ± 18</td>
</tr>
<tr>
<td>Albumin/creatinine ratio, mg/dL</td>
<td>14 (3-192)</td>
</tr>
</tbody>
</table>

Magnetic resonance imaging; BSA=body surface area.

SA-PO1091

Prognostic Implications of Chronic Active T-Cell-Mediated Rejection Diagnosed on Renal Allograft Protocol Biopsies

Arun L. Kalaria, Hussain A. Karimi, Matthew Pittapilly, Massiel P. Cruz Peralta, Sundaram Hariharana, Chethan M. Putturajappa, Puncet Sood, Akhil Sharma, Rajii B. Mehta. UPMC, Pittsburgh, PA.

Background: Banff 2017 introduced Chronic Active TCMR(CA-TCMR) into the classification of rejection. However, the significance of this finding on early protocol biopsies has not been explored.

Methods: We identified a cohort of patients with serial protocol biopsies performed between Oct 2018-Jan 2022. Biopsies were done at 3- and 12-months. We chose the protocol biopsy closest to the 1-year time point. We included both living and deceased donor kidney transplants. De novo and repeat kidney transplants were included. We excluded biopsies with borderline rejection, antibody mediated rejection or BK virus nephritis. Biopsies that qualified for TCMR were further divided into acute TCMR(n=31) and CA-TCMR(n=36). Biopsies with no major abnormalities (NMA) were used as control. The maximum follow up period was 5.5 years with a median follow up of 3.5 years. All patients received induction therapy with anti-thymocyte globulin and maintenance immunosuppression with tacrolimus and MMF. Patients with cPRA>90% also received maintenance steroids.

Results: See below

Conclusions: CA-TCMR is common in early protocol biopsies and is more common in deceased donor kidney transplants. Allograft survival was lower in biopsies with CA-TCMR. Finding of CA-TCMR on early protocol biopsies prognosticates long-term allograft outcome.

SA-PO1092

Leveraging Machine Learning Methods and Novel Data Sources to Develop Race-Free Algorithms to Predict Deceased Donor Kidney Outcomes

Jeremy Rubin,1 Jarcy Zoe,1 Sarah J. Ratcliffe,1 David S. Goldberg,1 Michael O. Harhay,1 Chirag R. Parikh,1 Emily A. Vail,1 Peter Abt,1 Peter P. Reese,1 Vishnu S. Potluri.1 1University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 2Johns Hopkins Medicine, Baltimore, MD; 3University of Miami School of Medicine, Miami, FL; 4University of Virginia, Charlottesville, VA.

Background: To help transplant professionals choose appropriate kidneys for patients, the national transplant organization uses the Kidney Donor Risk Index (KDRI) that predicts the risk of graft failure. Unfortunately, the KDRI has modest predictive accuracy (C-statistic 0.6). The KDRI has been criticized for penalizing hepatitis C virus (HCV), given recent therapies, and race, given ethics concerns. We aimed to develop machine learning based, race-free models and longitudinal organ donor lab data to predict 3-year all-cause kidney (graft) survival and delayed graft function (DGF, dialysis in the first week post-transplant).

Methods: Using registry data, we assembled a cohort of adult (≥18 years) recipients of deceased donor kidneys between 5/1/07-12/31/21. We developed models with different combinations of donor and recipient characteristics using standard regression (Cox and logistic regressions) and machine learning algorithms (Random Forest, Ridge, Lasso, Elastic Net).

Results: The final cohort included 162,905 recipients of kidneys from 95,811 donors. Median donor age was 39.5 years (IQR 27-51) and 38% were female. For 3-year kidney survival, the C-statistic of KDRI was 0.59. Removal of donor race and HCV covariates, or inclusion of donor longitudinal data, made little difference, but inclusion of recipient covariates improved the C-statistic to 0.63-0.64 across different algorithms (Figure). For DGF, the KDRI had a C-statistic of 0.60. Refitting models with or without donor race had similar C-statistics of 0.68-0.69. The inclusion of recipient covariates improved the C-statistics for DGF to 0.74-0.75.

Conclusions: These models demonstrated the feasibility of eliminating donor HCV and race without a meaningful decrement in predictive accuracy for kidney survival and DGF outcomes. The addition of recipient characteristics substantially improves prediction of both outcomes.

SA-PO1093

Inflammation Alters Relationship Between High-Density Lipoprotein Cholesterol and Risk of CKD: Results from UK Biobank Study

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Background: Under inflammatory condition, the functional changes of high-density lipoprotein-cholesterol (HDL-C) can transition from a protective role to a proatherosclerotic direction. We aimed to investigate whether inflammation could modify the relationship between HDL-C and risk of incident chronic kidney disease (CKD).

Methods: We conducted an observational study in 342,204 European adults, aged 38 to 73 years, who were free of CKD at recruitment between Mar 13, 2006, and Oct 1, 2010.
2010, from the UK Biobank study. The main exposure was HDL-C level. The presence of inflammation was defined when high sensitivity C-reactive protein (hs-CRP) level was above the median (>1.31 mg/L). The primary outcome was incident CKD.

Results: During a follow-up period of 3,983,553 person-years (median, 11.9 years), the primary outcome occurred in 13,950 (4.1%) participants. Overall, a higher HDL-C level was associated with a decreased risk of incident CKD in multivariable Cox analysis after adjustment of confounders. There was a significant interaction between HDL-C and the presence of inflammation on the risk of incident CKD (P-interaction<0.019). In patients without inflammation, the protective association of a higher HDL level remained similar. The hazard ratios (HRs) (95% CI) for HDL-C of <30, 30-39, 50-59, 60, 60-70, 70-79, ≥80 mg/dL were 1.20 (0.93-1.56), 1.13 (1.03-1.24), 0.92 (0.85-1.00), 0.88 (0.80-0.96), 0.85 (0.75-0.95), 0.73 (0.64-0.85), respectively, compared with HDL-C of 40-49 mg/dL. However, this association was attenuated in patients with inflammation, particularly for HDL-C ≥80 mg/dL. Notably, a lower HDL level was associated with a higher risk of CKD in all patients with a stronger increased risk observed in patients with inflammation.

Conclusions: A higher HDL-C level is associated with decreased risk of incident CKD, but this association was weak under inflammatory condition. These findings suggest that inflammation may modify the relationship between HDL-C and the development of CKD.

SA-PO1095
Incidence of CKD in Prediabetes
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Background: Diabetes complications may occur in persons with prediabetes mellitus (PDM) defined by hyperglycemia below the threshold for diabetes diagnosis. The study aim was to assess the incidence of chronic kidney disease (CKD) in PDM in a real-world population.

Methods: The study population was derived from the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry of electronic health records from Providence and UCLA Health systems. PDM was defined by HbA1c 5.7-6.4%. 2 measures of fasting (100-125 mg/dL) or random (140-189 mg/dL) blood glucose at least 1 day apart, or ICD-9-10 codes. CKD was defined by estimated GFR-EPI 2021 glomerular filtration rate (eGFR) <60 mL/min/1.73 m², urine albumin/creatinine ratio ≥30 mg/g, or urine protein/creatinine ratio ≥0.15 g/g ≥90 days apart, or ICD-9-10 codes. Incidence of CKD was estimated in persons ≥18 years old with PDM and without CKD in the previous 6 months. Estimates for 2015-2020 were standardized to the 2020 US population.

Incidence rate ratios (IRR) compared CKD incidence within age, race/ethnicity, and sex groups.

Results: Persons with PDM (N=256,829) were 55% women and 56±15 years old. At baseline, mean eGFR was 93±16 mL/min/1.73 m²; mean HbA1c and systolic blood pressure were 5.8±0.9% and 127±16 mmHg. After a median follow-up of 2.6 years (interquartile range 1.5-3.8), CKD was identified in 7%. Of these, 43% had an eGFR <60 mL/min/1.73 m². Standardized incidence rate of CKD was 30.4 cases/1,000 person-years (95% CI 29.8-31.0). IRRs are presented in the Figure.

Conclusions: CKD developed among 1 in 14 persons with PDM in a short period of time. Older age and non-White race groups with PDM, except the Asian patient group, had higher incidence of CKD compared to the White group, whereas women had lower risk than men. These results suggest that certain demographic groups may benefit from targeted awareness, detection, and strategies to prevent CKD progression.

SA-PO1096
Impact of Hyperglycemia on Renal Prognosis in Lean Individuals
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Background: Obesity not only affects blood glucose but also influences haemodynamics and adipocytokines, making it unclear to what extent hyperglycemia alone contributes to organ damage. Therefore, our aim was to investigate the specific impact of hyperglycemia on renal prognosis in lean individuals with elevated blood glucose levels.

Methods: In this single-center study from 2012 to 2022, we analyzed body mass index (BMI), estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1c) data. Individuals with a BMI <18.5 at any time were selected, excluding those under 18 years old, on dialysis, or with one year of data. Participants with HbA1c >6.5% were assigned to the hyperglycemic group (HGB), while the rest formed the control group (CG). Propensity score matching adjusted for background factors, and both groups underwent time-to-event analysis for a 40% eGFR decline. A 12-month landmark analysis minimized geographic bias.

Results: Among individuals with recorded BMI, 14.2% experienced a BMI below 18.5 during the study. Out of the initial 3149 individuals, 516 were classified as HBG, having a significantly higher average age than CG (74.3 vs. 63.7 years). Among those who did not reach a renal function endpoint within one year of enrollment, we selected a final sample of 484 patients in each group after adjusting for background factors including gender, age, first-year eGFR, duration of observation, and minimum BMI. The selected participants had a mean age of 74.9 years, mean duration of observation of 1755.4 days, and mean minimum BMI of 16.5. Survival time analysis showed that HBG reached the endpoint significantly more often than CG (Hazard ratio: 1.56 (95%CI 1.20-2.03), P<0.001).

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Conclusions: Lean individuals with hyperglycemia, who were more likely to be elderly, exhibited a significantly higher prevalence of impaired renal function compared to background-matched controls.

SA-PO1097
Changes in the Thyroid, Pituitary, and Gonadal Hormones in CKD Patients During One-Year Follow-Up
Aleksandra Rymarczuk, Ksyzema Lesniak, Stanislaw Niemczyk. Wojskowy Instytut Medycyny - Państwowy Instytut Badawczy, Warszawa, Poland.

Background: Hormonal disorders are common complications of chronic kidney disease (CKD). Endocrine disturbances interplay with nutritional status and both are associated with kidney function and influence long term outcomes. The aim of the study was to examine changes of serum levels of chosen hormones, changes in kidney function and nutritional parameters in CKD patients during one-year follow-up.

Methods: Male CKD patients with eGFR lower than 45 ml/min/1.73m² on conservative treatment formed cCKD group and male patients treated with hemodialysis for more than three months formed HD group. In both groups serum levels of total (TT), free testosterone (FT), dehydroepiandrosterone sulfate (DHEA-S), sex hormone binding globulin (SHBG), luteinizing hormone (LH), prolactin (PRL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), creatinine (Cr), albumin (A) were measured at the moment of inclusion and after one year.

Results: 21 men aged 67±8 were included to cCKD group and 20 aged 63±8 to HD group. Over one-year follow-up in cCKD group serum levels of LH, PL and TSH increased significantly whereas DHEA-S decreased. Serum levels of TT, FT, SHBG, IT, IT4 as well as Cr, A and levels did not change significantly. In HD group over one year follow-up serum levels of fT3 and fT4 significantly decreased. Whereas the rest of parameters did not change significantly.

Conclusions: In male with CKD on conservative treatment significant changes of DHEA, LH, prolactin and TSH were observed during one-year follow-up whereas at the same time Cr, eGFR and nutritional markers did not change significantly. In HD group only fT3 and fT4 decreased significantly. We can suspect that hormonal changes can precede decline in kidney function and deterioration of nutritional status in CKD patients.

SA-PO1098
Impact of Lifestyle Changes on Quality of Life in Patients with CKD: Results from a Real-World Study
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Background: Lifestyle changes can slow progression of chronic kidney disease (CKD) but can be difficult for patients to implement. We assessed the impact of lifestyle changes on quality of life in patients with CKD.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a cross-sectional survey of physicians and patients conducted in the USA from Jan-June 2022. Non-dialysis patients completed the Short Form Health Survey 12-item (SF-12) and provided information on the successes in implementing recommended lifestyle changes. Two groups were formed: 'successfully implemented' and 'unsuccessfully implemented'. T-tests were used to compare groups.

Results: Overall 221 patients provided data, the mean [SD] age was 63.2 [12.58], 55% were male, and 66% were white. Lifestyle changes were recommended to 74%, and 95% of these patients reported trying to implement the change(s), of which 20% found it very/extremely difficult. In the SF-12 physical health domain, stopping/reducing alcohol consumption, improving sleep pattern, starting/increasing exercise and reaching/maintaining a healthy weight had the largest difference in composite scores between successful vs unsuccessful (p <0.001) [Table 1]. In the SF-12 mental health domain, stopping/reducing alcohol consumption, stopping/reducing smoking, reaching/ maintaining a healthy weight, reducing potassium intake, and consulting a nutritionist had the largest difference in composite scores between successful vs unsuccessful (p <0.05) [Table 1].

Conclusions: High numbers of patients describe difficulty implementing lifestyle changes recommended by their physician. Unsuccessful implementation can lead to a greater impact on physical and mental quality of life. Support is needed to help patients with these changes, provide optimal care and better patient outcomes.

SA-PO1099
Factors Influencing Quality of Life in Moderate to Severe CKD
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Background: Improving quality of life is one of the targets of CKD management which are involved in several factors including physical, mental and social factors. In addition to factors in general population, evaluation tools for health related QoL (HRQoL) in CKD patients should include kidney related parameters. KDQOL-SF1.3 is a tool developed and established to demonstrate QoL in ESRD, but data in non-dialysis CKD is scarce. Therefore, this study is to present factors contributing to HRQoL in stage 3-5 CKD.

Methods: There were 94 stage 3-5 CKD patients followed up at Siriraj CKD Clinic, Faculty of Medicine Siriraj Hospital, included into the study from November 2021 and August 2022. The data were collected at the baseline for age, gender, comorbidities, CKD etiology, household incomes and education, current medications and pill numbers, blood pressure, nutritional status, physical activity, muscle mass, handgrip strength, and physical performance. Laboratory data included serum creatinine based estimated CKD-EPI GFR, hemoglobin, serum albumin, calcium, phosphate and intact parathyroid hormone (PTH). HRQoL was assessed by KDQOL-SF1.3.

Results: Demographic data were demonstrated in table 1. There was no difference of overall scores of HRQoL in each stage of CKD (stage 3; 70.0 ± 15.3, stage 4; 69.0 ± 18.3 and stage 5; 73.5 ± 16.2, p = 0.545). However, lower HRQoL scores were associated with poorer physical capacity parameters and PTH. Mean ±SD of physical component summary (PCS) scores was 42.1±10.9 vs. 49.2±11.6 in patients with HRQoL <50 vs ≥50, respectively. PCS was associated with lower physical component summary (PCS) scores [mean ±SD of PCS: 42.1±10.9 vs. 49.2±11.6 in patients with HRQoL <50 vs ≥50, respectively; p<0.025].

Conclusions: Lower physical capacity is strongly associated with poor QoL in moderate to severe CKD. Factors associated with physical activity and skeletal health in CKD should be further evaluated to intervene for improving the outcomes.

Funding: Government Support - Non-U.S.
SA-PO1100
An Investigation into the Relationship Between Frailty and Health-Related Quality of Life in Patients with CKD and Heart Failure
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Background: An increasing number of patients have comorbid Chronic Kidney Disease (CKD) and Heart Failure (HF). Patients with CKD and HF have high frailty levels. Frailty is a predictor of morbidity; however, its association with health-related quality of life (HRQOL) is poorly understood. The aim of this study was to investigate the relationship between frailty and HRQOL in patients with CKD-HF.

Methods: This was a single centre, cross-sectional study of adults with CKD stage 3-5 with HF. Frailty was defined as Modified Frailty Phenotype (MFP) score ≥ 3. HRQOL was assessed using the validated Short Form (SF-36) Health Survey. All data was collected at one point in time.

Results: The characteristics of the 103 included participants were: median age 76 years (IQR 13), 62% (64/103) male, mean BMI was 28.7 (SD 6.3) and median eGFR 30 (IQR 17). Fifty-one (50%) of participants were frail, and 52 (51%) were non-frail according to the MFP. Compared to non-frail patients, frail patients had significantly worse physical functioning scores (frail 20.88±/−14.48, non-frail 53.24±/−25.94, p-value <0.001), general health scores (frail 29.51±/−16.86, non-frail 45.00±/−20.05, p-value <0.001), bodily pain scores (frail 46.29±/−33.60, non-frail 63.27±/−29.22, p-value 0.008), social functioning scores (frail 52.23±/−29.65, non-frail 72.58±/−28.05, p-value 0.001) and energy levels (frail 26.37±/−18.31, non-frail 49.71±/−19.22, p-value<0.001). Most respondents cited ‘better quality of life’ as their healthcare priority.

Conclusions: Better quality of life is a priority for patients with CKD-HF. Frailty is negatively associated with quality of life. Early detection and intervention of frailty should be a priority for healthcare professionals.

Funding: Other NIH Support - This study received £1,000 from St George's University Academic Training (GAT) Faculty 'Small Grant Fund' - St George's University, GAT office, Crammer Terrace, London, SW17 0RE.

SA-PO1101
Sleep Duration and Kidney: Does Weekend Sleep Matter?
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Background: Weekend sleep duration is linked to health issues, including mortality. However, how weekend sleep duration can impact chronic kidney disease (CKD) still needs to be understood. Therefore, we aimed to analyze how weekend sleep duration is associated with kidney function.

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Graphs representing the relationship between frailty and several parameters of HR-QOL; energy, general health, physical functioning, social functioning, bodily pain and mental health.

SA-PO1102
Depressive Symptoms Do Not Worsen over Time in Individuals with CKD: The BRINK Study
Christopher D. Kung,1,2 Allan Y. Gao,1 Nicholas S. Roetker,1 Kayla L. Horak,1 Ashley Farnum,1 Allyson Hart,1 Kenneth L. Johansen,2 Anne M. Murray,2 Hennepin Healthcare System Inc, Minneapolis, MN; 2University of Minnesota Twin Cities, Minneapolis, MN.

Background: The prevalence of depression is high in the chronic kidney disease (CKD) (20-40%) and dialysis (30-50%) populations. It is unclear how depression symptoms change over time in patients with CKD.

Methods: Participants in the Brain in Kidney Disease (BRINK) cohort completed a Patient Health Questionnaire (PHQ-9) and an eGFR annually. We completed a retrospective longitudinal analysis of this cohort using a mixed linear effects model to examine the mean change in PHQ-9 score by CKD stage compared with the changes among people without CKD. We also compared changes in depression scores among those who initiated dialysis and those with CKD5.

Results: We followed 571 participants for up to five years, of whom 31% reported a diagnosis of depression at baseline. Baseline PHQ-9 scores were 3.5, 4.4, 4.3, 4.7, and 4.8 for participants without CKD (n=147) and those with CKD5a (n=98), 3b (n=190), 4 (n=112), and 5 (n=24), respectively. After adjustment for baseline PHQ-9 score and covariates, mean PHQ-9 scores improved by 0.20 points per year (95% confidence interval [CI] 0.08-0.33) for people who remained without CKD, and improved by 0.30 points (95% CI 0.14-0.47) and 0.19 points (95% CI 0.07-0.32) for people with CKD 3a and 3b (figare), while annual mean PHQ-9 scores among patients with CKD 4 or 5 and dialysis-dependent CKD did not change significantly. Compared with participants who did not develop CKD, no differences in changes in PHQ-9 scores for any CKD subgroup were observed, nor when comparing change in PHQ-9 scores between people with dialysis-dependent CKD and CKD 5. Results were similar in a sensitivity analysis that excluded 141 individuals reporting anti-depressant use.

Conclusions: We found that mean PHQ-9 scores improved slightly over time in people without CKD and those with stage 3 CKD, but not among those with later stage CKD. However, when we directly compared changes in PHQ-9 scores between those with any stage of CKD and those without CKD, we did not observe significant differences. Our study suggests that progression of CKD may not result in worsening depressive symptoms.

Funding: Other NIH Support - National Institute on Aging Grants R01 AG03755 and R01 AG058729, Private Foundation Support.
SA-PO1103

**CKD-Associated Pruritus (CKD-aP): Associations with Cardiovascular and Infection Events in Non-Dialysis CKD Patients**

Jennifer S. Scherer,1 Charlotte Tu,2 Ronald L. Pisoni,2 Eolodie Speyer,2 Antonio A. Lopes,2 Warren Wen,2 Frederique Menzaghi,3 Josh Cirilli,4 Natalia Alencar de Pinho,5 Roberto Pecotis-Filho,6 Angelo Karayobas,7 New York University Grossman School of Medicine, New York, NY; 1University of Washington, Seattle, WA; 2Yale School of Medicine, New Haven, CT; 3Universidade Federal da Bahia, Salvador, Brazil; 4Cara Therapeutics Inc, Stamford, CT; 5Merck Sharp & Dohme Corp; Nikkiso Co., Ltd; ONO Pharmaceutical Co., Ltd; Terumo Japanese Society for Peritoneal Dialysis; JMS Co., Ltd; Kidney Foundation Japan; Bard Peripheral Vascular, Inc.; Baxter Healthcare Corp; Bayer AG & Bayer Yakuhin, Inc. (since 1996, founding sponsor); Akebia Therapeutics, Inc.; Astellas Pharma Inc.; AboutUs/Support.aspx. As of May 5, 2023, the DOPPS program is supported by Amgen and other funders. For details see https://www.dopps.org/Commercial Support - This manuscript was directly supported by Cara Therapeutics. Global support for the ongoing DOPPS Programs is provided without restriction on publications by a variety of funders. For details see https://www.dopps.org/

**Background:** Chronic kidney disease associated pruritus (CKD-aP) is a disturbing symptom of CKD. We describe the prevalence of CKD-aP in non-dialysis CKD, treatment patterns, and associations with clinical outcomes.

**Methods:** We analyzed 4,020 patients from 91 clinics in Brazil, France, and US enrolled in the DOPPS (2013-2021), a prospective cohort of adults not on dialysis with an eGFR <60 mL/min/1.73m². CKD-aP was self-reported by response to the question: “During the past 4 weeks, to what extent were you bothered by itchy skin? Associations with time-to-event outcomes were investigated using Cox regression models adjusted for potential confounders.

**Results:** The proportion of patients not at all, somewhat, moderately, very much, and extremely bothered by itchy skin was 49%, 27%, 13%, 7%, and 3%, respectively. Among patients at least moderately bothered, 25% were prescribed at least one pharmacotherapy – 35% of the US, 19% in France, 4% in Brazil – including antihistamine (10%), gabapentin (6%), topical corticosteroids (4%), pregabalin (3%), or sedating antihistamine (3%). The hazard ratio (95% CI) for patients extremely (vs. not at all) bothered was 1.84 (1.22, 2.75) for cardiovascular events and 1.36 (0.80, 2.31) for infection events.

**Conclusion:** CKD-aP can cause significant discomfort for individuals, however, we found less than a quarter impacted in our cohort received treatment, and medications chosen can have significant side effects. We also found an increased risk of adverse clinical events with worsening CKD-aP. These results highlight the need for further investigation and education about CKD-aP.

**SA-PO1104**

The Association of the Influenza Vaccination with CKD Progression to ESKD in a High-Risk Patient Population

Clara Wilson,1 Jun Li,1 Crystal K. Jobson,1 Molly Fisher,1 Tanya S. Johns,1 Michal L. Melamed,1 Montefiore Medical Center, Bronx, NY; 2Yale School of Medicine, New Haven, CT.

**Background:** Individuals with CKD who received influenza vaccination have lower risk of infection-related hospitalizations, cardiovascular events, and mortality compared to unvaccinated. However, the association between influenza vaccination status and risk of progression to ESKD has not been studied.

**Methods:** We described a cohort of 4,020 adult patients with CKD stage 3b or 4 (eGFR < 60 mL/min/1.73 m²) identified through ATLAS and FluSurv-Net database from 9/2008 to 9/2010 (index dates) at risk for progression to ESKD. Primary exposure was receipt of influenza vaccine during the index period. Patient were followed to ESKD (primary outcome) or administratively censored at 12/31/2019. Cox proportional hazards models were used to determine the association between influenza vaccination status and progression to ESKD.

**Results:** We identified a total of 180 cases and 3,889 controls (mean age 69 years, female 48%, White 97%, mean eGFR 71 mL/min/1.73 m³). The receipt of PCV13, PPSV23, and both was seen in 42%, 76%, and 39% among cases, and 51%, 78%, and 48% among controls. In the overall population, the adjusted PCV13 VE was 36% (95% CI 2.6 – 58%), and adjusted PCV13 & PPSV23 was 40% (13 – 59%), but not significant for PPSV23 (VE 16% [95% CI 93 – 31%]). When stratified by eGFR, the adjusted PCV13 VE was consistent in eGFR <60 (VE 38% [95% CI 5.2 – 64%]) and 30-59 mL/min/1.73 m² (VE 57% [95% CI 11 – 79%]) without significant interaction; but not calculable for eGFR >60 mL/min/1.73 m² due to small sample size.

**Conclusions:** Receipt of PCV13 was associated with reduced risk of pneumococcal infections in individuals with reduced kidney function.

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**SA-PO1105**

PCV13 and PPSV23 Effectiveness in Individuals with and Without a Reduced Kidney Function

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**Background:** Individuals with chronic kidney disease have increased risk of infection and decreased serologic response to pneumococcal vaccination. The comparative effectiveness of pneumococcal vaccination in individuals with and without CKD is unknown.

**Methods:** Test negative design of all hospitalized adults at Geisinger Health System with a pneumococcal urine antigen test from 2016 – 2021. Cases were defined by a composite of positive urine test, body fluid culture, or diagnostic code for pneumococcal disease. Controls were those who tested negative. We used doubly robust estimation by controlling for the probability of receiving a pneumococcal vaccine using inverse probability of treatment weighting as well as multivariable logistic regression to estimate the odds ratios (ORs) of receiving vaccination between cases and controls. VE was calculated as 1-OR^100.

**Results:** We identified a total of 180 cases and 3,889 controls (mean age 69 years, female 48%, White 97%, mean eGFR 71 mL/min/1.73 m³). The receipt of PCV13, PPSV23, and both was seen in 42%, 76%, and 39% among cases, and 51%, 78%, and 48% among controls. In the overall population, the adjusted PCV13 VE was 36% (95% CI 2.6 – 58%), and adjusted PCV13 & PPSV23 was 40% (13 – 59%), but not significant for PPSV23 (VE 16% [95% CI 93 – 31%]). When stratified by eGFR, the adjusted PCV13 VE was consistent in eGFR <60 (VE 38% [95% CI 5.2 – 64%]) and 30-59 mL/min/1.73 m² (VE 57% [95% CI 11 – 79%]) without significant interaction; but not calculable for eGFR >60 mL/min/1.73 m² due to small sample size.

**Conclusions:** Receipt of PCV13 was associated with reduced risk of pneumococcal diseases in individuals with reduced kidney function.

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**SA-PO1106**

**Progress Against Progression? CKD Management in the Age of Telenephrology**

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**Background:** Nephrology has seen an uptick in transition to remote care delivery, but there has been limited direction for optimal selection of patients appropriate for this method of care. Furthermore, there is limited literature to show which profile of patients utilize the telenephrology platform. In this study, we report the baseline population differences between telenephrology and in-person care groups that are naturally selected when this option is available.

**Methods:** Single center retrospective cohort analysis involving 1,305 patients seen across 4,230 visits over a 3-year period at a well-established nephrology clinic within the Veterans Affairs health system. Baseline characteristics and health profile data were assessed based on grouping of individuals to the telenephrology group (>50% virtual visits) or in-person group (≤50% virtual visits).

**Results:** Baseline characteristics including demographic information and comorbid conditions were similar between the two groups. A higher preponderance of those living in rural defined areas, as compared to those in urban settings, were found to receive in-person care. Individuals who received in-person care were noted to have twice as many emergency department (ED) visits and hospitalizations throughout the course of the study. Similarly, those seen in-person were significantly more likely to be referred for hospice/palliative services.

**Conclusions:** Understanding the health profiles of those who receive telenephrology versus in-person care can inform future decision-making for appropriate utilization. It was surprising to see a higher degree of telemedicine visits occurring with individuals residing in urban locations. Discomfort with aspects of technology and/or lack of reliable internet for those living in rural areas are possible factors implicated in this. More surprising was the increase in ED visits, hospital admissions, and palliative care by those seen in-person. It could be that those seen in-person were more ill, this was a use of convenience due to proximity, or that care is being missed with telenephrology. These findings make future research on the cause of these differences, as well as the impact of telenephrology on CKD progression, imperative.

**SA-PO1107**

**Exploring the Implementation of Telenephrology in the Iowa City Veterans Affairs Health Care System: A Qualitative Study**

**Melissa L. Swee,1,2 Bradley S. Dixon,2 Mary V. Sarrazin,3 Qianyi Shi,1 Benjamin R. Griffin,1 Masaaki Yamada,1,2 Meenakshee Sambharria,1 Diana I. Jalal,1,2 University of Iowa Hospitals and Clinics, Iowa City, IA; Iowa City VA Medical Center, Iowa City, IA.**

**Background:** Telenephrology has emerged as a promising approach to improve access to nephrology care, particularly for Veterans residing in rural areas. This qualitative study aimed to explore the implementation process and identify key factors influencing the adoption and utilization of telenephrology in the Iowa City Veterans Affairs Health Care System.

**Methods:** A multidisciplinary team collaborated to create a scalable and flexible dashboard system in the Iowa City Veterans Affairs healthcare system. Using iterative Plan-Do-Study-Act cycles and employing thematic analysis, nephrologists, primary care physicians, and case managers actively contributed to dashboard design. The Kano Model was utilized to prioritize features based on user needs. The project was initially piloted in four rural clinics, and subsequent cycles focused on refining parameters and enhancing efficiency as telenephrology was implemented in additional rural clinics.

**Results:** Findings from the semi-structured interviews revealed several important themes. Participants expressed appreciation for the potential of telenephrology to improve access to specialized nephrology care, particularly for Veterans living in remote areas. The convenience and reduced travel burden were highlighted as major advantages. However, concerns were raised regarding the coordination of care and potential increases in workload for primary care practitioners. Autonomy and the need for clear guidelines in integrating telenephrology into existing care processes were also discussed.

**Conclusions:** This qualitative study sheds light on the experiences and perspectives of key stakeholders involved in the implementation of telenephrology in the Iowa City Veterans Affairs Health Care System. The findings underscore the potential benefits of telenephrology in improving access to nephrology care for Veterans in remote areas. Addressing concerns related to care coordination, workload, and autonomy is crucial for successful adoption and integration of telenephrology. The insights gained from this study can inform future initiatives to optimize the implementation and utilization of telenephrology in similar healthcare settings.

**SA-PO1109**

**Initiatives to Enhance the Quality of Referrals from Primary Care to Nephrology: A Systematic Review**

**Ankul Ghiqm,1,2 Feng Ye,1 Vinisha K. Hariraman,1 Abdullah Abdulrahman,1 Somkanya Tungsang,1 Ikechi G. Okpechi,1 Aminu K. Bello,1 University of Alberta Faculty of Medicine & Dentistry, Edmonton, AB, Canada; 2University of Calgary, Calgary, AB, Canada.**

**Background:** Excessive referrals to nephrology are major determinants for prolonged wait times to access specialist kidney care. We conducted a systematic review of initiatives aimed at improving the quality of referrals to the nephrology service.

**Methods:** Studies published from inception to April 1, 2021, that were designed to increase guideline concordant (GC) referrals or to reduce wait times and/or total referrals of adult patients with chronic kidney disease from primary care (PCP) to nephrology services were included. The primary outcomes of interest were changes to wait times, changes in the total number of referrals, and changes in the proportion of guideline-concordant referrals. The review was performed using a pre-specified protocol and reported using the PRISMA model. The results are reported based on taxonomy of interventions (provider education, provider reminder system, audit and feedback, multiple interventions, and other).

**Results:** 27 studies met eligibility criteria, including 16 pre-post designs, 5 observational studies, 3 interrupted time series studies, and 2 randomized control trials. Among 6 studies that provided information on the relative change in total referrals after an intervention was applied, the proportionate change in total referrals was 15.3% [IQR: -16.7-80.6%]. 8 studies showed an increased trend in absolute number of referrals for the study periods with a median 23.2 [IQR, 22.0-56.2]. Among four pre-post design studies that reported the mean change in wait times, a significant reduction in the overall wait time was noted (median -26.3 [IQR, -104.2-1.6] days). Three studies used multiple interventions per each initiative, and two of these studies showed a relative increase by 11-fold in GC referrals pre and post intervention.

**Conclusions:** Practice-based initiatives designed to improve the quality of referrals from PCP to nephrology services had different effects on their outcomes of interest. It appears that multifaceted interventions are more appropriate for a greater impact as no single intervention in our study showed a greater effect over another on reducing wait times, absolute number of referrals, or proportion of GC referrals.
SA-PO1110

Identifying Opportunities to Improve Early Referral for Hematuria with Concomitant Proteinuria in a Large Health System
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1Geisinger Health, Danville, PA; 2Novartis Pharmaceuticals Corporation, East Hanover, NJ.

Background: Hematuria is a common problem encountered in primary care though limited data exists on appropriate referral patterns. The purpose of this study was to examine opportunities to improve workup of hematuria for early diagnosis of important associated conditions such as glomerulonephritis and urologic malignancy.

Methods: The study cohort included adults 18+ years of age, with hematuria (defined as ≥1+ greater blood on dipstick), who received care at Geisinger, a large regional health system in Central and Northeast PA from 01/01/2022 to 9/30/2022. The proportion of patients with hematuria who were referred to nephrology or urology within 3 months were examined. Characteristics of patients who were referred vs. not referred were compared using descriptive statistics and non-parametric tests as appropriate.

Results: Out of 507,423 patients who had at least 1 outpatient visit during the study period, 63,895 underwent urinalysis; of these, 8,790 patients had ≥1+ greater hematemia. After excluding 3,102 who had a prior nephrology or urology appointment, 419 of 5,688 (7.4%) had a nephrology or urology appointment within 3 months and 483 (8.5%) had a nephrology or urology appointment within 6 months. Completion of nephrology or urology appointments at 3 months was higher for patients with greater hematemia (1+: 5.7% vs. 2+: 9.9%; p<0.0001) and for patients with concomitant proteinuria (no proteinuria: 5.1%; trace: 8.3%; 1+: 7.7%; 2+: 7.3%; 3+: 9.3%; p<0.0001). In a sensitivity analysis excluding patients with positive nitrile and leukocyte esterase (suggestive for possible infection risk), rates of completed nephrology or urology appointments were similarly low (3 months: 234/2,968 [7.9%]; 6 months: 265/2,968 [8.9%]; p<0.0001 for chi-square test). Other factors associated with higher completed nephrology or urology appointments included male sex, White race, having a Geisinger primary care provider and having concomitant proteinuria.

Conclusions: In a regional health system, we identify lower referral rates to nephrology and urology after hematuria diagnosis, even among patients with concomitant proteinuria. Future studies are needed to determine optimal strategies to improve follow-up and management of hematuria.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO1111

Palliative and Hospice Care Utilization Among a National Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis
Yoko Narasaki,1 Kamyar Kalantar-Zadeh,1 Ji Hoon Yoon,1 Csaba P. Kovesdy,3 Dana B. Mukamel,1 Susan T. Crowley,1 Lisa Le,1 Seungsook You,1 Danh V. Nguyen,1 Connie Rhoe,1 University of California Irvine School of Medicine, Irvine, CA; 2Harbor-UCLA Medical Center, Torrance, CA; 3The University of Tennessee Health Science Center, Memphis, TN; 4Yale University, New Haven, CT, Harbor-UCLA Medical Center, Torrance, CA.

Background: Given the high symptom burden of the aging and ailing advanced CKD population, there is compelling need for palliative or hospice care in routine nephrology management to optimize quality of life. Little is known about the comparative utilization of palliative/hospice care in advanced CKD patients treated with conservative management (CM) vs. dialysis.

Methods: We examined a national cohort of advanced CKD patients (≥1 eGFR <25) separated by ≥90 days) treated with CM vs. dialysis (defined as non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25) over 1/1/2017-6/30/20 20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/Medicare Advantage enrollees, and EHR data. In secondary analyses, we examined finer gradations of dialysis timing, defined as earlier dialysis (ED) vs. later dialysis (LD) (eGFRs ≥1.5 vs. <1.5 at dialysis transition); in tertiary analyses we compared ED, intermediate dialysis (ID), vs. very-late dialysis (VLD) (eGFRs ≥1.5, 10–15, vs. <10 at dialysis transition). We compared rates of hospitalization (primary outcome) and days hospitalized (secondary outcome) in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio with a caliper distance of ≤0.2 using Poisson regression.

Results: Among 28,850 CM patients PS-matched to 28,850 dialysis patients, dialysis transition was associated with higher rates of hospitalization and days hospitalized vs. CM: IRRs (95%CI) 2.21 (2.19, 2.23) (Fig A) and 2.80 (2.75, 2.86) (Fig B), respectively. In secondary and tertiary analyses, compared to CM patients, those who transitioned to dialysis had higher rates of hospitalization and days hospitalized vs. CM, irrespective of timing of dialysis initiation.

Conclusions: Patients treated with CM had lower rates of hospitalization and days hospitalized vs. those who transitioned to dialysis. Further studies are needed to determine the downstream sequelae of the differential hospitalization patterns in CM vs. dialysis patients.

Funding: NIDDK Support

SA-PO1112

Hospitalization Outcomes in a National Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis
Connor Rhee,1 Ji Hoon Yoon,1 Yoko Narasaki,1 Seungsook You,1 Csaba P. Kovesdy,2 Dana B. Mukamel,1 Susan T. Crowley,2 Matthew D. Nguyen,1 Danh V. Nguyen,1 Kamyar Kalantar-Zadeh,1 1University of California Irvine School of Medicine, Irvine, CA; 2The University of Tennessee Health Science Center, Memphis, TN; 3Yale University, New Haven, CT; 4Harbor-UCLA Medical Center, Torrance, CA.

Background: Hospitalization has been the default treatment strategy in advanced CKD patients progressing to ESKD, yet may be associated with higher healthcare utilization in certain subgroups. We compared hospitalization outcomes in a national cohort of advanced CKD patients treated with conservative management (CM) vs. dialysis.

Methods: We examined advanced CKD patients treated with CM vs. dialysis (defined as non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25) over 1/1/2017-6/30/20 20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/Medicare Advantage enrollees, and EHR data. In secondary analyses, we examined finer gradations of dialysis timing, defined as earlier dialysis (ED) vs. later dialysis (LD) (eGFRs ≥1.5 vs. <1.5 at dialysis transition); in tertiary analyses we compared ED, intermediate dialysis (ID), vs. very-late dialysis (VLD) (eGFRs ≥1.5, 10–15, vs. <10 at dialysis transition). We compared rates of hospitalization (primary outcome) and days hospitalized (secondary outcome) in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio with a caliper distance of ≤0.2 using Poisson regression.

Results: Among 28,850 CM patients PS-matched to 28,850 dialysis patients, dialysis transition was associated with higher rates of hospitalization and days hospitalized vs. CM: IRRs (95%CI) 2.21 (2.19, 2.23) (Fig A) and 2.80 (2.75, 2.86) (Fig B), respectively. In secondary and tertiary analyses, compared to CM patients, those who transitioned to dialysis had higher rates of hospitalization and days hospitalized vs. CM, irrespective of timing of dialysis initiation.

Conclusions: Patients treated with CM had lower rates of hospitalization and days hospitalized vs. those who transitioned to dialysis. Further studies are needed to determine the downstream sequelae of the differential hospitalization patterns in CM vs. dialysis patients.

Funding: NIDDK Support

SA-PO1113

QI Project: Identify Modifiable Risk Factors and Improve the Safety of Performing Kidney Biopsies
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Background: Bleeding events are the most feared complication in patients undergoing kidney biopsies (KB). Certain factors have consistently shown to carry an increased risk such as CKD. Not assessed in all prior studies was whether KBs done under real-time CT vs ultrasound (USG) guidance or whether transplanted kidneys (TK)
versus native kidneys (NK), or whether the use of automated trocar-guided biopsy guns (ATGBG) or the use of non-trocar guided biopsy guns (NTGBG) of various sizes carried any differential risk.

**Methods:** All KBs performed at our hospital between 2015 to 2022 were included. Two independent physicians reviewed the charts to acquire the data. Quantitative variables were presented as means +/- SDs using the Wilcoxon test, while qualitative variables as frequencies or %s and compared using the chi-square or Fisher’s exact test. Only factors with p-value <0.3 were included for logistic regression.

**Results:** Overall, information on 174 biopsies performed was collected, of which native was 83% and 17% in a transplanted kidney. Blacks constituted 90% of cases. The median age was 42 Years [7-78 years]. Detailed descriptive results are in Table 1. Univariate analysis showed bleeding risk statistically higher in >65 years and lower in CT-guided KB. In multivariable analysis, age was the most influential risk factor with every 5 years increased bleeding by 24%. Every 5-unit increase in BMI increased bleeding by 43% but not statistically. Fig 1

**Conclusions:** Our study found that additional safety measures needed to be considered when performing biopsies in the elderly. Using CT instead of USG guidance might be warranted for additional safety. We did not find any additional differential in risk of bleeding between NK versus TK or by the use of ATGBG versus NTGBG as far as some real time procedures were utilized.

### Demographic

<table>
<thead>
<tr>
<th>Total Biopsy (174)</th>
<th>Native kidney (144)</th>
<th>Transplanted kidney (30)</th>
</tr>
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<tbody>
<tr>
<td>Biopsy type</td>
<td>2x2</td>
<td>1x2</td>
</tr>
<tr>
<td>Biopsy gun</td>
<td>ATGBG</td>
<td>NTGBG</td>
</tr>
</tbody>
</table>

**Multivariate analysis of bleeding**

**SA-PO1114**

**A Comparison of Standard Survival Analysis and Recurrent Event Analysis in the KNOW-CKD Study**

Dha Woon Im,1 Jayoung Kim,2 Ji Hyo Kim,2 Minsang Kim,2 Kook-Hwan Oh.1

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**Background:** Recurrent events are typically defined as events that occur repeatedly. While many clinical studies primarily focus on identifying risk factors for the first occurrence of an event, known as incident events, there is also interest in investigating the risk factors associated with recurrent events and examining whether there are differences compared to a conventional method.

**Methods:** We conducted a recurrent event analysis on cardiovascular(CV) events using data from the KoreaAN Cohort Study for Outcomes in Patients With Chronic Kidney Disease(KNOW-CKD). Statistical models employed in the analysis included Poisson regression, proportional intensity model, Prentice-Williams-and Peterson total time and gap time models, and frailty model. Furthermore, we compared the results of these models with those from Cox proportional hazards model.

**Results:** During a median follow-up period of 7.205 years, a total of 2,238 participants were included in the analysis. Among these participants, 155 experienced a CV event for the first time, while 35 experienced a second recurrent event, and 4 experienced a third recurrent event. Using Poisson regression model, we further identified associations between recurrent CV events and sex, mean blood pressure, alcohol consumption, hemoglobin levels, and urine protein-creatinine ratio. However, we found that BMI was only associated with incident events and not with recurrent events. Other models did not yield any significant differences compared to the results obtained from Cox proportional hazards model.

**Conclusions:** Our analysis of recurrent event data provided us with valuable insights that were not attainable through a conventional survival analysis focused solely on the time to the first event.

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

### SA-PO1115

**Kidney Outcomes Associated with Adherence to Recommendation from Evidence-Based Clinical Practice Guidelines for CKD 2018 in Japanese Real-World Clinical Practice**

Hirokazu Okada,1 Zannatun Nyma,2 Yuichihiro Yano,3 Hiroshi Kanegae,4 Kaori Kitaoita,1 Nomimayara,1 Seiji Kishi,1 Hajime Nagasue,1 Naoki Kashiwara,1 Saitama Ika Daiyaku, Iruma-gun, Japan; Shiga Ika Daigaku, Otsu, Japan; ‘Genki Plaza Medical Center for Healthcare, Tokyo, Japan; ‘Kawasaki Ika Daiyaku, Kurashiki, Japan.

**Background:** Adherence to recommended treatment is critical in chronic kidney disease (CKD) to prevent complications and progression to kidney failure. The purpose of this study was to explore the adherence to recommendation of patients with CKD, using the Japan Chronic Kidney Disease Database (J-CKD-DB-Ex).

**Methods:** We developed clinical questions (CQ) recommendation scoring from Clinical Practice Guidelines for CKD 2018 (see Table). We quantified adherence to each of the 8 component metrics, with metric scores ranging from 0 points (poor adherence to recommendation) to 8 points (meeting recommendation). Kidney failure defined estimated glomerular filtration rates (eGFR) <15 mL/min/1.73 m² or eGFR ≥30% reduction. We evaluated the adherence of CQ recommendations and the decline of eGFR and composite kidney outcomes by the Cox proportional hazards models adjusted for age, sex, and eGFR baseline.

**Results:** Among 4,455 CKD patients, mean age was 67.2 years, mean eGFR was 54.6 mL/min per 1.73 m², and women were 46.5 % at baseline. Scores of CQ recommendation of 0-5 points group was 12.0%, 6 points group was 29.3%, 7 points group was 41.1%, 8 points group was 17.6%. 838 composite kidney outcomes occurred, more than 6 points groups were at significantly lower risk (6 points: HR 0.67, 95% CI 0.54–0.83).

**Conclusions:** Great adherence of CQ recommendations was associated with prevention of complications and progression to kidney failure.

**Funding:** Other U.S. Government Support

Clinical questions scoring from Clinical Practice Guidelines for CKD 2018

<table>
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<tr>
<th>Variable</th>
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<th>0 point</th>
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<tbody>
<tr>
<td>(A) Serum Potassium (mmol/L)</td>
<td>≤5.4</td>
<td>&gt;5.4</td>
</tr>
<tr>
<td>(B) Sodium - Chloride (mmol/L)</td>
<td>≤133</td>
<td>&gt;133</td>
</tr>
<tr>
<td>(C) Administration of RAS inhibitors</td>
<td>≤7.0</td>
<td>&gt;7.0</td>
</tr>
<tr>
<td>(D) Serum Calcium (mg/dL)</td>
<td>≤8.4</td>
<td>&gt;8.4</td>
</tr>
<tr>
<td>(E) Serum Phosphorous (mg/dL)</td>
<td>≤6.0</td>
<td>&gt;6.0</td>
</tr>
<tr>
<td>(F) Low-density lipoprotein cholesterol (mg/dL)</td>
<td>≤120</td>
<td>&gt;120</td>
</tr>
<tr>
<td>(G) Hemoglobin (g/dL)</td>
<td>≤11.0</td>
<td>&gt;11.0</td>
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### SA-PO1116

**Fatty Kidney: A Meaningful Diagnosis?**

Sri Vihavari Guntupalli, W. Charles O’Neill. Emory University School of Medicine, Atlanta, GA.

**Background:** Fatty kidney has been proposed as a detrimental metabolic condition akin to fatty liver, related to obesity and metabolic syndrome. It has primarily been recognized as an increase in fat within the renal sinus which purportedly exacerbates hypertension and CKD. Whether this condition truly exists and can be diagnosed based on...
the amount of sinus fat remains unclear because the parameters that normally determine the amount of sinus fat are unknown. This was explored retrospectively in patients who underwent renal sonography in an outpatient nephrology clinic.

**Methods:** 137 sonograms performed in an outpatient nephrology clinic over a 5 month period were reviewed. Kidneys with cysts or hydronephrosis or that were inadequately visualized were excluded. Both kidneys were excluded in 49 studies and one kidney was excluded in 20. Total kidney and sinus fat volumes were estimated by measuring areas on longitudinal images using Image J software. Data are presented as means, standard errors, and ranges.

**Results:**

- **Patient age was 59 ± 2 (59-89), weight 84 ± 2.3 kg (37-142), height 67 ± 0.5 m in (59-76), eGFR 46 ± 2 ml/min/1.73 m² (5-70), and body mass index (BMI) 29 ± 0.7 kg/m² (12.45).**
- Diabetes was present in 44%, and 77% had hypertension.

**Conclusions:** In this cohort comprising mostly patients with CKD, the amount of sinus fat was determined almost entirely by kidney size and did not correlate with the degree of CKD or with any metabolic parameters after adjustment for kidney size. Correlations with sinus fat volume previously reported are likely explained by the renal enlargement that occurs with obesity or hyperglycemia.

**Funding:** Clinical Revenue Support

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**SA-PO1118**

**Concordance Between Laboratory- and ICD-10 Code-Defined Stages of CKD Among Patients Hospitalized with Heart Failure in a Large US Integrated Health System**

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

**Background:** The presence of chronic kidney disease (CKD) in patients with heart failure (HF) conveys increased cardiovascular risk, while informing use of some forms of guideline-directed medical therapy. Accordingly, we sought to better understand the level of concordance between laboratory- and ICD-10 code-defined stages of non-dialysis-dependent CKD in this population.

**Methods:** We performed a retrospective cross-sectional analysis of patients admitted to a large integrated health system within the western US between January 1, 2018 and October 1, 2022 with a principal diagnosis of HF (defined by ICD-10 codes: I50.2, systolic heart failure; I50.3, diastolic heart failure; I50.4, combined systolic and diastolic heart failure; I51.0, hypertensive heart disease with heart failure; and I51.3, hypertensive heart disease with heart failure and CKD). CKD was assessed using pre-discharge laboratory data (based on the 2021 CKD-EPI equation) as well as ICD-10 codes.

**Results:** Over nearly 5 years, 61,238 HF hospitalizations occurred, involving 43,234 patients with 94% having a serum creatinine available. Stage 3a, 3b, 4, and 5 CKD was noted in 21%, 22%, 17%, and 11% of hospitalized patients, respectively, based on laboratory data (Table). Among patients with an ICD-10 code for stage 3-5 CKD, rates of concordance with laboratory-defined CKD rose from 6% to 80% (Table and Figure) as renal function worsened.

**Conclusions:** Concordance between laboratory- and ICD-10 code defined stages of CKD rose as CKD severity increased.

**Funding:** Commercial Support - Lexicon Pharmaceuticals, Inc.

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**SA-PO1119**

**Association Between Longitudinal eGFR and Sudden Cardiac Death Among CKD Patients**

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

**Background:** The risk of sudden cardiac death (SCD) is high among dialysis dependent patients, but is poorly characterized in earlier chronic kidney disease (CKD) stages. We aimed at analyzing the relation between longitudinal eGFR and the risk of SCD in patients with moderate to severe CKD.

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**SA-PO1117**

**Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) and Carotid Intima-Media Thickness (cIMT) in Patients with CKD:**

**Background:** Monocyte to high-density lipoprotein cholesterol ratio (MHR) is an emerging prognostic marker of cardiovascular diseases, including atherosclerosis. Circulating monocytes contribute to plaque development, whereas, high-density lipoprotein (HDL) cholesterol neutralizes the pro-inflammatory and pro-oxidative properties of monocytes, resulting in an atheroprotective effect. Indeed, in the general population, MHR is associated with carotid intima-media thickness (cIMT; a measure of subclinical atherosclerosis). However, this association has not been assessed in a cohort with chronic kidney disease (CKD), a population with atherosclerotic disease.

**Methods:** This pooled analysis included baseline data from four clinical studies (2 published [PMID: 27647856; 36636575] and 2 unpublished [NCT Number: NCT04911491; NCT05471518]) that measured monocyte number, serum HDL cholesterol levels, and cIMT in patients with stage 3-4 CKD. Univariate and multivariate regression models were used to evaluate associations of MHR with cIMT and to further adjust for clinically relevant covariates.

**Results:** A total of 59 patients (39% female; 76% white; mean SD age 65±10 years; eGFR 41±13 ml/min/1.73 m²; MHR 14±7, cIMT 0.7±0.26 mm) were included. There was an association between MHR and cIMT (β=0.286; P=0.03) in the unadjusted model (Figure). The association between MHR and cIMT was slightly attenuated after fully adjusting for age, sex, body mass index, and low-density lipoprotein cholesterol (β=0.266; P=0.06).

**Conclusions:** MHR may be associated with cIMT in patients with CKD; this observation should be explored further in a larger cohort.
Methods: We analyzed data from the CKD-REIN cohort study, which enrolled adult patients with CKD stage 3 to 5 from 40 nationally representative outpatient nephrology clinics in France. All cardiovascular (CV) deaths were reviewed, and causes were adjudicated by two cardiologists. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) of SC death and CV death were estimated with shared frailty joint models. Non-CV death and kidney replacement therapy were competing events. Models were adjusted for age, gender, urine albumin-creatinine ratio, diabetes, systolic blood pressure, body mass index, smoking, alcohol consumption and education.

Results: We included 3020 patients: 65% men, mean age 67±13 years, eGFR 34±13 mL/min/1.73m2, 30% with history of heart failure or coronary heart disease. Over a median follow-up of 5 years (interquartile range 4.6-5.2), patients underwent 12 (8-17) eGFR measurements, and the mean eGFR slope was -2 mL/min/1.73m2/year. Forty-four SC and 102 CV deaths from other causes occurred; incidence rates were 3.7 (95% CI 2.7-5.0) and 8.7 (7.1-10.6) per 1000 person-years, respectively. Lower current eGFR value was similarly associated with the risks of SC and other CV deaths (40 to 60% higher event hazard per 10mL/min/1.73m2 eGFR decrease, with overlapping 95% CI), whereas current eGFR slope was only associated with the risk of other CV deaths (Table).

Conclusions: Patients with more advanced CKD had higher risks of both SC and CV deaths from other causes, but steeper eGFR decline seemed more closely related with CV deaths rather than SC death.

Funding: Commercial Support - Fresenius Medical Care; GlaxoSmithKline; Vifor France; Sanofi-Genzyme; Baxter and Merck Sharp & Dohme-Chibret; Amgen; Lilly France; Otsuka Pharmaceutical; and AstraZeneca., Government Support - Non-U.S.

CKD Epidemiology, Risk Factors, Prevention - III

Funding: Other NIH Support - K24HL155861 and R01DK115534

SA-PO1121

Association Between CKD and Venous Thromboembolism Post-Hospitalization

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Background: Chronic kidney disease (CKD) has been implicated as a risk factor for venous thromboembolism (VTE), but the evidence is limited to relatively healthy populations. The objective of the current study is to discern whether parameters of kidney function and damage are associated with the occurrence of VTE after hospitalization.

Methods: We conducted a retrospective study including 24,048 and 11,737 adult individuals hospitalized within Geisinger Health and NYU Langone Health from 2004 to 2019 and 2012 to 2022, respectively. A Poisson model was used to evaluate adjusted incidence rates of post-hospitalization VTE according to estimated glomerular filtration rate (eGFR) and albuminuria stages of CKD in each cohort. Cox proportional hazards models were used to analyze associations of eGFR and urine albumin to creatinine ratio (ACR) with VTE.

Results: In the Geisinger cohort, the incidence of VTE after hospital discharge increased from 10.7 (95% CI 9.2 – 12.6) events per 1000 person-years in individuals in G1A1 (eGFR≥90 mL/min/1.73 m2 and ACR <30 mg/g) to 27.7 (95% CI 20.7 – 37.3) events per 1000 person-years in individuals with G4-5A3 (eGFR<30 mL/min/1.73 m2 and ACR >300 mg/g), with similar findings in the NYU cohort. Meta-analysis of the two cohorts showed that every 10 mL/min/1.73m2 reduction in eGFR below 60 mL/ min/1.73m2 and each two-fold increase in ACR were associated with a higher risk of VTE (HR 1.08, 95% CI [1.02 – 1.15] and HR 1.05, 95% CI [1.03 - 1.08]) respectively.

Conclusions: Both eGFR and ACR are independently associated with increased risk of VTE after hospitalization. The incidence rate increases with the severity of CKD. This suggests the potential need for targeted strategies of VTE prophylaxis after hospitalization in individuals with CKD.

Funding: Other NIH Support - K24HL155861 and R01DK115534

SA-PO1120

The Relationship Between Smoking Cessation and Atherosclerotic Cardiovascular Disease Development Among Patients with CKD

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Background: Previous studies evidenced that smoking is associated with higher atherosclerotic cardiovascular disease (ASCVD) and mortality risk. However, whether quitting smoking is associated with reduced ASCVD risk compared to maintaining smoking in patients with chronic kidney disease (CKD) is unclear. Here we evaluated the association between smoking cessation and ASCVD in patients with CKD.

Methods: We analyzed 1698 participants with non-dialysis dependent CKD enrolled in the KNOW-CKD cohort study. ASCVD was defined as a composite of myocardial infarction, stroke, or cardiovascular mortality. The ASCVD event was defined as a composite of myocardial infarction, stroke, or cardiovascular mortality. The ASCVD event was defined as a composite of myocardial infarction, stroke, or cardiovascular mortality.

Results: During 12,108 person-years of follow-up (median 8.0 years), the ASCVD event occurred in 52 (3.06%) participants, and 111 (6.26%) participants died among the KNOW-CKD participants. There were 19 (2.03%), 18 (4.09%), and 15 (6.46%) ASCVD events in never (n=935), former (n=440), and current smokers (n=323), respectively. The incidence of ASCVD was higher in current smokers (6.6 per 1000 person-years) than in former (5.7 per 1000 person-years) and never-smokers (2.8 per 1000 person-years) (p=0.02). A multivariable Cox regression showed that continuing smoking is significantly associated with ASCVD even after adjustment of age, sex, diabetes mellitus, estimated glomerular filtration ratio, and proteumaria. However, the risk of ASCVD events in former smokers was comparable to never smokers (Hazard ratio, 1.83; 95% confidence interval, 0.95-3.52).

Conclusions: In the present analysis, quitting smoking was associated with reduced risk for ASCVD compared to continuing smoking in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO1122

Longitudinal Trajectory Triglyceride-Glucose (TyG) Index Associated with Adverse Renal Outcome in Metabolic Dysfunction-Associated Fatty Liver Disease

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Background: Nonalcoholic fatty liver disease (NAFLD) is considered a multisystem disease that is significantly associated with an increased risk of chronic kidney disease (CKD), cardiovascular disease and extrahepatic malignancies. Recent study demonstrated that the metabolic dysfunction-associated fatty liver disease (MAFLD) definition identified a higher proportion of individuals at risk of developing incident CKD than the NAFLD definition. Triglyceride-glucose (TyG) index is a marker for predicting metabolic syndrome and also shows an insulin resistance state. This study aimed to evaluate the association between the longitudinal trajectory TyG index and CKD progression in patients with MAFLD.

Methods: In the data from the medical records database in Gangnam Severance Hospital from 2006 through 2020, a longitudinal analysis included participants with MAFLD. MAFLD was diagnosed in individuals with hepatic steatosis and at least one of the conditions as follows: 1) overweight or obese (defined as body mass index [BMI] ≥23 kg/m2), 2) type 2 diabetes mellitus, or 3) two or more

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metabolic abnormalities. Adverse renal outcome was defined by a reduction in the estimated glomerular filtration rate (eGFR) ≥30% of baseline. The changing trend of TyG index over time was classified using latent variable mixture modeling with TyG index during the exposure period. Logistic regression analyses were used to determine the association between TyG index and progression of CKD by adjusting for the influence of confounders.

Results: The study included 4,286 patients, of whom 1287 had MAFLD. Mean age was 52.3 ± 10.9 years. Two distinct groups of TyG index trajectories were identified during the exposure period: decreasing (n = 649) and increasing (n = 638). During the event accrual period, 16 patients (2.87%) developed adverse renal outcomes, and the risk was higher in the increasing TyG trajectory group than in the decreasing TyG trajectory group (hazard ratio 2.265, 95% CI (1.114-4.608), P = 0.024). The results were similar after adjustment for baseline clinical characteristics, comorbidities, anthropometric and laboratory findings, and eGFR.

Conclusions: An increasing tendency of TyG index was associated with a higher risk of adverse renal outcomes in patients with MAFLD.

SA-POI123

Exploratory Study on Renal Dysfunction and Its Risk Factors in Patients with Inflammatory Bowel Disease

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Background: Many studies have consistently demonstrated a higher incidence of renal function decline and progression to chronic kidney disease in patients with inflammatory bowel disease (IBD), primarily attributed to factors such as dehydration, malnutrition, medication side effects, and the impact of the underlying inflammatory bowel disease. However, there is a scarcity of data regarding the precise association between IBD and impaired renal function, as well as the specific risk factors involved. This study aims to investigate the frequency of renal function decline and identify the associated risk factors among patients diagnosed with IBD.

Methods: We performed a retrospective observational cohort study of patients at Yokohama City University Medical Center in Japan. We enrolled patients diagnosed with ulcerative colitis (UC) and Crohn’s disease (CD) between 2016 and 2021 who had an eGFR of ≥60 mL/min/1.73 m² or higher at the time of diagnosis. We collected data including eGFR and other blood test results, from patients over a period of two years. The participants were divided into two groups: a group that experienced a decline of 30% or more compared to baseline eGFR, and a group that did not experience a decline based on eGFR, two years later. The study then evaluated the differences in baseline values between these two groups. Risk factors for renal dysfunction were assessed by univariate and multivariate analysis.

Results: A total of 351 eligible patients with UC and 184 with CD were included. The mean age at the time of diagnosis was 41.9 years with UC and 36.1 years with CD. The frequency of eGFR decline of 30% or more was 19.0% (67 patients) with UC and 17.3% (32 patients) with CD. Univariable analysis demonstrated several possible risk factors, including albumin with UC and hemoglobin with CD at the time of diagnosis. Multivariate regression analysis demonstrated albumin was an independent determinant factor with UC (95% confidence interval(UC): -2.22-0.60, P < 0.01) and hemoglobin was an independent determinant factor with CD (95% CI: 0.53-0.87, P < 0.01).

Conclusions: Patients with IBD have a high incidence of concurrent renal impairment, which has previously been associated with albumin levels at diagnosis and in CD, hemoglobin levels at diagnosis were found to be significantly associated with decreased renal function at 2 years.

SA-POI1124

Fibrotic Burden in Patients with Hepatitis B Virus-Related Cirrhosis Is Independently Associated with Poorer Kidney Outcomes

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Background: Liver cirrhosis and chronic kidney disease (CKD) are chronic conditions that share cardiometabolic risk factors and pathogenic mechanisms. We investigated whether higher fibrotic burden was independently associated with poorer kidney outcomes in patients with hepatitis B virus (HBV)-related cirrhosis.

Methods: A total of 1,691 patients with HBV-related cirrhosis without baseline CKD who underwent transient elastography (TE) between March 2012 and August 2018 were selected. The study outcome was the composite of development of incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m² or proteinuria (≥1+ on dipstick) on two consecutive measurements during follow-up, 50% decline in eGFR or onset of end-stage kidney disease, or all-cause mortality.

Results: The mean age was 53.4 years and 1,030 (60.9%) patients were male. During 8,779 person-years of follow-up (median 5.2 years), 60 (3.5%) patients experienced study outcomes. When stratified according to TE-defined fibrotic burden, multivariable Cox models revealed that risk of poorer kidney outcomes was 2.19-fold (95% CI, 1.16-6.63, P < 0.001) higher in patients with cirrhotic range liver stiffness (≥11.7 kPa), compared to those without significant liver fibrosis (≤7.9 kPa).

Conclusions: Higher fibrotic burden assessed using TE was independently associated with poorer kidney outcomes in patients with HBV-related cirrhosis.

SA-POI1125

Risk of Incident CKD Among Patients with Urolithiasis: A Nationwide Longitudinal Cohort Study

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Background: Urolithiasis has been increasingly implicated to have a causal association with chronic kidney disease (CKD). Recently, several studies have demonstrated the relationship between urolithiasis and CKD. However, the generalizability of their results is limited. We aimed to examine the association between the long-term effects of urolithiasis and the risk of incident CKD.

Methods: From the longitudinal National Health Insurance Service data, this nationwide population-based cohort study identified 219,570 Korean adults with incident urolithiasis requiring procedural interventions and without prior kidney disease and 219,570 controls without urolithiasis matched by age and sex. The primary outcome of interest was the de novo development of CKD, defined as an estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73 m² for at least two consecutive measurements at least 90 days apart. In the sensitivity analyses, the risk of incident CKD was further examined using the outcome defined by the newly occurring diagnostic codes indicating CKD.

Results: Over a mean follow-up of 6.0 years, 12,338 (2.8%) primary outcome events of CKD were observed, with an incidence rate of 4.6 per 1,000 person-years. Multivariable Cox analysis revealed that patients with urolithiasis were associated with a higher risk of incident CKD compared with controls, with an adjusted hazard ratio of 1.41 (95% confidence interval, 1.36–1.46). This association remained consistent across all clinically relevant subgroups and when the CKD outcome was defined based on the diagnostic codes in the sensitivity analysis.

Conclusions: In this large national cohort study, patients with urolithiasis were associated with a higher risk of incident CKD than those without urolithiasis. Further studies are warranted to establish the benefits of preventing urolithiasis in reducing CKD development.

SA-POI1126

The Association of Kidney Function with Disposition After Inpatient Noncardiac Surgery: A Population-Based Cohort Study

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Background: People with advanced kidney disease have more non-cardiac surgeries compared to the general population and a higher risk of postoperative cardiac events and death. However, whether post-operative length of hospitalization and discharge disposition vary with kidney function is not known. In this population-based cohort study from Alberta, Canada, we explored differences in postoperative length of stay (LOS), the number of days spent at home after surgery within 30 days (home time), and the discharge disposition according to preoperative kidney function.

Methods: We identified adults undergoing inpatient surgery between April 2005 and February 2019, and categorized them by preoperative outpatient kidney function based on eGFR in mL/min/1.73 m²: ≥ 60 (G1-2), 45-59 (G3a), 30-44 (G3b), 15-29 (G4), < 15 not receiving dialysis (G5ND) and receiving dialysis (G5D), and kidney transplant recipients (G5T). Outcomes of interest were LOS, home time, and discharge disposition. We estimated associations between eGFR category and outcomes with multivariable generalized estimating equation (GEE) models to account for multiple surgeries clustered at the patient level.

Conclusions: We observed higher risk of adverse kidney events by fibrotic burden. Log-rank test P < 0.001. Abbreviations: TE, transient elastography.

Figure 1. Cumulative incidence of adverse kidney events by fibrotic burden. Log-rank test P < 0.001. Abbreviations: TE, transient elastography.

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than people with G1-2 kidney function (Adjusted Rate Ratio [ARR] of 2.21 [95%CI 2.10, 2.32]). This group also had the lowest home time, with an ARR of 0.69 (95%CI 0.67, 0.70) compared to people with G1-2 function. Most people were discharged home without support after surgery (82.8%), though people with G5D function were discharged to a facility with 24-hour nursing care nearly 4 times more often than the G1-2 group. There were graded increases in risks of these outcomes among adults with G3-G5D kidney function.

Conclusions: Patients with advanced kidney disease spend significantly more time in hospital after surgery, and less time at home. They are also more likely to be discharged with additional support at home or to a facility with nursing support. These findings may help inform perioperative resource planning and shared-decision making.

SA-POI127

Association of Albuminuria with Interstitial Lung Abnormalities

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Background: Pulmonary microvascular dysfunction has been implicated in the pathogenesis of pulmonary fibrosis. Albuminuria, a marker of endothelial dysfunction, may be a risk factor in the early development of interstitial lung disease (ILD). We hypothesized that higher UACR would be associated with interstitial lung abnormalities (ILA), which may represent early stages of pulmonary fibrosis.

Methods: A subset of the U.S. population-based Multi-Ethnic Study of Atherosclerosis cohort (n = 2,260) had spot UACR and full-lung CT measurements at Exam 5 (2010-2012). The association between UACR and ILA was examined cross-sectionally using a generalized linear mixed model accounting for clustering by study site. Due to potential differential associations by age, we performed a stratified analysis with an age cutoff of 65 years. Kaplan-Meier estimation was used to examine whether UACR modified the association of ILA with all-cause mortality (2010-2019).

Results: Compared to participants without ILA, those with ILA (11.8%) were older (74.2±9.1 vs. 68.2±9.0 years), had higher UACR levels (8.4 [IQR, 4.0–20.3] vs. 5.8 [3.5–12.6] mg/g creatinine), and a higher prevalence of smoking history. After adjustment for covariates, UACR was not associated with ILA in the overall group (P=0.71). An association was observed in the age65 group (P=0.002) but not in the age≤65 group (P=0.88). Adjustment for age in stratified analysis did not change the estimates considerably. The presence of both ILA and higher UACR (≥10 mg/g) was associated with greater risk of death when compared with fulfilling only one or none of the two criteria (Figure; log-rank P=0.001).

Conclusions: Albuminuria was associated with more ILA and worse survival in older community-dwelling adults. Albuminuria may be a risk factor in early ILD and requires further investigation.

Funding: Other NIH Support - NHLBI (NIH) grants R01-HL077612, R01-HL093081, and R1C-HL100542 and contracts (HSN268201500033, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169).

SA-POI1128

Impact of CKD on Incidence of Visual Impairment: The Singapore Epidemiology of Eye Diseases Study

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Background: To examine the impact of chronic kidney disease (CKD) on the incidence and severity of visual impairment (VI) in a population-based sample of Asian adults.

Methods: We analysed data from 4732 Chinese, Malay and Indian adults who participated in the baseline (2004-2011), aged 40-80 years and 6-year (2011-2017) follow-up visit of the Singapore Epidemiology of Eye Diseases and were free of VI at baseline. CKD (n=447, 9.4%) was defined as an estimated glomerular filtration rate (eGFR)<60 ml/min/1.73 m2 and severity of CKD was categorized into stages G1-5. Participants underwent comprehensive eye examinations including refraction and slit-lamp examinations. Incident VI was defined as best-corrected visual acuity (BCVA) <20/20 in the better eye. Severity of VI was defined as normal, low vision and blindness (20/40, ≤20/40 to >20/200 and ≥200/200). Associations between CKD and VI were examined using Logistic regression models adjusted for age, gender, ethnicity, diabetes, and hypertension status.

Results: The incidence of VI was significantly higher in individuals with CKD compared to those without (14.3% vs. 3.3%, p<0.001). In severity analyses, incidence of low vision and blindness were also higher in those with CKD (13.4% and 0.9%) compared to those without (3.3% and 0%, p<0.001). There was a clear trend of increasing incidence of VI with the progression of CKD stages, with rates of 3.3%, 13.5%, and 16.3% in stage G1-2, G3a, and G3b-G5 (p-trend <0.001, Figure 1). After adjusting for other factors, CKD was independently associated with an increased risk of any VI, with an odds ratio of 1.47 (95% confidence interval: 1.03–2.10).

Conclusions: Our results suggest that the presence of CKD increased the risk and severity of VI in Asian adults. Given the increasing prevalence of CKD worldwide, these findings highlight the importance of regular ocular examinations for individuals with CKD to reduce the risk of VI.

Figure 1: Incidence of VI by baseline CKD stage

SA-POI1129

Time Is Nephron: Chronic Urinary Bladder Herniation Resulting in ESKD

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Introduction: Inguinal hernias involving the urinary bladder occur in 0.4-3% of cases. They are often asymptomatic but can result in lower abdominal discomfort, urinary tract infections, and kidney complications. We present a patient with an inguinal urinary bladder hernia presenting with end-stage kidney disease.

Case Description: 43-year-old class 3 obese male was admitted for an enlarging right inguinal hernia. The surgeon advised him to return to the specialty clinic for his monthly check-up after seeking urological assistance and deciding on his choice of surgical option offered. Three weeks before admission, he was noted to be uremic and oliguric. On admission, his vital signs were stable, and physical examination revealed bilateral inguinal hernia, and lab results showed S. Cr 14.07mg/dL, BUN 226mg/dL, S. K 6.1mmol/L, and S. Bicarb 7mmol/L. The CT scan revealed a grossly distended urinary bladder herniating into the right inguinal canal and bilateral hydronephrosis. The patient declined kidney replacement therapy due to concerns about his quality of life. He was managed medically and discharged home on hospice care at his request. His S. Cr levels stabilized (in the high 7s), and he passed away one month after hospitalization.

Discussion: Urinary bladder herniation(UBH) can occur as direct inguinal hernia and, less commonly, as indirect inguinal or femoral hernia. Male gender, advanced age, obesity, bladder obstruction, and abdominal wall weakness are contributing factors. Most cases are asymptomatic, but some experience groin pain, urinary retention, hematuria, flank pain, or lower urinary tract symptoms. If left untreated, long-standing urinary bladder hernias cause renal failure, bladder perforation, recurrent stones, or hydronephrosis.
Symptomatic UBH usually require emergency management, initial drainage using a Foley catheter before definitive surgery. Ultrasound, computed tomography scan, or MRI can aid in diagnosis and surgical planning. Open repair of urinary bladder herniation involving reduction of the bladder, followed by a standard herniorrhaphy technique, is the typical approach; however, conventional and robotic-assisted laparoscopic repairs have also been reported. UBH is a rare and overlooked condition more prevalent in high-risk populations such as overweight men. Timely diagnosis and surgical repair are crucial to prevent irreversible kidney damage and fatal outcomes.

SA-PO1130

Dynamic Bayesian Networks (DBN) Predicted ≥40% Decline in eGFR over Six Years

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Background: A ≥40% decline in eGFR over two years is associated with an adjusted hazard ratio of ~10 for progression to kidney failure in patients with chronic kidney disease (CKD). Here, we predicted ≥40% eGFR decline at least one year in advance and simulated missing values among a patient’s CKD trajectory.

Methods: Electronic health records from patients with and at-risk (diabetes, prediabetes, hypertension) for CKD (by diagnosis code and eGFR <60 mL/min/1.73 m^2) from the CURE-CKD Registry (1/1/2006-12/31/2020; N=2,580,806) at Providence Health System (N=1,917,619) and UCLA (N=333,187) Health were used. A DBN for CURE-CKD was created using the Ranking Approaches for Unknown Structures software. The DBN was trained, tuned, and validated on a blind test set. We included demographics, comorbidities, lab values, medications, and vitals over 6 years. The primary outcome was an annual ≥40% decline in eGFR from baseline.

Results: Using observations before the prediction year, the DBN predicted the outcome of the target year despite an average rate of 29% missing values across most variables. Model performance improved over time, suggesting that longer follow-up improved the simulation of missing values and the prediction of ≥40% eGFR decline. By the 6th year, the model achieved an area under the receiver operating characteristic curve (AUROC) of 0.83 and an average precision (AP) of 0.21 (Figure). When stratified, patients with albuminuria/proteinuria had the highest prevalence of ≥40% eGFR decline, and were most accurately predicted (Table), and higher performance was observed in Hispanic and Black groups, who had a higher prevalence of ≥40% eGFR decline versus the whole population.

Conclusions: DBNs can simulate missing data to predict ≥40% eGFR decline in patients with CKD and in racial and ethnic minority groups. Model performance dramatically improved with longer follow-up.

Funding: Other NIH Support - NIMHD

Model performance for >≥40% eGFR decline in the 6th year

PUB001

Characterization of Acid-Base Status of Critically Ill COVID-19 Patients by Stewart’s Methodology

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Background: SARS-CoV-2 infection is associated with unfavorable outcomes and high costs. Although the occurrence of electrolyte derangements in the affected patients is expected to have significative clinical impact, more detailed description and associations to outcomes remains scarce, and limited to the traditional approach of Hendelsson-Hasselbach.

Methods: We conducted a cohort of adult patients with ICU stay of more than 4 days that had blood gas analysis and a typical chest CT involvement at admission. SARS-CoV-2 infection was diagnosed by a positive PCR from nasal swab. Data was analyzed in the PSPN statistical package, version 1.2.1.

Results: A total of 799 patients had a COVID-19 diagnosis in our hospital, and 456 were admitted to an intensive care unit. From these, 211 patients had at least a 4 day ICU hospital and were analyzed; the mortality rate of this group was 13.7%. Overall, 149 patients (70.6%) presented alkalemia, 28 acidaemia (13.3%) and the remaining 34 patients (16.2%) had a normal arterial pH. From those presenting acidaemia, most had a low aSICD (920 patients, 9.5%); within the group with alkalemia, 128 (61% of all patients) had respiratory origin. The non-survivors were older, had more co-morbidities and a higher Charlson’s and SAPS 3 scores. Bacterial infections were also more common in this group. Blood gas variables were similar in both groups; overall, we did not find severe acid-base derangements in this population. Stewart’s variables analyzed - SICD eff, SICD app, SIH, and the albumin, lactate, phosphorus and chloride effect were not different between both groups.

Conclusions: The description of acid-base variables in SARS-COV-2 infected patients remains scarce, and limited to the traditional approach. Alkalemia was the most prevalent acid base disturbance in this population, and mainly of respiratory origin. Although we did not found association between acid-base variables by Stewart’s methodology and mortality, dialysis and respiratory failure, the use of this innovative methodology may provide valuable insights in the description of this severe disease.

PUB002

COVID-19 Is Associated with Hyponatremia up to 90 Days, but Long COVID Is Not Associated with Chronic Hyponatremia

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Background: Hyponatremia has also been reported with high frequency (25% to 45%) and to predict mortality among patients hospitalized with COVID–19. There are no studies that address hyponatremia at longer periods after COVID – 19 diagnosis.

Methods: This is a retrospective cohort studying using data from TriNetX research network containing 93 million unique EMR records. Exposure: COVID-19 diagnosis. Outcomes: serum sodium levels, mild (130-134 mmol/L), moderate (125-129 mmol/L), or severe (<124mmol/L) hyponatremia. Differences in outcomes between the respective cases and control cohorts were evaluated after propensity score matching with student t-test for the continuous variables and chi-squared test for dichotomous variables. We report risk differences and differences in mean sodium level.

Results: In high-risk patients, COVID - 19 cases had lower sodium values up to 30 days after COVID-19 and had higher risk of hyponatremia up to 90 days following COVID–19 than the controls. In low-risk patients, COVID-19 cases had lower sodium values up to 14 days after COVID-19 and had a higher risk of mild or moderate hyponatremia up to 30 days following the COVID-19 diagnosis than the controls and higher risk of severe hyponatremia up to 7 days after COVID-19 than the controls; whereas at all greater time points, there were no differences in rates of hyponatremia between the cases and controls.

Conclusions: COVID – 19 is associated with the development of mild, moderate and severe hyponatremia that persists for durations longer the acute time frame. COVID – 19 during the sub-acute phase can be complicated by hyponatremia, but that durations >90 days (long COVID), are not associated with hyponatremia.
Clinical Outcomes of CKD Patients on Dialysis with Severe to Critical COVID-19

**PUB005**

**An Unusual Presentation of Acquired Thrombotic Thrombocytopenic Purpura in a Young Patient with COVID-19**

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**Introduction:** Acquired thrombotic thrombocytopenic purpura (aTTP) is a medical emergency. Untreated thrombotic thrombocytopenic purpura is usually fatal, but with proper treatment, survival rates are over 90%. Cases of aTTP have been described in a population greater than 55-year-old. Very few cases after COVID-19 infection in a population between 20 and 30 years old.

**Case Description:** We describe a 36-year-old man, no past medical history, who developed a progressive worsening shortness of breath during active COVID-19 infection. He had been diagnosed with COVID-19 disease 10 days before admission. The patient was admitted with moderate abdominal pain, 7/10 intensity, localized upper and left side of the abdomen, non radiated, constant, that worsening any time the patient breath. Patient has 38.6°C of temperature at ER, and after 2 hours of this episode he started to have numbness and weakness in left arm, one episode of left arm involuntary movement, facial drooping, general weakness. Labs shows anemia, thrombocytopenia, with echocardiogram on peripheral smear, acute renal failure and normal coagulation profile, Direct Coombs Test negative and was order Adams13 test Antibody.

**Discussion:** The association of this episode of aTTP with COVID-19 infection, with no other discernable cause in this patient, made COVID-19 infection the most likely the trigger to produce this disease. Circulating SARS-CoV-2 attaches and enters into the cytoplasm of monocytes, platelets, and endothelial cells causing their activation and release of pro-inflammatory and pro-coagulant activators leading to a hypercoagulable state. In four of six reported cases reviewed, aTTP was present at the time of the COVID-19 diagnosis or within 10 days. Four out of six COVID-19 infected patients who developed aTTP had a mild course of COVID-19 infection. All patients reported had recovered after treatment, however, three patients had a prolonged and complicated recover. This case highlights the fact that TTP may occur with days after be diagnosed of COVID-19 infection. Clinicians should be aware of this association for prompt recognition and timely treatment. There is a significant increase in acquired thrombotic thrombocytopenic purpura in patients with COVID 19 infection, however, with the correct treatment, the severity of acquired thrombotic thrombocytopenic purpura may have short-term prognostic significance.

Prevalence and Risk factors of aKI in Hospitalized Patients with COVID-19

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**Background:** Acute kidney injury (AKI) has been frequently described in Covid-19 patients. Positive reports confirm the negative impact on Covid outcomes.

**Methods:** This prospective cross-sectional study focused on all admitted Covid19 patients between September and December 2020. A total of 480 patients were enrolled. Patient demographics, medical records, and laboratory data were gathered. Patients were split into two groups: AKI and non-AKI. Comparisons comprised demographics, labs, ICU transfer, need for ventilation and oxygen therapy, medications, hospital stay, and deaths.

**Results:** Showed incidence rate of 40.83% of AKI. The prevalence of HTN was 57.1% in the AKI group which was statistically significantly higher as compared with the non-AKI cases, as well as the prevalence of DM was 67.3% in the AKI group which was significantly higher. Fever was the most common clinical presentation (93.3%) followed by fatigue (70.8%), cough (65.8%) and headache (60%). The prevalence of critical Covid19 disease severity was 44.9% in the AKI group which was significantly higher as compared with the non- AKI (19.7%) (p= 0.005). The duration of hospital admission was statistically significantly longer in the AKI cases. In terms of ICU transfer, 55.1% of patients with AKI were transferred to the ICU and 33.8% of the non-AKI group (P<0.001). Regarding overall mortality11.7% died in hospital. Among AKI patients, 16.3% died compared to 8.5% among non-AKI group (P=0.008). Also severity of the disease was 44.9% in AKI group and 19.7% in non AKI patients (P<0.005).

**Conclusions:** Acute kidney injury in patients infected with Covid-19 is associated with a significant increase in patients’ morbidity and mortality. Identification of the risk factors is crucial for early anticipation and management of this dreadful complication. This study showed that risk stratification and targeted scoring systems for the prediction of AKI in Covid 19 patients in order to early manage the problem in high-risk cases by protective measures.

**Funding:** Other NIH Support - Tanta university

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

Underline represents presenting author.
Analysis of Reasons for Refusing COVID Vaccination or Boosters in Central Washington Patient Populations with CKD

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Background: Numerous studies have demonstrated improved hospitalization outcomes and reduced mortality rates in COVID-vaccinated patients with CKD, including those who have received a booster. The Nephrology Associates of Yakima (NAY), located in rural Central Washington manages a diverse patient population who are on dialysis, are immunosuppressed with kidney transplants, and are diagnosed with early CKD. These patients are associated with high mortality rates with COVID infections. Despite all the public health emphasis, it is concerning that vulnerable high risk populations, such as patients with CKD, continue to exhibit vaccine hesitancy.

Methods: We screened 345 patients in central Washington area to identify individuals who either refused all COVID vaccines or refused the COVID booster after receiving the initial Covid vaccine series during the encounter period of December 2022 to March 2023. Of the 40 patients who were identified during the screening process, 36 individuals (52% women and 48% men) agreed to participate. Surveys were conducted during appointments at the NAY clinic and the 5 DaVita Dialysis Centers located in Yakima and Kittitas County. In total 4 patients refused to fill the survey.

Results: Of the total 36 pts identified, 23 patients had ESKD and were on dialysis, 2 pts had Kidney Transplant and remaining 11 had Other CKD issues. The Age spread : 6 pts were less than 40 yrs old, age group 40 to 60 yrs included 7 pts and Age group More than 60 yrs included 23 total pts. The Race/Ethnicity data : Caucasian pts total included 25, Hispanic pts total included 10, Asian pt was total only 1. Native American pts and African American pts were none in the Covid vaccine refusal group. Our Results showed 36.11% of the 36 patients indicated, "worried about new mRNA vaccine technology" as the primary reason for refusal, followed by, "worried about side effects" at 22.22%, and "unsure of vaccine effectiveness" at 16.66%. Other reasons given were "patient believes in natural immunity" at 13.88%, "patient usually does not take any vaccines" in 8.33% and "Religious reasons" in 2.77% of patients.

Conclusions: This pilot study highlights the critical need for further patient education, especially in high-risk population. We need to improve the general public’s understanding of mRNA technology for better Covid vaccine acceptance.

Funding: Clinical Revenue Support

SARS-CoV-2 Nucleocapsid Antibodies in Kidney Transplant Recipients Are Common After Reinfction

Matthew R. D’Costa, Hersharan K. Sran, Emmett Tsz Yeung Wong, Zi Yun Chang, Anantharaman Vathsala. National University Hospital, Singapore, Singapore.

Background: There remains limited data on SARS-CoV-2 immunity after COVID-19 infection in kidney transplant recipients (KTR), and the severity of COVID-19 reinfection (RI) in KTR is uncertain.

Methods: We performed a retrospective, single-centre study of all SARS-CoV-2-infected KTR confirmed by PCR during the Delta (09/17-12/28/21) and Omicron BA.2, BA.4, BA.5 and XBB (12/29/21-12/31/22) waves. SARS-CoV-2 spike antibody (SpAb) levels were assessed at diagnosis. RI was defined as a new infection confirmed by PCR >90 days after recovery of first infection including symptom resolution and (SpAb) levels were assessed at diagnosis. RI was defined as a new infection confirmed by PCR during the Delta (09/17-12/28/21) and Omicron BA.1, BA.2, BA.4, BA.5 and XBB (12/29/21-12/31/22) waves. SARS-CoV-2 spike antibody (SpAb) levels were assessed at diagnosis. RI was defined as a new infection confirmed by PCR >90 days after recovery of first infection including symptom resolution and repeat surveillance PCR cycle threshold (CT) >25. Post-infection immunity was assessed including SpAb and SARS-CoV-2 nucleocapsid (NAb) antibody >42 days post-infection.

Results: In all, 276 KTR had ≥ 1 COVID-19 infection. They were a mean 53 ± 9 years old, 52% male, 65% ethnic Chinese, 19% obese, 36% diabetic, 91% vaccinated of mRNA technology for better Covid vaccine acceptance.

Conclusions: RI in KTR was relatively mild in our well-vaccinated cohort. NAb is common in KTR with RI likely due to a memory response from prior infection. More studies are needed on the longevity and efficacy of NAb on future RI in KTR.

Effect of CKD on the Severity of COVID-19 in Hypertensive Subjects

Javier Nieto,1 Maravillas Sánchez Macarrón,2 Javier Sobrino,3 Francisco Vallés-Roca,4 Jesús Iтурralde-Iriso,5 Rafael Crespo Sabarís,6 Fernando García Romanos,7 Francisco Fuentes-Jiménez,8 Alcibiades Segundo Díaz Vera,9 Angeles Velasco Soríu,10 Manuel Angel Gömez Marcos,11 José Abellán Alemán,12 HTA-COVID-19 Study Group. 1Hospital General Universitario de Ciudad Real, Ciudad Real, Spain; 2Universidad Católica San Antonio de Murcia, Murcia, Spain; 3Fundación Hospital de l’Esperit Sant, Santa Coloma de Gramenet, Spain; 4Sociedad Valenciana de HTA y RV, Valencia, Spain; 5Unidad de Atención Primaria La Habana-Cuba, Vitoria, Spain; 6Dirección Médica de Atención Primaria, Logroño, Spain; 7Centro de Salud Santa Catalina, Palma, Spain; 8Hospital Universitario Reina Sofia, Cordoba, Spain; 9Centro de Salud El Olivo, Pamplona, Spain; 10Centro de Salud San Andrés, Murcia, Spain; 11Unidad de Saludamán, Salamanca, Spain.

Background: Comorbidities such as hypertension (HTN) or chronic kidney disease (CKD) may worsen the prognosis of subjects infected by SARS-Cov-2 and hypertensives are at greater risk of suffering renal dysfunction. The purpose of this study is to assess the effect of CKD on the progression of COVID-19 in hypertensive patients.

Methods: Multicenter, observational, cross-sectional, retrospective and analytical study. Patients, over 18y, were selected by random sampling in 10 autonomous regions of Spain, among subjects with treated HTN, infected by SARS-Cov-2 under Primary Care Health. CKD was defined as GFR<60 mL/min/1.73m2 and/or UACR>30 mg/g creatinine. The Pearsons test and multivariate logistic regression analysis adjusted for age, sex, smoking, and obesity were used to assess the association between the severity of COVID-19 and the presence of CKD in our hypertensive population.

Results: 1372 patients were recruited, mean age 67y, women 51%, smoking 13%, obesity 44%, diabetes 28%, controlled HTN 56% (BP<140/ 90mmHg). The severity of the progression of COVID-19 was defined as mild-asymptomatic 971 (71%), hospital admission 401 (29%), ICU admission 74 (5.4%), death 48 (rate of lethality 4%). CKD had CKD with a worse prognosis, since of total hospitalizations we found 69% with CKD vs 31% without it (p=0.0064). 18% of patients with CKD<60 (77y, 54% women) also progressed worse, with 44% hospitalizations, 8% in the ICU, and mortality11%. Comparing mild-asymptomatic patients, those with reduced GFR had an unfavorable course (OR=2.4; 95%CI:1.6-3.7; p<0.001), without significant differences in BP. There was also greater severity of COVID-19 in smoking patients with CKD (OR=6.8; 95%CI:2.4-19.5; p=0.001) for hospitalization and (OR=6.0; 95%CI:1.7-21.6; p=0.05) for ICU admission. We did not found any effect of RAS inhibitors, statins or antiinflammatory drugs.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The prevalence of AKD among hypertensive subjects infected by SARS-CoV-2, in our Primary Care environment is very high. CKD, even without a reduced GFR, is related to a greater severity in the progression of COVID-19. Smoking seems to exert a deleterious modulatory effect associated to CKD for the disease outcomes.

PUB010
Detailed Analysis of Kidney Transplant Recipients Admitted to a Tertiary Care Transplant Center with SARS-CoV-2

Background: Kidney transplant recipients (KTR) are a vulnerable immunocompromised population at risk of severe disease and mortality from COVID-19.

Methods: We retrospectively describe all adult KTRs who were hospitalized at our center during their first episode of COVID-19 between 04/2020 and 04/2022 and had at least 12 months follow-up (unless they experienced graft failure or death). Outcomes of interest included length of hospitalization, intensive care unit admission, respiratory symptoms at admission, uncensored graft failure at the last follow up, and death related to COVID-19.

Results: 98 KTRs were hospitalized at our center due to their first episode of COVID-19 between 04/2020 and 04/2022. The mean age at COVID-19 diagnosis was 57±14.2 yrs. 57% of the cohort received at least one vaccine dose against SARS-CoV-2. Of those unvaccinated, 33% (14) had death at last follow-up compared to 26.7% (15) of those vaccinated. The most common cause of end stage kidney disease was diabetes mellitus (29%). The average length of hospitalization was 11.5 days, with 66% of KTRs presenting with respiratory symptoms on admission and 21% requiring intensive care unit admission. 30% died during the study period, of which 19% were COVID-19-related (Figure 1). Mortality was highest within a month of COVID-19 diagnosis.

Conclusions: In this single-center descriptive retrospective study of 98 KTRs, one fifth of those hospitalized at our center died related to COVID-19. KTRs still have high COVID-19-related morbidity and mortality.

PUB013
Effect of the Paxlovid on Glomerular Disease Patients
Miguel Uriel Riven, Estela M. Rödenas, Felipe I. Ojeda, Sonia Jiménez, Aina Obrador. Hospital Universitario Son Espases, Palma, Spain.

Background: The reported efficacy of nirmatrelvir-ritonavir (Paxlovid®) in reducing the risk of severe COVID-19 progression in high-risk patients is well-known. However, there is limited evidence regarding its effects on glomerular disease patients (GDP).

Methods: We retrospectively assessed the influence of nirmatrelvir-ritonavir on the risk of death and hospitalization in GDP. We also examined the changes in estimated glomerular filtration rate (eGFR) before and after COVID-19 infection. Proteinuria was defined as urine protein/creatinine ratio > 0.2 mg/mg. Nine patients were included. The mean age of 46 years. Six patients were female. The mean follow-up was 10 months (range from 9 to 11). The etiology of glomerulonephritides included ANCA-associated vasculitis (n=1), membranous nephropathy (n=1), minimal change disease (n=1), lupus nephritis(n=1), membranous proliferative (n=1) glomerulonephritis, IgA nephropathy (n=2), membranous nephropathy (n=1), and minimal change disease (n=1). Our COVID-19 management protocol involved discontinuing immunosuppression and administering Paxlovid according to the datasheet: nirmatrelvir (2 tablets) and ritonavir (1 tablet) twice a day for 5 days. Weekly uroraphygeal samples were collected for COVID-19 PCR testing to confirm viral negativization, following which immunosuppressants were reintroduced. Four patients had proteinuria before infection.

Results: None of the patients died or required hospitalization. At the time of infection, eGFR decreased by 8.9 mL/min/1.73m² (P = 0.021); however, it recovered at month six. There was significant difference in serum potassium when patients were grouped according to severity of COVID 19 infection. Patients with hyperkalemia were found to develop critical COVID 19 infection. There wasn’t significant difference in serum potassium when patients were grouped according to severity of COVID-19 infection. Patients with hyperkalemia were found to develop critical COVID 19 infection. Patients with lower serum calcium was found to be at higher risk for developing critical COVID 19 infection. This indicates that serum calcium is a potential biomarker for severe COVID-19 infection.

Conclusions: AKI is a frequent complication in patients with COVID-19, with risk factors involved in its development, as well as in its evolution to AKD or CKD.

PUB012
Serum Electrolyte Profile Among COVID-19 Patients in a Tertiary Health Facility from April to September 2020
Andrew Paul M. Candog, Ariel S. Indo. Vicente Sotto Memorial Medical Center, Cebu City, Philippines.

Background: Around December of 2019, an outbreak of unknown epidemic was noted in the province of Hubei in Wuhan China. This infectious agent was identified from the SARS family and was termed as 2019-nCoV, the causative agent associated with the COVID 19 disease. The disease was then considered pandemic after it has infected a number of countries across the globe. The aim of this study was to determine the serum electrolyte profile among COVID 19 patients admitted in a tertiary hospital in Cebu City from April to September 2020.

Methods: Retrospective research design was used in the study. The charts of moderate severe and critical cases of COVID 19 admitted at Vicente Sotto Memorial Medical Center from April to September 2020 were reviewed. The investigator collected the patients’ age, sex, and co-morbid conditions. Once these data have been collected, the researcher determined the patients’ baseline serum electrolytes upon admission. In particular, the serum Sodium, Potassium, and Calcium were obtained. This were classified either as low, normal, or high. This was compared as regards the severity of cases of COVID 19 patients.

Results: Most patients had moderate and critical COVID 19 infections wherein most of these patients were in their late 50s (58.8±15.2). The largest number of patients was male (54.7%). The most prevailing underlying comorbidities, which are more prevalent in men are Hypertension (59.0%) and Diabetes Mellitus (27.7%). Hyponatremia had the largest number of patients (63.9%) common among moderate COVID 19 infection (132.7±5.4). Hyperkalemia was found to develop critical COVID 19 infection (4.4±1.2). Hypocalcemia was common in moderate and critical COVID 19 infection (1.2±0.1 and 1.2±0.2) respectively.

Conclusions: Hyponatremia was observed in the largest number of patients where the largest number of cases of patients had moderate COVID 19 infection. Patients who developed hyponatremia were found to have developed critical COVID 19 infection. There was significant difference in serum potassium when patients were grouped according to severity of COVID-19 infection. Patients with hyperkalemia were found to develop critical COVID 19 infection. Patients with lower serum calcium was found to be at higher risk for developing critical COVID 19 infection. This indicates that serum calcium is a potential biomarker for severe COVID-19 infection.

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**PUB014**

**Ethical Analysis on Mandating COVID-19 Vaccination Prior to Kidney Transplantation in Brazil**

Virgilio P. Delgado, Danielle F. Cunha, Alvimar G. Delgado. Renal Asistência Médica, Rio de Janeiro, Brazil.

**Background:** With the advent of the COVID-19 pandemic, we saw the debate on the best social protection strategy. In what extent can the principle of individual autonomy be limited by the need for social protection? Would it be licit to limit access to health measures, such as kidney transplantation? The cost of refusing the vaccine has an impact on society, on the transplant program and on other patients admitted to the transplant unit. In kidney transplantation, we have the possibility of analysis and investigation regarding the guiding principles of bioethical decisions, discussing how we should proceed when candidates for transplantation object to vaccination.

**Methods:** Primary bibliographical research of indexed scientific articles, by the search tools “Google Scholar” and “Pubmed”, with the keys of “renal transplantation” and “COVID-19 vaccine refusal”. Bibliographical research on technical norms for kidney transplantation and in bioethics related philosophical and ethical foundations.

**Results:** The false opposition between autonomy and beneficence is secondary to a market and principialism vision. However, autonomy must be exercised responsibly, in a relational way. It requires a qualified choice, based on an individual’s narrative identity with: coherence component and socially shared reality. Several countries have different approaches to conduct. Some with severe restrictions or prohibitions, some with financial punishments, others discretionary. The reasons for vaccine objection are multiple, we can summarize three main ones: the presence of religious or philosophical motives, medical and will to benefit without sharing risks.

**Conclusions:** Although the authors have different bioethical views, we can draw common points in the construction of a minimum ethics. Most understand the application of coercive measures as a mistake, but that we should value specific situations. To create objective criteria on organ allocation we should acknowledge that the autonomy of the individual is not opposed to social beneficence. The vaccination requirement for deceased donor kidney transplantation is ethically valid. It should be illicit in urgent transplantation, pediatric transplants or related living donor. In the above cases, the patient must accept the universal protection measures determined by the transplant service.

**PUB015**

**A Comparative Study of COVID-19 and Viral Hemorrhagic Fevers**

Claudia G. Olano,1 Andrea L. Urrutia,2 Sami M. Akram,3 Nehemias Guevara.4

1Harbor-UCLA Medical Center, Torrance, CA; 2Universidad de San Carlos de Guatemala, Guatemala, Guatemala; 3Loma Linda University Medical Center, Loma Linda, CA; 4St Barnabas Hospital, Bronx, NY.

**Background:** Coagulation and platelet dysfunction are hallmarks of covid-19 and viral hemorrhagic fevers (VHF). Agents of VHF have the potential to cause the next pandemic. Examining the differences between the two will help prepare for the next pandemic and efficiently meet the healthcare resources.

**Methods:** Patients admitted to a community hospital formed the study group between February 2020 and April 2020. A published cohort of viral hemorrhagic fevers formed the historical cohort. The historical VHF cohort case reports were reviewed for comparison. Descriptive statistics were applied. First, the groups were compared using independent t-tests. A p-value of <0.05 was considered significant. Proportions of patients with Lung infiltrates, AKI, and who required MV, ICU, and RRT were then compared using student t-tests. Finally, the proportion of patients who died in the two groups was compared. A P-value of less than 0.05 was considered significant.

**Results:** COVID-19 group (Covid19 SG) had 51 patients. The control group had 79 cases, of which 61 were selected. The COVID-19 SG had 51 patients. The VHF-CG had 61 patients. Comorbidities included were diabetes, hypertension, and chronic disorders. See Table 1. Diabetes and hypertension were present in 58.8% of patients in the study group. There was no difference in the sex distribution among the groups. The need for mechanical ventilators is five times greater in the COVID-19-SG compared to VHF-CG. See Table 2.

**Conclusions:** The odds ratio of a patient dying because of covid-19 alpha variant was six times greater compared to viral hemorrhagic fever. The need for RRT increases as the ICU stay increases.

<table>
<thead>
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<th>TABLE NO.1</th>
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**PUB016**

**Effect of Phase Angle by Electrical Bioimpedance on the Incidence and Severity of AKI Following Cardiac Surgery**

Mauricio Carvallo Venegas,1 Jorge Andrade-Sierra,2,3 Enrique Rojas-Campos,1 Luis G. Gonzalez-Correa,1 Miguel Medina Perez,1 Adriana Banda Lopez,1 Jose Ignacio Cerrillos,1 Ricardo Parra Guerra,1 Alfredo Gutierrez Govea,1 Luis Alberto Evangelista-Carrillo,1 Saul Tejeda Del Toro.1 Instituto Mexicano del Seguro Social Delegacion Jalsico, Guadalajara, Mexico; 2Universidad de Guadalajara, Guadalajara, Mexico.

**Background:** Bioimpedance (BE) measures the electrical characteristics of the body to evaluate the patient’s fluid, nutritional, and pathological condition by measuring resistance, reactance, and phase angle (PA). Low preoperative PA is related to greater morbidity and mortality, although the exact relationship with the development of acute kidney injury (AKI) is unclear. Our objective was to determine whether or not preoperative PA increased the risk for AKI following cardiac surgery.

**Methods:** Prospective Cohort from Aug-2022-Apr-2023 that included 78 patients ≥18 years old, undergoing elective valve replacement, coronary bypass surgery, or both, in a single surgical procedure. PA was measured 24 hours before surgery and standardized PA was calculated using data from the Mexican population. Serum creatinine was assessed, and the occurrence and severity of AKI were confirmed 7 days following surgery.

**Results:** The mortality rate was 15% (12 patients) and the incidence of AKI was 30% (23 Pt); 22% (17 Pt) experienced mild AKI, whereas 8% (6 Pt) developed moderate-severe. SEAK. A PA ≥4.5 was not associated with postoperative AKI and mortality. A standardized PA >0.54 was related to a lower incidence of mild AKI, 5% (1/20 Pt) vs 28% (16/58 Pt) (p<0.035), with a RR 0.18 (95%CI:0-3-1.16), with no difference in the incidence of moderate-severe AKI and mortality.

**Conclusions:** PA ≥ 4.5° did not increase the risk of AKI and mortality while a standardized PA >0.54 could be protective for mild AKI.

**TABLE NO.2**

<table>
<thead>
<tr>
<th>Study Parameters</th>
<th>Proportion of Covid19 SG</th>
<th>Proportion of VHF-CG</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
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<tbody>
<tr>
<td>AKI</td>
<td>51/51</td>
<td>31/31</td>
<td>2.27 (1.16-4.42)</td>
<td>0.0128</td>
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<tr>
<td>Mechanical ventilation</td>
<td>30/30</td>
<td>5/5</td>
<td>1.62 (1.004-2.62)</td>
<td>0.040</td>
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<tr>
<td>Intensive Care Units</td>
<td>19/19</td>
<td>7/7</td>
<td>2.29 (1.024-5.13)</td>
<td>0.043</td>
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<tr>
<td>Renal Replacement</td>
<td>1/15</td>
<td>1/14</td>
<td>1.00 (0.04-2.47)</td>
<td>0.999</td>
</tr>
<tr>
<td>Mortality at 7 days</td>
<td>7/78</td>
<td>4/78</td>
<td>1.15 (0.51-2.59)</td>
<td>0.722</td>
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</tbody>
</table>

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1052
PUB017
Comparison of 4 Predictive Scoring Methods as Assessment Tools for Cardiac Surgery-Associated-Acute Kidney Injury in Post Coronary Artery Bypass Surgery Patients: A Single-Center Retrospective Study

Cathleen B. Iway, Harriet Torres. Perpetual Succour Hospital, Cebu City, Philippines.

Background: Cardiac surgery associated acute kidney injury (CSA-AKI) is a common hospital-acquired AKI precipitated by perioperative factors. The surrogates for AKI are in-hospital mortality and post-operative need for renal replacement therapy. Our study goal was to determine the relationship between the development of CSA-AKI and the four scoring methods as its predictors. Confidence interval is set at 95%, comparison significant at <0.05, hypotheses tested at 0.05 level of significance. Therefore, if the p-value is less than or equal to the significance level, it can be concluded that there is a statistically significant association between the response variable and the predictor.

Results: There were a total of 114 cases of open heart surgeries. A sample size of 86 were reviewed. There were 43 patients (50%) who developed CSA-AKI within 5 patients (5.81%) eventually progressed to renal replacement therapy. The p-values for the Cleveland Clinical Score and Simplified Renal Index are greater than the significance level. With the p-values less than the significance level, there is a statistically significant association between the Mehta (p value 0.019) and AKICS scores (p value 0.011) and the development of CSA-AKI. The odds ratios for both Mehta Score (1.10) and AKICS Score (1.19) are also greater than 1, indicating that AKI is more likely to occur if the Mehta score or the AKICS Score increases.

Conclusions: In this single-center study, AKI was more likely if the scores for both Mehta and AKICS scoring methods increase. This supports the hypothesis that either Mehta or the AKICS scoring systems are useful methods that can be employed to predict CSA-AKI among patients who underwent coronary artery bypass.

PUB018
Incidence, Risk Factors, and Outcomes of Postoperative AKI in China: A Multicenter Retrospective Analysis

Shuwan Ge, Yichun Cheng. Tongji Hospital affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.

Background: Postoperative acute kidney injury (AKI) is a common condition after surgery, however, the available data about nationwide epidemiology of postoperative AKI in China from the large and high-quality studies is limited. This study was aimed to determine the incidence, risk factors, and outcomes of postoperative AKI among patients undergoing surgery in China.

Methods: This was a large, multicenter, retrospective study performed in 16 tertiary medical centers in China. Adult (at least 18 years old) patients who undergoing surgical procedures from January 1, 2013 to December 31, 2019 were included. Postoperative AKI was defined by the Kidney Disease: Improving Outcomes creatinine criteria. The associations of AKI and in-hospital outcomes were investigated using logistic regression models adjusted for potential confounders.

Results: Among 252,977 patients included in our study, 25,830 (5.0%) patients developed postoperative AKI. The incidence of postoperative AKI varied by surgery type, which was highest in cardiac (34.6%) surgery, followed by urologic (8.7%), and general (4.2%) surgeries. 89.2% postoperative AKI cases were detected in the first 2 postoperative days. However, only 584 (2.3%) patients with postoperative AKI were diagnosed with AKI on discharge. Risk factors for postoperative AKI included advanced age, male sex, lower baseline kidney function, pre-surgery hospital stays or ≥ 7 days, hypertension, diabetes mellitus, and use of PPIs or diuretics. The risk of in-hospital death increased with the stage of AKI. In addition, patients with postoperative AKI had longer length of hospital stay (12 vs 19 days), were more likely to require intensive unit care (13.3% vs 45.0%) and renal replacement therapy (0.4% vs 7.7%).

Conclusions: Postoperative AKI was common across surgery type in China, particularly for patients undergoing cardiac surgery. Raising the awareness and care (13.1% vs 45.0%) and renal replacement therapy (0.4% vs 7.7%) are useful methods that can be employed to predict CSA-AKI among patients who underwent coronary artery bypass.

PUB019
Outcomes of AKI Hospitalizations Among Patients with Heart Failure and Atrial Fibrillation: A Nationwide Analysis

Idris Abubakar, Fatayi, Michael Amin Alzamara, Muayyad Alzamara, Funlola O. Bada, Abid K. Rajput. TriHealth, Cincinnati, OH; St Ann Bay, St Ann, Jamaica.

Background: Acute Kidney Injury (AKI) has a high incidence among patients with heart failure (HF) and atrial fibrillation (AF). The primary aim of our study is to compare rates of in-hospital mortality and morbidity for patients admitted with AKI only, AKI with AF, AKI with HF, and AKI with both HF and AF. This was a retrospective study with data obtained from the National Inpatient Sample database. We included all adults who were admitted with a principal diagnosis of AKI between 2018 & 2020. The cohort was stratified into patients with AKI only, AKI with AF and HF, and AKI with both HF and AF. The primary outcome was inpatient mortality. Secondary outcomes included acute coronary syndrome, cardiogenic shock, STEMI, length of stay (LOS), average hospital cost, average patient charge, and acute respiratory failure. Univariate and Multivariate Logistic, Linear & Poisson regression model were used for analysis.

Results: Patients with AKI alone had the lowest rates of in-hospital mortality (1.45%). Compared to the AKI only group, patients with AKI and AF had higher rates of in-hospital mortality (2.90%), acute coronary syndrome (3.64%), STEMI (0.92%), cardiace arrests (0.68%), cardiogenic shock (0.20%), acute respiratory failure (73.1%), and septic shock (1.27%), with an average LOS of 4.93 days and an average patient charge of $43.564. Compared to the AKI only group, patients with AKI and CHF had even higher rates of in-hospital mortality (2.77%), cardiace arrests (0.32%), cardiogenic shock (0.064%), acute respiratory failure (15.95%), and septic shock (1.29%), with an average length of stay of 5.39 days and an average patient charge of $49.126. AKI patients with both AF and CHF had the poorest outcomes, with higher rates of in-hospital mortality (4.38%), acute coronary syndrome (4.54%), STEMI (1.16%), cardiace arrests (0.96%), cardiogenic shock (1.21%), acute respiratory failure (17.67%), septic shock (1.40%), with an average length of stay of 5.52 days and an average patient charge of $49.153.

Conclusions: In conclusion, our study demonstrated that mortality and morbidity is significantly higher in patients with concurrent cardiac co-morbidities, compared to AKI alone. There was an incremental increase in poorer outcomes with AF, CHF, and combined CHF with AF, respectively.

PUB020
Racial Disparities Following Severe AKI

Andrew Zhang, Svaty Pahyamr, Elizabeth Spranger, Jonathan Wang, Michael Heung. University of Michigan Michigan Medicine, Ann Arbor, MI.

Background: Acute kidney injury requiring dialysis (AKI-D) is a severe complication during acute hospitalizations. AKI survivors remain at risk for adverse outcomes and follow-up care has been shown to be suboptimal. The goal of this study was to identify any racial disparities in post-AKI follow-up care and outcomes, laying the groundwork for future interventions to reduce racial disparities.

Methods: Single-center retrospective analysis of consecutive patients with AKI-D in 2021 who were discharged alive and off dialysis. Patients discharged to hospice or with a history of ESRD or kidney transplant were excluded. Patient demographics, labs, documented education, follow-up recommendations, and 12m post-discharge outcomes were collected.

Results: A total of 78 patients were included: mean age 57y, 71% male, mean baseline eGFR 64. Mean duration of dialysis was 12d and length of hospital stay 41d. Most patients self-identified as White (55, 70%) or Black (18, 23%), so analyses were limited to comparing these groups. 54% of Black patients had documented recommendation for post-discharge nephrology follow-up compared to 31% of White patients (p = 0.002). Among these patients, 54% of Black patients completed follow-up compared to 94% of White patients. Overall, 39% of Black patients and 29% of White patients followed up with a nephrologist. 12-month mortality was over four times higher for African American patients than Caucasian patients (p = 0.016).

Conclusions: Compared to White patients, Black patients were more likely to have a nephrology follow-up visit recommended as well as completed. Despite this, Black patients still had lower survival compared to Caucasian patients. These findings suggest the need to explore additional, modifiable factors to reduce excess mortality experienced by this population.
PUB021

Evaluating the Consequences of Delirium on Patient Outcomes During Hospitalizations for AKI
Anish Surapaneni, Akil S. Kavcar, Meghana Vallabhaneni, Cameron T. Lawson, Chadi Y. Saad, Garden City Hospital, Garden City, MI; East Carolina University, Greenville, NC.

Background: Delirium frequently accompanies acute kidney injury (AKI) during hospitalizations and can lead to increased healthcare usage and poorer outcomes. This study delves into the specific impact of delirium on AKI hospitalizations.

Methods: We conducted a cohort study using the National Inpatient Sample (NIS) database from 2019-2020. The International Classification of Disease-10 codes were used to identify hospitalizations with AKI as the primary diagnosis and then stratified them based on whether they had delirium. The outcomes that were measured included in-patient mortality, length of stay, total hospital charges, and complications during the hospitalization. We used multivariate regression analysis to adjust for confounders.

Results: Of 9,121,794 AKI hospitalizations, delirium was present in 198,664. The delirium group had a higher average age (74 vs. 67, p < 0.001), with a majority being male (56%, p = 0.003) and Caucasian (66%, p < 0.001). After adjusting for patient demographics, comorbidities, and hospital characteristics, delirium-associated hospitalizations demonstrated significantly higher odds of mortality (aOR=1.19, p < 0.001, CI: 1.14 - 1.25), acute ischemic stroke (aOR=1.4, p < 0.001, CI: 1.34 - 1.46), acute respiratory failure (aOR=1.18, p < 0.001, CI: 1.09 - 1.28) and acute coronary syndrome (aOR=1.06, p = 0.003, CI: 1.02 - 1.1). Length of stay (coefficient=6.85, p < 0.001, CI: 6.62 - 7.12) and total hospital charges (coefficient=96,303, p < 0.001, CI: 86,976 - 105,629) were also increased in the delirium group.

Conclusions: AKI hospitalizations with concurrent delirium exhibited worse outcomes in terms of mortality, length of stay, total hospital charges, acute ischemic stroke, acute respiratory failure, and acute coronary syndrome. This highlights the critical need for early identification and management of delirium in AKI hospitalizations.

Figure 1. Impact of AKI on SARS-CoV-2 Pneumonia Hospitalizations

PUB022

The Influence of AKI on Patient Outcomes in SARS-CoV-2 Pneumonia Hospitalizations
Anish Surapaneni, Akil S. Kavcar, Meghana Vallabhaneni, Cameron T. Lawson, Chadi Y. Saad, Garden City Hospital, Garden City, MI; ECU Health, Greenville, NC.

Background: Acute Kidney Injury (AKI) is a recurrent complication in patients with SARS-CoV-2 pneumonia, often leading to adverse outcomes and inflated healthcare costs. The aim of this study was to elucidate the effects of AKI on mortality and other in-hospital outcomes in SARS-CoV-2 pneumonia hospitalizations.

Methods: We conducted this study using the National Inpatient Sample (NIS) database from 2020. SARS-CoV-2 pneumonia hospitalizations were identified, classified, and stratified by AKI presence using International Classification of Diseases-10 codes. Mortality served as the primary outcome, with in-hospital complications as secondary outcomes. Confounding factors were adjusted through multivariate regression analysis.

Results: Out of 1,038,815 hospitalizations with SARS-CoV-2 pneumonia, 265,925 involved AKI. Patients with AKI were typically older (median age 70 vs 62, p < 0.001), predominantly male (51%, p < 0.001), and Caucasian (53%, p < 0.001). Total hospital charges and average length of stay were significantly higher in the AKI group by 53,132 (P < 0.001) and 2.67 days (P < 0.001), respectively. Figure 1 illustrates the adjusted odds ratios for complications and mortality.

Conclusions: AKI presence in SARS-CoV-2 pneumonia hospitalizations is associated with increased mortality risk, in-hospital complications, length of stay, and total hospital charges. These findings underscore the necessity of prompt AKI detection and management in this patient population.

Figure 1. Impact of AKI on SARS-CoV-2 Pneumonia Hospitalizations

PUB023

Development and Validation of a Least Absolute Shrinkage and Selection Operator (LASSO) Prediction Model for Cisplatin-Induced Nephrotoxicity: A Case-Control Study in China
Fei Deng, Shijie Ma, Wei Zhou, Yuwei Kang, Wei Yang, Sichuan Academy of Medical Sciences and Sichuan People's Hospital, Chengdu, China; People's Hospital, Chengdu, China; The Affiliated Hospital of Southwest Medical University, Luzhou, China.

Background: Early identification of high-risk individuals with cisplatin-induced nephrotoxicity (CIN) is crucial for avoiding CIN and improving prognosis. In this study, we developed and validated a CIN prediction model based on general clinical data, laboratory indications, and genetic features of lung cancer patients before chemotherapy.

Methods: We retrospectively included 696 lung cancer patients using platinum chemotherapy regimens from June 2019 to June 2021 as the test set to construct a predictive model using Absolute shrinkage and selection operator (LASSO) regression, cross validation, and Kakei's information criterion (KIC) to select important variables. We prospectively selected 283 independent lung cancer patients from July 2021 to December 2022 as the validation set to evaluate the model's performance.

Results: The prediction model showed good discrimination and calibration, with AUCs of 0.9217 and 0.8288, sensitivity of 79.89% and 45.07%, specificity of 94.48% and 94.81%, in the test and validation sets respectively. Clinical decision curve analysis suggested that the model has value for clinical use when the risk threshold ranges between 0.1 and 0.9.

Conclusions: Predictive models based on laboratory and demographic variables can serve as a beneficial complementary tool for identifying high-risk populations with CIN.

PUB024

Association Between Serum Osmolality and AKI in Critically Ill Patients: Prospective Observational Study
Kharirwar Mahesh Prasad, Aditya S. Handargule, Alan F. Almeida, Rasika Sirsat, Ayan K. Dey, PD Hinduja National Hospital and Medical Research Centre, Mumbai, India.

Background: AKI is common in hospitalised patients and especially in critically ill patients. There has been growing research on AKI concerning biomarkers of renal injury to predict AKI. These markers are not readily available and cost constraints have limited their use in Indian settings. There have been limited studies that have used serum osmolality as a tool to determine the volume status and predict AKI. We wanted to study whether low or high serum osmolality was associated with new-onset AKI and mortality during the ICU stay.

Methods: The study was a prospective observational study conducted on patients admitted to the ICU of tertiary care hospital in India. From April 2022 to Jan 2023, 1300 patients were recruited. Patients having abnormal creatinine at baseline were excluded at the time of admission. Serum osmolality was calculated at the time of admission. Serum osmolality of 280-295 mmol/l was considered normal. Patients were followed up for the development of AKI and mortality during their stay in ICU. Univariate and Multivariate analysis was done for various cofactors and AKI and Mortality in ICU.

Results: Incidence of AKI was 26%. Abnormal serum osmolality showed a significant association with AKI. Abnormal serum osmolality had an OR 12.97 (CI 9.24-18.2). On sub-analysis of patients with abnormal serum osmolality, there was an incidence of AKI was 44.25% (OR:11.14 CI 7.9-15.70) in the group with low serum osmolality and 81.97% (OR: 63.8 CI 31.13-130.88) in the group with high osmolality as compared with 6.65% in patients with normal osmolality (p < 0.0001). AKI had a significant association with mortality in ICU with a prevalence of 78.6% (p < 0.0001). High or low serum osmolality was independently associated with an increased risk of mortality with low osmolality < 280 having an odds ratio of 3.1056 (CI 1.63-5.88) and high serum osmolality > 295 having an odds ratio of 13.11 (CI 5.83-29.47).

Conclusions: Both high and low serum osmolality at the time of admission were independently associated with an increased risk of development of AKI compared with normal serum osmolality. Low and high serum osmolality was associated with an increased risk of mortality during the stay in the ICU.

PUB025

Incidence, Etiology, and Outcome of AKI in the Coronary Care Unit: A Retrospective Study from a Single Center in Thailand
Solas Jaturapisanukul, Supassara Nimkulrat, Punawat Laungchaeyachok, Wanjak Pongsitsukaj, Vajira Renal-Rheumatology-Autoimmune Disease Research Group, Navamindradhiraj University, Bangkok, Thailand.

Background: AKI can lead to complications such as fluid overload, uremic symptoms, electrolyte disturbance, and metabolic acidosis. It is associated with increased morbidity, mortality, and incidence in critically ill patients. However, data on AKI in the CCU in the low to middle income countries are limited. This study aims to assess AKI incidence, etiology, risk factors, survival rate, and occurrence of ESKD and KRT in CCU patients in Thailand.

Methods: A retrospective cohort study was undertaken on patients admitted to the CCU at Vajira Hospital, a tertiary care facility located in Bangkok, Thailand, from January 2019 to September 2020. The analysis encompassed various CCI markers including baseline characteristics, comorbidities, CKD stage, medications, volume of contrast media, hypotension upon admission, use of inotropes, mechanical ventilator utilization, as well as EKG and CXR characteristics.
**PUB026**

**Atypical Hemolytic Uremic Syndrome Secondary to Transcatheter Aortic Valve Replacement (TAVR)**

**Solabomi O. Ojenyi, Dina R. Gonzalez Hernandez. MedStar Union Memorial Hospital, Baltimore, MD.**

**Introduction:** Atypical hemolytic uremic syndrome (aHUS) is a rare subtype of TMA mediated by complement dysregulation with an incidence of 0.23-0.43 cases per million population. It can manifest in a diverse range of conditions and presentations, but acute kidney injury is a common prominent feature because of the apparent propensity of the glomerular circulation to endothelial damage and occlusion. We present a case of aHUS developed after an elective TAVR.

**Case Description:** An 86-year-old man with PMH of aortic stenosis who presented for an elective TAVR which was successfully done. However, post-operative day 1, he developed new onset hematuria [dark brown to tea colored urine] and elevated BUN/Creatinine [Baseline serum creatinine of 0.9 to 1 mg/dL]. He continued to have hematuria and worsening renal function. Laboratory studies were remarkable for thrombocytopenia, low haptoglobin, and low fibrinogen. Normocytic anemia. Schistocytes on peripheral smear. Elevated D-dimer, CK, LDH, total bilirubin, direct bilirubin, AST. ADAMS 12 activity was greater than 5%. UA showed trace blood and 4-5 RBC. Complements, vasculitis panel, hepatitis panel, coagulation panel, cryoglobulinemia, and direct antiglobulin test were all negative. The patient remained asymptomatic throughout the hospital stay. He was managed symptomatically with antihypertensives for blood pressure control, intravenous hydration with normal saline, and platelet transfusion for thrombocytopenia. With the improvement of renal function, thrombocytopenia, and resolution hematuria. The patient was discharged home to follow-up with Nephrology and hematology.

**Discussion:** Atypical hemolytic uremic syndrome is most commonly due to a loss of function of a regulatory protein either by genetic mutation or autoantibody. The most common triggers include infections, autoimmune conditions, drugs, malignancies, or pregnancy. Treatment can be supportive, plasma exchange and anticomplement therapy. Although aHUS are associated with significant mortality and morbidity, including end-stage renal disease [ESRD], prompt diagnosis and initiation of supportive and specific management can transform outcome.

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**PUB027**

**External Validation of a Simple Prediction Model for AKI After Noncardiac Surgeries**

**Youlou Zhao, Jinwei Wang, Damin Xu, Jicheng Lv, Li Yang. Peking University First Hospital, Beijing, China.**

**Background:** The Simple Postoperative AKI Risk (SPARK) index is a practical prediction model for postoperative acute kidney injury (PO-AKI) in patients undergoing non-cardiac surgery. Its universality needs more verification.

**Methods:** This single-center retrospective cohort included adults who had surgery under general anesthesia from 2018 to 2020 at Peking University First Hospital (Figure 1). PO-AKI was defined according to KDIGO-Ser criteria. Critical AKI was defined as AKI stage 2 or greater or requiring dialysis. The area under the receiver operating characteristic curves (AUC) and the Hosmer-Lemeshow test were assessed.

**Results:** Among 8484 participants, 4710 (55.52%) were male, 183 (2.16%) developed PO-AKI stage 1, and 55 (0.65%) developed critical AKI. Compared with the SPARK cohort, participants in our cohort were older (median [IQR] age, 61 [49-69] years vs 56 [44-66] years) and had a higher prevalence of dipstick albuminuria (urine albumin +1) (37.61% vs 9.5%). The incidence of PO-AKI and critical AKI increased as the scores on the SPARK index increased (Figure 2a). The SPARK index showed fair discrimination and calibration power for both the PO-AKI and the critical AKI (Figure 2b,c,d,e).

**Conclusions:** SPARK index can be a reliable tool for predicting PO-AKI and identifying high-risk patients in Chinese population.

**Funding:** Government Support - Non-U.S.
superiority when compared to treatment with high doses of steroids and Rituximab. Early treatment in DAH is fundamental for survival. More studies need to be done to prove the benefits of PLEX in DAH and to support treatment without it, especially in facilities where plasmapheresis access is limited. This case supports the theory of early treatment with good outcomes despite no PLEX.

**PUBL029**

**AKI and Its Outcome in Filipinos 100 Days After Hematopoietic Stem Cell Transplantation: A Single-Center Retrospective Study**

**Leo Guillermo T. Villalobos. The Medical City, Pasig City, Philippines.**

**Background:** Hematopoietic stem cell transplantation (HSCT) is a complex life-saving procedure that has significantly made an impact in the management of various hematologic disorders. However, it exposes patients to several complications such as infusion reactions, medication side effects, infections, graft rejection, kidney injury, and cardiovascular events. Acute kidney injury (AKI), in particular, is a common complication linked to higher morbidity and mortality affecting the overall outcome of HSCT. Locally, data focusing on HSCT is very limited due to the modest increase in transplant procedures recording only 207 cases until the year 2018. Hence the study aimed to determine the incidence of AKI and its outcomes in Filipinos who underwent HSCT in a single tertiary hospital.

**Methods:** The study included Filipino patients aged 18 years and above, and excluded those who were maintained on dialysis during the time of transplantation. Data were collected retrospectively by chart review from July 2016 to June 2022, consisting of patients’ demographics and medical history, laboratory results, HSCT details and the reported complications.

**Results:** A total of 49 patients were included, with a mean age of 47 years, 42% were male, 36% were hypertensive, 12% were diabetic and 12% had chronic kidney disease. Baseline creatinine showed a mean of 0.83 ± 0.27 mg/dL and a mean eGFR of 95.7 ± 21.84 mL/min/1.73 m². AKI was documented in 14% of patients, with a median of 28 days (18 to 44) from the day of transplant, median creatinine of 1.22 mg/dL (1.07 to 1.29) and a median peak creatinine of 1.32 mg/dL (1.23 to 1.48). The study showed that AKI was statistically higher in allogeneic transplants (p <0.001) and in those who had an acute graft versus host disease (aGVHD) (p =0.001). Infections (p =0.012) and exposure to carbapenems (p =0.041) were also associated with increased risk of AKI after HSCT.

Clinical outcomes such as length of hospital stay (p =0.003), readmissions (p =0.031) and mortality (p =0.016) were all statistically significant in patients with AKI.

**Conclusions:** AKI is a common complication in Filipinos following HSCT and is associated with increased mortality, longer hospital stay and higher rate of readmissions. The presence of factors such as allogeneic HSCT, infections, and aGVHD predisposes patients to higher risk of AKI 100 days after HSCT.

**PUBL030**

**No, It’s Not Bilateral Hydronephrosis: It’s Pseudohydronephrosis!**

Macaulay A. Orujobi, Jessica Okrant. University of Vermont Larner College of Medicine, Burlington, VT.

**Introduction:** Bilateral hydronephrosis remains the sine qua non diagnostic criterion for clinically relevant obstructive uropathy. Therefore, renal sonograms are often utilized for this diagnostic step. Conversely, pseudohydronephrosis, renal imaging characteristics that mimic obstructive uropathy without obstructive pathology has only been very scantily reported.

**Case Description:** An 80-year-old male with coronary artery stent in 2005 was diagnosed in November 2022 with biopsy-proven red cell aplasia. He started cyclosporine 3mg/kg BID and prednisone 25mg/day. He was admitted two months later with HSV1-positive facial and oral lesions and started Valacyclovir 1000mg BID. He continued on Bactrim, lisinopril, and atorvastatin. Renal sonogram showed bilateral moderate hydronephrosis, serum creatinine, sodium, potassium, as well as bicarbonate. It has not been previously published that cryptosporidiosis can bring about kidney disease in Human Immunodeficiency Virus (HIV) infected adults. Here, we present a patient with acute kidney injury induced by Cryptosporidium.

**Case Description:** A 33-year-old man presented with general weakness and watery diarrhea for several days. He was diagnosed of AIDS three months ago but did not take any antiviral agents afterward. He had dry oral mucosa, dry skin turgor, mild diffuse abdominal tenderness, and symmetrically decreased proximal muscles strength. Laboratory exams
revealed serum sodium(Na) 128 mmol/L, potassium(K) 1.6 mmol/L, chloride(Cl) 107 mmol/L, bicarbonate 10 mmol/L, pCO2 24.1 mmHg, blood urea nitrogen 100 mg/dL, creatinine 4.2 mg/dL, serum pH 7.23, CD4 count 47/mm^3. Urea unaltered creatinine 106.7 mg/dL, Na 5 mmol/L, K 5.1 mmol/L, Cl 15 mmol/L. He was treated with saline infusion, intravenous potassium chloride, and oral potassium gluconate. Watery diarrhea persisted. His stool PCR was detected positive for Cryptosporidium parvum. Triumeq tablet was prescribed on the fourth day. Diarrhea subsided gradually, and no more potassium supplement was needed.

Discussion: Kidney injury and hypokalemia can be attributed to significant loss from diarrhea in our case. It reminds us that Cryptosporidium may be a crucial origin of kidney disease in HIV patients with poor compliance to anti-viral treatment. Hypokalemia, azotemia and metabolic acidosis implies intestinal loss of potassium and bicarbonate. Aggressive fluid supplement, close monitor and rapid replenish of electrolytes imbalance assist renal function full recovery. Antiretroviral therapy remains the most important treatment.

Level of kidney function, sodium, potassium and stool amount.

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PUB035
Severe Obstructive Uropathy due to Mycobacterium avium Complex in an HIV Patient
Irene Nunuń, Carrie L. Phillips, Chad A. Zarse. Indiana University School of Medicine, Indianapolis, IN.

Introduction: Tuberculosis is a well-known cause of genitourinary (GU) tract infection and obstructive uropathy, however, non-tuberculosis (non-TB) mycobacterium has not been commonly reported as a cause for kidney injury. Here, we present an HIV patient presenting with severe acute kidney injury (AKI) from bilateral obstructive uropathy that improved with treating Mycobacterium Avian Complex (MAC).

Case Description: 32yo with HIV on HAART therapy and CKD III (Cr 1.5 mg/dL, six months prior) presented with back pain and AKI. Prior cystoscopy for gross hematuria months before showed erythematous bladder mucosa due to chronic active cystitis. Admission Cr was 4.2. Urinalysis detected large esterase with WBC and RBC >100/hpf despite two negative urine cultures. CT imaging revealed severe bilateral hydronephrosis with diffuse urethropelial thickening. Cr worsened to 6.2, so bilateral nephrostomy tubules were placed. Chest CT showed small tree-in-bud nodularities in a bronchovascular distribution of the RLL consistent with granulomatous disease. Kidney biopsy specimen showed mild tubular atrophy and interstitial fibrosis with scant interstitial infiltrates of lymphocytes and no detectable acid-fast organisms. Renal cores sent for viral, bacterial, and fungal/AFB cultures were negative at 6 weeks. Of 4 serial early morning voided urine specimens sent for culture, only one grew MAC at week 8. She was treated with Azithromycin, Ethambutol, and Rifabutin. Nephrostomy tubules were removed without worsening obstruction. Six months post discharge Cr improved to 1.2.

Discussion: Ascending TB and non-TB GU infections are rare and difficult to diagnose. Susceptible patients presenting with kidney failure and sterile pyuria require thorough work up. Infections can cause obstructive uropathy via ascending tract inflammation and subsequent kidney injury. In our case, kidney biopsy and serial urine AFBs were necessary to identify a pathogen and rule out other HIV related renal pathology. Remarkably, only 1 of 4 serial urine AFBs were positive for non-TB MAC, detectable only at week 8, demonstrating that physicians should remain vigilant to rule out infectious pathogens with close coordination with pathology and microbiology colleagues. Prompt treatment allowed for improvement of the inflammatory obstructive process and renal function.

PUB036
Can Quality Indicators in Continuous Renal Replacement Therapy (CRRT) Be Achieved in Middle Income Countries? A Comparison Between a Public and Private Hospital
Juan P. Gomez Villarreal,1 Paola Borbolla,2 Ricardo A. Garza Treviño,1 Mara C. Oliver Gutierrez,1 Elisa M. Guerrero Gonzalez,1 Lilia M. Rizo Topete,1,2 1Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico; 2Hospital Christus Muguerza Alta Especialidad, Monterrey, Mexico.

Background: As mentioned in ADQI 22nd, there are few studies that have examined the Quality of Care (QoC) provided to patients with AKI that require RRT. As proposed by the experts, QoC is suboptimal, and substantial knowledge-to-care gaps need to be addressed so that we can provide an adequate care and safety therapy for those who require.

Methods: We performed a dual - center retrospective analysis chart review of adults who required CRRT during the last year in the Hospital Universitario de Monterrey Dr. Jose Eleuterio Gonzalez (public hospital) and the Hospital Christus Muguerza Alta Especialidad (private hospital) in Nuevo Leon, Mexico. The quality assessments were: Patients prescribed dose, fluid management, filter life and small solute clearance which was compared to the ADQI QoC. Data was extracted from clinical records, all the patients that received CRRT in that period of time given were included; patients with incomplete clinical records were excluded. The analysis was performed with R version 4.0.0.

Results: A total of 22 patients were included, 11 in each cohort, overall results were as follows: 68.2% (15) were men, in 95.5% (21) the patients the modality used was CVVHDF and 4.5% (1) received SCUF, the mean prescribed dose was 2450 ml/min, the ultrafiltrate was 75.5 ml/h, the initial serum creatinine was 3.07 mg/dL, and in the day 2 the mean serum creatine was 2.18 mg/dL the mean life of the filter was 64 hrs, in 59.1%. In the overall accomplishment of the goals, 77.3% accomplished the filter life >60 hrs, 68.2% accomplished goal for ultrafiltrate for at least 60% and, 90.0% accomplished the clearance goal. In comparison between hospitals, in the public hospital the filter life > than 60 hours was accomplished in 72.7% of the therapies, while in the private one in 81.8%, the ultrafiltrate goal was accomplished in 54.5% and 81.8% respectively, and the clearance goal in a 90.9% in both hospitals.

Conclusions: This comparison helped us to discern between what we can improve in both hospitals and what QoC and security measures we have accomplish already. It is important to mention that the quality indicators are not in order of importance as they should be and we must change this concept.

PUB037
Severe Hypercalcemia with Parathyroid Crisis Results in Acute Renal Failure Ending in Fatal Acute Respiratory Distress Syndrome (ARDS)
Towfigul A. Chowdhury. University of Rochester Medical Center, Rochester, NY.

Introduction: We present a remarkable case of severe hypercalcemia resulting in a catastrophic outcome.

Case Description: A 52-year-old male with past medical history of obesity, hyperlipidemia, and BPH presented with fatigue, abdominal pain, constipation, and confusion. Medications included atorvastatin and tamsulosin. At the presentation vital signs and exam were unremarkable. Initial workup revealed: serum Ca 34.2, ionized Ca 7.0, Ban-Cr 58/6.60, iPTH 1180, PTTH 2.2, and 1,25 Dihydroxy Vitamin D <0.5. Gastroenterology with citrate regional anticoagulation was initiated. Imaging suggested an underlying parathyroid adenoma and/or carcinoma. Parathyroidectomy was recommended by Endocrine Surgery. On hospital day 2, the patient developed acute hypoxic respiratory failure attributed to aspiration pneumonia. Chest X-ray revealed bilateral pleural and mediastinal infiltrates. Echocardiogram showed normal LV systolic function. She was diagnosed with ARDS and septic shock requiring multiple pressors. Due to persistent critical illness, the patient never became sufficiently stable to undergo parathyroidectomy, and the family opted for comfort measures.

Discussion: In addition to infectious causes, there are additional potential mechanisms for the development of ARDS. Severe hypercalcemia can lead to calciphylaxis affecting small and medium vessel walls, leading to intimal proliferation, fibrosis, and necrosis. It has been suggested that hypercalcemia may also produce sepsis-like syndrome and acute respiratory distress syndrome by increasing plasma nitrate/nitrite, free radicals, proinflammatory cytokines, and procalcitonin. There have only been 4 cases reported since 1974 linking hypercalcemia to ARDS. In some cases, autopsy findings revealed metastatic calcification of the alveolar surface and the destruction of the alveolar-capillary barrier in the setting of serum calcium levels > 20. Malignant hypercalcemia with multiorgan failure is known to increase mortality in the setting of CKD and CAD. Malignant hypercalcemia resulting in metastatic calcification is expected, but accompanying ARDS is seen less frequently. More study is needed to clarify a mechansitic link between malignant hypercalcemia and ARDS if one does indeed exist.

PUB038
Hypertriglyceridemia-Induced Acute Pancreatitis and Renal Failure Requiring Plasma Exchange and Continuous Veno-Venous Hemofiltration
Alina Cheema, Nataliya Dyatlova, Kiran Singh-Smith, Genaro E. Herrera Cano, Srimathi Manickarajun. UConn Health, Farmington, CT.

Introduction: Severe hypertriglyceridemia is defined at a level of greater than 1000 mg/dL and accounts for 1-4% of patients with acute pancreatitis. Rapid lowering of triglyceride levels is achieved with plasmapheresis (PLEX), and when there is concomitant renal failure and shock, continuous veno-venous hemofiltration (CVVH) is the treatment of choice. We describe a case of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) and renal failure where triglyceride levels were > 5000 mg/dL.

Case Description: A 48-year-old male with history of CKD stage 3a, 2T2M, HTN and hyperlipidemia presented to the hospital with an altered mental status. Vital signs: T 100.9 ºF, HR 111 beats/min, RR 29 breaths/min, and BP 73/56 mm/Hg. The patient was intubated and placed in acute respiratory distress requiring intubation. Complete blood count: WBC 11,300, hemoglobin 12.8 g/dL, hematocrit 37.3% and platelet count 69,000. Complete metabolic panel: creatinine 6.60 mg/dL, BUN 62 mg/dL, glucose 1,422 mg/dL, CO2 16 mEq/L, anion gap 30 mmol/L, serum osmolality 431 mOsm/kg, AST 267 U/L, ALT of 112 U/L, GGT 43 U/L, lipase >5,000 U/L, and triglycerides >5,376 mg/dL. He was admitted to the ICU for HTG-AP and hyperromosal hyperglycemic state requiring vasopressors and insulin infusion. Given his severe hypertriglyceridemia and acute kidney injury, PLEX was immediately initiated followed by CVVH. After two sessions of PLEX, triglyceride levels decreased to <500. Images were negative for necrotizing pancreatitis. However, the patient had worsening rhabdomyolysis with CK > 20,337 U/L, requiring CVVH for 7 days. Once hemodynamic and metabolic parameters improved, the patient was transitioned to intermittent dialysis. Serum creatinine had peaked at 7.4 mg/dL and was 3.9 mg/dL with GFR of 18 when he came off dialysis at the time of hospital discharge. On outpatient follow up, creatinine had further improved to 2.26 mg/dL.

Discussion: This is a complicated case of HTG-AP and renal failure that was highly responsive to both PLEX and CVVH, resulting in meaningful renal recovery. More than one observational study shows that the combination of PLEX and CVVH for the management of HTG-AP with organ dysfunction has better outcomes than CVVH alone. Our case supports the benefit of combination therapy in the setting of severe cases of HTG-AP.

PUB039
Combined Extracorporeal CO2 Removal and Renal Replacement Therapy in a Patient with Acute Respiratory Distress Syndrome (ARDS) Marcelo D. Silveira,1,2 Júlia B. Cabral,1,2 Fernanda O. Coelho,1,2 Paulo Benigno P. Batista,1,2 Rogerio Passos,1,2 1Hospital Alliance, Salvador, Brazil; 2Hospital Sao Rafael, Salvador, Brazil.

Introduction: In critically ill patients, concomitant lung and kidney damage can determine unfavorable outcomes. Combination renal extracorporeal support for patients with acute respiratory distress syndrome (ARDS) and hypercapnia can benefit from extracorporeal

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
CO2 removal (ECCO2R). ECCO2R in ARDS allows lung-protective ventilation (LPV) with low tidal volumes. We describe the case of a patient with severe hypoperfusion, threatening acidemia and acute kidney injury treated with ECCO2R membrane combined with continuous renal replacement therapy (CRRT).

**Case Description:** A 69-year-old man with a history of systemic arterial hypertension, diabetes and rheumatoid arthritis was admitted to the intensive care unit with severe pneumonia, septic shock and ARDS, also evolving with severe AKI. Chest tomography showing inflammatory infiltrate involving more than 80% of the parenchyma. Initial treatment involved ventilatory and circulatory support. Even after adjustments and ventilatory strategies, blood gas data showed persistent hypercapnia. PaCO2 reached 92 mmHg with resulting respiratory acidosis (arterial pH 7.30). He evolved with oliguria and severe hyperkalemia (K+ 5.7 mEq/L) and was treated with an ECCO2R membrane inserted in series after a hemofilter in a CRRT platform. Nitric oxide and reverse prone were additional strategies used to rescue refractory hypoxemia. After 18 hours of therapy there was an improvement in hypercapnia with PaCO2 37mmHg and pH 7.41. After 72 hours maintaining metabolic balance, the use of ECCO2R was discontinued. The patient was extubated on the sixth day. He was discharged after 27 days of hospitalization without the need for supplemental oxygen and with normal renal function (SCR: 0.7mg/dl).

**Discussion:** We describe a case of success with the use of ECCO2R associated with CRRT in a critically ill patient. This combined therapy ensured an efficient metabolic balance and favored a substantial clearance of carbon dioxide, allowing LPV and greater lung protection, minimizing future.

**PUB040**

**Continuous Urine Output Monitoring to Guide De-escalation of Continuous Renal Replacement Therapy**

Yacov Shacham, 1 Aliza D. Goldman, 1-2 Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; 1RenalSense, Jerusalem, Israel.

**Introduction:** Of heart failure patients with acute kidney injury (AKI), 20% progress to dialysis (AKI-D). We present a case of acute decompensated heart failure (ADHF) with CRRT de-escalation until successful withdrawal leading to gradual withdrawal of CRRT 60 hours after initiation, and UO increase and pulmonary congestion. Initial fluid removal was 120 ml/h. After 36 hours of CRRT, a gradual persistent increase of 0.1-0.2 ml/kg/h persisting over 24 hours. SCr increased to 2.8 mg/dl within 12 hours of dialysis initiation. CRRT was initiated due to AKI, fluid accumulation, and pulmonary congestion. Initial fluid removal was 120 ml/h. After 36 hours of CRRT, a gradual persistent increase of 0.2-0.4 ml/kg/h in UO was recorded. Consequently, CRRT fluid removal was reduced to 100 ml/h (Fig 1). Successful withdrawal of CRRT was followed by a polyuric stage over 36 hours gradually decreasing to 1.13 ml/kg/h until Foley removal four days later. Concurrently, SCr decreased to 1.82 mg/dl.

**Discussion:** Heart failure patients with AKI-D have increased risk of dialysis dependence and higher mortality. Optimal timing for CRRT initiation has been more widely studied than that for withdrawal. Predictive factors for successful CRRT cessation include UO, SCr, and time on CRRT. In this study, changes in UO guided CRRT fluid removal leading to gradual withdrawal of CRRT 60 hours after initiation, and UO increase to 120 ml/h. This case study suggests using continuous electronic UO monitoring to guide de-escalation from CRRT.

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

**Underline represents presenting author.**
Case Description: A 73-year-old female with a history of breast cancer on evernustatin, GERD, HTN, and atrial fibrillation was referred to an emergency department with a pruritic, erythematous rash spreading from the chest to the extremities and face over two days. She had a vertebral fusion complicated with MRSA-vertebral osteomyelitis, treated with prolonged IV vancomycin. Physical examination was unremarkable except for diffuse erythema and pruritis covering the trunk, upper arms, and peripheral eosinophilia, elevated liver enzymes, and acute kidney injury with an initial creatinine 0.9 mg/dL. Her clinical condition deteriorated after high-dose prednisone, with new onset hypoxic respiratory failure, pleural effusions, and worsening kidney function (creatinine 1.9 mg/dL). A kidney biopsy was confirmed DB with chronic tubulointerstitial nephritis, with a kidney biopsy consistent with severe acute interstitial nephritis. Given the steroid-resistant AIN and pulmonary involvement, cyclosporine, and mycophenolate mofetil were initiated. Her overall clinical condition gradually improved with symptoms. Serum creatinine down to 1.4 mg/dL.

Discussion: This case emphasizes the importance of promptly diagnosing AIN through renal biopsy in patients with worsening acute kidney injury despite discontinuation of the offending agent. Agressive follow-up and consideration of additional immunosuppressive measures may be necessary if steroids fail. Although the specific impact of each medication is difficult to discern, mycophenolate has shown promise as a therapeutic option for steroid-resistant AIN, warranting further investigation.

PUB046
A Rare Case of ANCA-Mediated Acute Interstitial Nephritis Without Glomerulonephritis
Luis B. Caraballo, Hima B. Doppalapudi, Kirti Basil, Vijay K. Vanguri.
University of Massachusetts Chan Medical School, Worcester, MA.

Introduction: Acute interstitial nephritis (AIN) is characterized by an inflammatory infiltrate in the kidney interstitium which is most commonly caused by drugs, with less common contributors being infections and systemic disorders, and generally leading to acute kidney injury. Here we present a case of an 80-year-old female patient with AIN thought to be caused by non-myeloperoxidase (MPO), non-proteinase-3 (PR-3) antineutrophil cytoplasmic antibody (ANCA) without glomerular involvement.

Case Description: An 80-year-old female was referred to the renal clinic with acute kidney injury and a one-month history of worsening fatigue, nausea, and poor appetite. Her medical history was notable for resistant hypertension, maintained in seven anti-hypertensives for over 40 years. Her creatinine was 4.2 mg/dL, with a baseline creatinine <1.0 mg/dL. The patient was admitted to the hospital about six months prior to presentation. Blood pressure was 132/68 mm Hg. Urine sediment showed several WBCs and WBC casts with no evidence of infection. She had minimal proteinuria and serologic work-up revealed positive c-ANCA with titers >1:640, but negative PR3 and MPO antibodies. A renal biopsy showed markedly active tubulointerstitial nephritis, predominantly composed of lymphocytes and plasma cells and minimal eosinophilia, along with mild granular immune complex deposition (1+ IgG, Aa, and C1q) in some tubular basement membranes and interstitium suggestive of an autoimmune etiology. All 33 glomeruli were unremarkable, with no crescents, immune complexes, or inflammation. She was treated with prednisone 1 mg/kg with a slow taper, and her creatinine continued to improve drastically along with a concurrent decline in c-ANCA titer.

Discussion: ANCA-associated vasculitides (AAV) are a group of disorders that typically cause pauci-immune glomerulonephritis, including granulomatosis with polymygitis, microscopic polyangitis, renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis. ANCA-associated AIN especially without glomerular involvement is rarely seen. Moreover, non-MPO and non-PR3 ANCA vasculitides are infrequent and could be pathologic in nature. Our case is suggestive of non-PR3 and non-MPO ANCA-associated AIN without glomerular involvement, which improved drastically with corticosteroid therapy. In cases of AIN without obvious causative drugs, serological work-up including ANCA screen should be considered.

PUB047
AKI and Spontaneous Rupture of the Urinary Collecting System

Introduction: Obstructive urethritis is an uncommon cause of AKI and usually associated with bladder neck dysfunction. Rupture of the renal calyx with bilateral(B-L) hydronephrosis in the absence of bladder neck dysfunction is even rarer. We are reporting a case of bilateral hydronephrosis causing rupture of left collecting system.

Case Description: An 81-year-old man was admitted with altered mental status, hyperkalemia and metabolic acidosis due to AKI with creatinine of 16mg/dL (BL 1mg/dL). Several weeks prior to admission while traveling abroad, he had developed left flank pain, painful urination and hematuria. CT scan abdomen revealed B-L hydronephrosis and a collection around the left kidney consistent with calyceal rupture of the renal pelvis. Postmortem was observed but the bladder was not distended. Despite the insertion of a Foley catheter, the patient remained anuric and required hemodialysis for altered mental status and severe metabolic acidosis. He then had a percutaneous nephrostomy tube placed in the left kidney with drainage of approximately 700 mL over 5 days of hospitalization. Cystoscopy revealed a necrotic partially calcified mass which engulfed the right lateral wall of the bladder, extended to the bladder neck, and was accompanied by a few small submucosal lesions on the posterior wall with distension of the trigone of the bladder. The bladder mass was revealed to be a papillary urothelial carcinoma. He was sent home with bilateral ureteral stents and a percutaneous drain on the left. The patient’s SCr down trended to a nadir of 0.9mg/dL prior to discharge.

Discussion: Spontaneous rupture of the collecting system is rare and is typically unilateral with the most plausible mechanism being, gradual increase of intraluminal pressures up to 75mmHg. About half of the cases of spontaneous urinary extravasation are caused by ureteral stents, while occurrences related to tumors are rare. Interestingly, when extravasation is associated with a tumor, it tends to occur more frequently on the left side rather than the right side. The exact reason for this asymmetry is not known, but it is hypothesized that the direct extension of tumor cells may be easier on the left side, creating weak points along the path of extension, leading to leakage and rupture.
A Case of Terbinafine-Associated Rhabdomyolysis and Drug-Induced Liver Injury (DILI) That Progressed to Acute Renal and Liver Failure

Gabriela S. Mosquera Cordero, Novant Health New Hanover Regional Medical Center, Wilmington, NC.

**Introduction:** Terbinafine is commonly prescribed for the treatment of onychomycosis. It has been associated with acute hepatic injury and rarely with rhabdomyolysis, acute renal failure (ARF) and liver failure (LF). Here we present a case of a patient presenting with general muscle weakness with elevated CK, abnormal renal and hepatic function. Notably, the only new medication reported was terbinafine 3 weeks prior to hospital admission.

**Case Description:** A 72-year-old female presented to the hospital for worsening of general muscle weakness. Patient completed treatment for onychomycosis with terbinafine 3 weeks prior. The patient denied any other new medications for the past few years. Lower extremity weakness was initially attributed to worsening of spinal stenosis. Lumbar MRIs were performed, and it showed progression of spinal stenosis but no cord compression. Neurosurgery consult advised against surgical intervention. Chemistry was relevant for CK > 9000; Cr 5.78; BUN 117; with a mixed hepatocellular and cholestatic pattern. Autoimmune and infectious etiologies were investigated but all were negative. USG and MRI showed CBD dilation correlated with age and post cholecystectomy status. Patient’s CK continued upward with minimal urine output. Patient rapidly decompensated, requiring transfer to ICU, and dialysis. Unfortunately, the patient passed away hours later.

**Discussion:** Terbinafine is a common antifungal drug used for onychomycosis that may cause hepatic or renal toxicity. The side effects are usually self-limiting, but can rarely progress to rhabdomyolysis, ARF, DILI and LF. Few cases of rhabdomyolysis and ARF associated with Terbinafine have been reported, and even less cases were associated with DILI leading to LF. There are limitations with the definitive diagnosis due the patient passed away before performing liver or renal biopsy. Treatment primarily consists of stopping the causative agent and NAC for DILI, but some cases with liver failure will require liver transplantation, and dialysis for worsening of renal failure. There is a lack of guidelines and cases associating Terbinafine with rhabdomyolysis, ARF and LF. Nevertheless, physicians need to be aware and carefully monitor patients when prescribing this medication, especially with prior history of chronic renal or liver conditions or any chemistry abnormalities related to its use.

**Conclusions:** 1. In the mouse model of hypoxia, the expression of Prdx1 in serum and kidney is increased; 2. Circulating Prdx1 aggravates hypoxia-induced kidney injury by activating MAPK/NF-κB mediated inflammation.

PUB051 Lymphadenopathy with AKI

Ramandeep Kaur, Brunavan V. Raguhanathan, Jason R. Pettus, Brian D. Remillard, Dartmouth Hitchcock Medical Center, Lebanon, NH.

**Introduction:** Immunoglobulin G4-related disease (IgG4-RD) can present with different manifestations simultaneously. We present a case of bilateral inguinal lymphadenopathy with AKI found to have IgG4-RD.

**Case Description:** A 77-year-old female with history of bladder cancer s/p resection and urostomy, DM-2, COPD, HTN and HLD presented with 2 weeks history of right sided flank pain after being treated for urinary tract infection. She endorsed poor oral intake, shortness of breath and persistent abdominal pain. On physical examination, bilateral inguinal lymphadenopathy was found. In the laboratory evaluation, serum creatinine was 2.57 mg/dL (reference range 0.8-1.5 mg/dL). Two months prior, it was 0.83 mg/dL. Immunological data revealed elevated IgG level at 3,994 mg/dL (reference range 700-1000 mg/dL). IgG4 level was 773.2 mg/dL (reference range 3.9-86.4 mg/dL). C3 and C4 complements were low at 32 mg/dL (reference range 90-180 mg/dL) and < 2 mg/dL (reference range 10-40 mg/dL). Computed Tomography showed mild pelvocalyceal dilatation and hydronephrosis. The biopsy of inguinal lymph node showed plasma cells with storiform pattern. A renal biopsy showed marked plasma cell rich interstitial chronic inflammation with a high fraction of IgG4-restricted plasma cells, proliferative fibrosis, and both
tubulointerstitial and glomerular immune complex deposits, consistent with IgG4-related kidney disease. The patient was treated with pulse steroids followed by steroid taper and IV Rituximab. Two months later, her IgG4 level has decreased. The creatinine has trended down to 1.17 mg/dL.

**Discussion:** We present a case of IgG4-RD diagnosed with renal biopsy with response to steroids and Rituximab.

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**Light Microscopy**

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<th>Light Microscopy</th>
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**PUB053**

**Giant Urinary Bladder Causing Massive Hydronephrosis**

Esosa U. Ukponmwan, Michigan State University, East Lansing, MI.

**Introduction:** Obstructive uropathy is caused by a structural or functional impairment in urinary flow. It is a potentially reversible cause of acute and chronic kidney disease, accounting for 10 percent of acute and chronic kidney disease.

**Case Description:** A 58-year-old man presented with fatigue, shortness of breath and dyspnea on exertion for eight months, worse over the previous week. He also complained of urinary frequency, urgency, hesitancy, feeling of incomplete urinary bladder emptying, terminal dribbling, abdominal pain and swelling. He was pale, dyspneic, diaphoretic and in respiratory distress. Rales present bilaterally, heart sounds were normal. Abdomen was tender and distended. No pedal edema. He had an elevated blood urea nitrogen of 120mg/dl and creatinine of 9.24mg/dl, high anion gap metabolic acidosis, hyperkalemia and hyperphosphatemia. CT-scan chest, abdomen and pelvis revealed pulmonary edema, severe bilateral hydronephrosis and hydrourereter down to the urinary bladder. Marked distention of the urinary bladder causing bowel obstruction. Cortical atrophy of the kidneys suggesting chronic obstruction. Foley catheter was placed with 3500mls of urine drained. Hemodialysis was started due to symptoms of pulmonary edema and uremia. Overall clinical status improved. He was placed on long-term foley catheter and tamsulosin started, with nephrology and urology follow up.

**Discussion:** Early recognition of obstructive uropathy is important in management of acute and chronic kidney disease. There is an inverse relationship between duration of obstruction and recovery.

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**PUB052**

**Atypical Hemolytic Uremic Syndrome Induced by Inflammatory Bowel Disease**

Fausto R. Cabezas, Charlie Spell, Sandeep R. Sasidharan, Sonalika Agarwal, Mary C. Mallappallil, Isha Puri. SUNY Downstate Health Sciences University, New York City, NY.

**Introduction:** Atypical hemolytic uremic syndrome (aHUS) is a congenital or acquired dysregulation of the complement alternative pathway that leads to thrombotic microangiopathy (TMA) and acute kidney injury (AKI). The prevalence of aHUS ranges from 2 to 10 cases per million. There have been few reports of aHUS associated with Inflammatory bowel disease (IBD). We present a case of a young man with IBD and biopsy proven TMA associated AKI.

**Case Description:** A 26-year-old male presented with 4 weeks of hematochezia. Laboratory data showed severe hemolytic anemia (hemoglobin 2.9 gr/dL, schistocytes on smear; LDH 1,415 U/L, haptoglobin <10 mg/dL, Coombs test), leukocytosis (52.87 k/uL), thrombocytopenia (107 k/uL); severe AKI (SCR 8.32 mg/dL, from previous normal eGFR), urinalysis showed 10 WBCs/HPF, RBC 9/HPF, protein 100 mg/dL. Kidney ultrasound was unrevealing. ADAMTS-13 activity was 430 with decreased complement levels (C3 40, C4 25, CH50 17). Negative Shiga toxin. Sigmoidoscopy showed diffuse mucosa inflammation throughout rectum, descending and transverse colon. Biopsies demonstrated chronic colitis. He received multiple transfusions and empiric antibiotics with no improvement. Intravenous methylprednisolone (0.5 mg/kg/day) was started. AKI started to improve before complement blockade therapy with Eculizumab. Kidney biopsy showed acute TMA with immune mediated C3 dominant diffuse proliferative glomerulonephritis (figures). Genetic panel testing for aHUS associated mutations showed no pathological variants.

**Discussion:** This patient presented with one month of gastrointestinal symptoms preceding the AKI and hemolytic anemia. Overlap of symptoms and laboratory markers pose a challenge when identifying aHUS. In contrast to our case, previous reports have shown remission of AKI and chronic relapsing IBD only after Eculizumab is started. This is a rare case of IBD induced aHUS which responded to a course of steroids and Eculizumab.
ESAs.

survival and also might be a way to avoid a potential risk on mortality of long-acting

Kaplan-Meier survival curve of the

were not significantly different between the EPO period and ±

than that of the HD patients in EPO period (66.6 ±

±

Kazumasa Shimamatsu, Yoshihiro Mimura. Shimamatsu Naika Iin, Chikushino, Japan.

Background: Long-acting erythropoiesis-stimulating agent (ESA), darbepoetin (DA) has a longer terminal half-life and a reduced dose frequency than short-acting epoetin (EPO). However, DA might be associated with increased mortality. To lower mortality risk concerned, we reported a novel half-and-half (DA/EPO) combination therapy consisting of a stable dose of DA occasionally assisted by EPO having resulted in reduced hemoglobin fluctuation, reduced ESA doses, and lower costs. Long-term safety/ outcome of the half-and-half therapy was evaluated.

Methods: All the 280 patients on maintenance hemodialysis (HD) during 31 years period were subject to this study. Out of 280 patients 189 belonged to EPO monotherapy period (EPO period), and 91 belonged DA/EPO combination therapy period (half-and-half period). For retrospective analysis, we selected 120 patients who had been transferred to our clinic within one year after the initiation of HD in EPO period and 64 patients in half-and-half period. The Kaplan-Meier survival curve of the half-and-half period was compared with that of the EPO period.

Results: The age of the HD patients in half-and-half period was significantly older than that of the HD patients in EPO period (66.6±11.8 vs. 60.1±14.9 yrs, p < 0.005). The gender, HD vintages at the time of transference to the clinic and original renal diseases were not significantly different between the EPO period and the half-and-half period. The Kaplan-Meier survival curve of the half-and-half period was significantly superior to that of the EPO period despite the older ages (Figure).

Conclusions: A novel half-and-half therapy may be safely feasible with rather better survival and also might be a way to avoid a potential risk on mortality of long-acting ESAs.

PUB805

Therapeutic Effect of Originator Erythropoiesis Stimulating Agents (ESAs) vs. Biosimilar ESAs on Hemoglobin Level in Hemodialysis Patients: A Single-Center Study

Ahmed Emara,1,2 Osama I. Azab,1,2 Goodluck R. Maro,2 Ahmed Y. Ali,1,2 
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Background: The use of ESAs and IV iron is the main line of treatment of renal anemia. There are few studies done to compare efficacy & cost benefit of originator vs. biosimilar ESAs. The aim of this study was to compare the therapeutic effect of originator ESA (Eprex®) vs biosimilar (Epoetin®) on maintaining HB to the target level among ESRD patients on Hemodialysis (HD).

Methods: Prospective cohort study involved 81 prevalent HD patients in Maadi Military Hospital, Cairo. patients were randomised into two cohorts, Originator ESA (Eprex®) (27 subjects) and biosimilar Epoetin® (54 subjects). Baseline data including HB, ESAs (dose & cost) and dialysis specifications and adequacy parameters were recorded at the time of enrollment, then monthly for 6 months for all patients. Iron studies were done at baseline & every 3 months.

Results: A total of 81 patients completed the study. both groups were age & gender matched. Eprex group (27 subjects) had more males (18/66.7%) and Epoetin group (54 subjects) had more female (29/37.5%) (p = 0.003). Baseline HB was lower in Eprex vs. Epotin group (9.9±1.3 g/dL vs. 10.8±1.2g/dL respectively) (p = 0.006). The absolute HB change relative to baseline for six months of follow up in Eprex vs. Epotin was ranging between 0.1 – 0.5g/dL vs. 0.4 – 0.1 g/dL respectively (p = 0.007). The median dose used in Eprex vs. Epotin were comparable, ranged between, 6-10 vs. 4-8 ampules per month, respectively (p >0.05). In both groups, no significant difference in the % of patients attained target HB in Eprex vs. Epotin (66.7% vs. 61.1% respectively” “p >0.05”). The total cost in the 6 months study period was significantly lower in Epoetin vs Eprex group, it ranged between 472-630 LE vs 2131-2648 LE respectively (p = 0.001).

Conclusions: Biosimilar epoetin® showed therapeutic equivalence with lower cost compared to originator drug (Eprex®) in maintaining HB to target level in ESRD patients on HD.

PUB806

Exploring the Potential of ChatGPT as an Artificial Intelligence (AI)-Powered Resource for Patient Education on a Renal Diet

Ahmad A. Qarajeh,1 Supawit Tangpanithande,2 Pajaree Krisanapana,1 Oscar A. Garcia Valencia,2 Maria Lourdes Gonzalez Suarez,2 Chariat Thongprayoon,2 Wissut Cheungpasitporn,2 1 The University of Jordan, Amman, Jordan; 2 Mayo Clinic, Minnesota, Rochester, MN; 3 Thammasat University Hospital, Klong Luang, Thailand.

Background: Patients with chronic kidney disease (CKD) require a customized renal diet to avoid complications such as hyperkalemia and hyperphosphatemia. However, managing the nutrition of CKD patients requires careful time-consuming analysis of food composition. ChatGPT, an AI language model, has the potential to serve as a patient education resource.

Methods: To assess ChatGPT’s accuracy in determining the potassium and phosphate content of food items, we presented 240 food items to ChatGPT in two separate sessions with a two-week interval between them. We selected the food items based on their potassium (149 items) and phosphate (91 items) content using the Mayo Clinic’s renal diet book for patients with CKD. We asked ChatGPT to categorize each food item as having high or low potassium and high phosphate content. We compared the results with those from the Mayo Clinic Renal Diet book and computed the overall concordance to determine ChatGPT’s accuracy and reliability.

Results: Our results showed that ChatGPT demonstrated moderate to high accuracy in identifying food items with high or low potassium and phosphate content in a renal diet. ChatGPT correctly classified 98 out of 149 (66%) food items as having high or low potassium content. Among the 81 food items with high potassium content, ChatGPT correctly identified 72 (89%), while it classified 26/68 (38%) of low potassium foods correctly. ChatGPT correctly classified 77 (85%) out of the 91 food items with high phosphate content. The concordance between the two ChatGPT sessions was 121/149.

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Underline represents presenting author.
(81%) for potassium-containing food items, with 54/68 (79%) and 67/81 (83%) for low and high potassium food items, respectively. The concordance between the two ChatGPT sessions was 82/91 (90%) for phosphate-containing food items.

**Conclusions:** ChatGPT exhibited moderate to high accuracy in identifying food items with high or low potassium and phosphate content in a renal diet. ChatGPT’s precision was higher for identifying food items with high potassium or phosphate content than those with low content. The overall concordance between two ChatGPT sessions was high, indicating ChatGPT’s consistency in producing results. Further research is required to optimize its performance and maximize its potential as a clinical tool.

**PUB057**

**Exploring the Use of Artificial Intelligence (AI) and Machine Learning in Nephrology Research: A Bibliometric Analysis**

Pajarree Krisanapan,1,2 Yuh-Shan Ho,3 Tibor Fulop,4,5 Wisit Cheungpasitporn.1

1 Mayo Clinic Minnesotia, Rochester, MN; 2Thammasat University Hospital, Khlong Nueng, Thailand; 3Asia University, Taichung, Taiwan; 4Medical Services, Ralph H. Johnson VA Medical Center, Charleston, SC; 5Medical University of South Carolina, Charleston, SC.

**Background:** Artificial intelligence (AI) and machine learning (ML) have increasingly been integrated into the field of nephrology in recent years. This study aimed to identify the most productive authors, institutions, and countries in this field, examine publication trends and patterns, and investigate the impact of collaboration on citations.

**Methods:** The study utilized the Science Citation Index Expanded (SCI-EXPANDED) of Clarivate Analytics Web of Science Core Collection to search for AI and machine learning publications related to nephrology from 1992 to 2021. The authors used quotation marks and Boolean operator “or” to search for keywords in the title, abstract, author keywords, and Keywords Plus. The ‘front page’ filter was applied to exclude non-research articles. A total of 5,425 documents were identified and analyzed.

**Results:** The results showed that articles represent 75% of the analyzed documents, with an average authorship ratio of 7.4 and an average number of citations per publication in 2021 of 18. English articles had a higher citation rate than non-English articles. The USA was preeminent in all publication indicators, followed by China. The USA was the most productive country, with 2,347 articles published, followed by China (1,055) and the UK (385).

**Conclusions:** This study provides a comprehensive analysis of the use of AI and ML in nephrology research publications from 1992 to 2021. Collaborative research was found to enhance citations in the field.

**PUB058**

Is Shared Decision-Making for Hemodialysis Adequate? The Rationale and Design of a Clinical Trial to Evaluate Video-Assisted Electronic Consent for Hemodialysis

Pedro H. Guo,1,2 Rebecca Sauderson,3 Marina Wainstein,1,4 Kelly C. Li,4 Matthew J. Damasiewicz,6,7 Vera Y. Miao,6 Kirsten S. Hepburn,3 Martin Wolley,6,7 Ann Bower,4 Helen G. Healy,1,4,5 The University of Queensland Faculty of Medicine, Brisbane, QLD, Australia; 2John Hunter Hospital, New Lambton Heights, NSW, Australia; 3The University of Sydney Faculty of Medicine and Health, Sydney, NSW, Australia; 4West Moreton Hospital and Health Service, Ipswich, QLD, Australia; 5Saint George Hospital, Kogarah, NSW, Australia; 6Monash Medical Centre Clayton, Clayton, VIC, Australia; 7Hornsby and Ku-ring-gai Hospital, Hornsby, NSW, Australia; 8Royal Brisbane and Women’s Hospital, Herston, QLD, Australia; 9Griffith University, Nathan, Qld, Australia.

**Background:** Current methods of informed consent have repeatedly been demonstrated to be inconsistent and inadequate. We hypothesise that quality informed consent improves decision-making and is key to preparing patients for hemodialysis (HD). Study aims: To demonstrate that video-assisted electronic consent (eConsent) (intervention) compared to standard paper-based consent (control) improves patient experience, with better comprehension, reduced anxiety, increased satisfaction, less decisional regret, and improved adherence.

**Methods:** This is a multi-center, open label, randomized controlled trial (RCT). Participants: Incident and prevalent adult HD patients randomised 1:1 to either the intervention or the control groups. Intervention group: Participants will be coached to an online platform that delivers a simple-to-understand video animation followed by a knowledge questionnaire prior to signing an eConsent form to receive HD. The animation, co-designed with consumers, will consist of human figures role-playing a patient-doctor interaction. Control group: Participants will be consented by a clinician and sign a paper form. All groups will have any questions answered by a clinician prior to consent. Figure 1 depicts the RCT design and outcomes of interest.

**Results:** This RCT outcomes directly address patient experiences in the decision-making processes for HD. It will also standardize the content of complex HD health information, which may impact in decision-making and patient satisfaction.

**Conclusions:** If video-assisted eConsent is proven superior to the existing consent process, this RCT will serve as a proof-of-concept for changes in nephrology.

**Funding:** Government Support - Non-U.S.
Impact of Behavioral Health on Kidney Disease Progression and Cost: Retrospective Analysis
Saravanan Balamuthusamy,1,2 Texas Christian University, University of North Texas Health Science Center, Fort Worth, TX; 2PGH Health, Fort Worth, TX.

Background: Kidney disease can be impacted by other chronic conditions like cardiovascular disease and diabetes. However, the impact of mental health on the progression of kidney disease and its impact on cost is unclear.

Methods: A retrospective analysis of 538,099 patients from a health analytics database was utilized for the analysis. Patients were stratified with and without behavioral health diagnosis. Patients with BHD were identified using relevant ICD-10, CPT codes and BH drug utilization for at least 3 months. Patients at risk for progression to high and ultra-high risk kidney disease were assessed using three different ML models (XG Boost, SVM and Random Forest). Cost prediction across patients with and without behavioral health for risk or kidney disease progression was assessed from claims records.

Results: The mean age of the analyzed cohort is 55+/−22, and 59% were males. The prevalence of kidney disease was 16.4% in patients with BHD. The risk of progression to high and ultra-high risk kidney disease was 1.05 (1.03-1.06, p < 0.001) in patients with BH diagnosis. The average cost per member amongst patients with BHD at risk for progression to high-risk kidney disease is $54,989.97 vs $87,797.

Conclusions: There is a significant impact of BHD on kidney disease progression and its cost consequences. Risk stratification based on BHD is necessary while predicting disease to understand the true impact of disease progression so that appropriate case management and behavioral therapy strategies can be utilized to bend the cost and disease curve accordingly.

Impact of Behavioral Health on Kidney Disease progression and cost: Retrospective Analysis

Table 1. Demographics

<table>
<thead>
<tr>
<th></th>
<th>BHD</th>
<th>No BHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>14754</td>
<td>75498</td>
</tr>
<tr>
<td>Men</td>
<td>8693</td>
<td>40,423</td>
</tr>
<tr>
<td>Women</td>
<td>6041</td>
<td>30,075</td>
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<tr>
<td>AA</td>
<td>2052</td>
<td>13964</td>
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<tr>
<td>Hispanic</td>
<td>3241</td>
<td>15434</td>
</tr>
<tr>
<td>Caucasian</td>
<td>8104</td>
<td>43363</td>
</tr>
<tr>
<td>CKD 3 and less</td>
<td>2357</td>
<td>9554</td>
</tr>
<tr>
<td>CKD4,5</td>
<td>144</td>
<td>492</td>
</tr>
</tbody>
</table>

Table 2: Association of Artificial Intelligence (AI) on Hospital Utilization in kidney transplant patients

<table>
<thead>
<tr>
<th></th>
<th>AI-DSS</th>
<th>No AI-DSS</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital Stay</td>
<td>2.5</td>
<td>3.1</td>
<td>0.001</td>
</tr>
<tr>
<td>UTI</td>
<td>4%</td>
<td>8%</td>
<td>0.003</td>
</tr>
<tr>
<td>Dialysis</td>
<td>15%</td>
<td>20%</td>
<td>0.005</td>
</tr>
<tr>
<td>Rejection</td>
<td>2%</td>
<td>4%</td>
<td>0.015</td>
</tr>
</tbody>
</table>

Bone and Vascular Changes in CKD-MBD over 2 to 3 Years Analyzed by Artificial Intelligence
Hartmut H. Malluche,1 Amr E. Moharred,1 Florence Lima,1 Jin Chen,1 Qi Qiao,1 David Pienkowski,1 University of Kentucky College of Medicine, Lexington, KY; 2University of Kentucky, Lexington, KY.

Background: Bone abnormalities and vascular calcifications occur with reduced GFR, but their relationships and progression are unclear.

Methods: Bone markers in serum and vascular calcifications were measured. Bone histology, Fourier transform infra-red spectroscopy of bone, and dual photon x-ray absorptiometry of hip and spine was done at baseline and after 2-3 years observation in 23 subjects with GFR 18-70 ml/min. Data were analyzed using artificial intelligence.

Results: Bone quality and quantity declined with early loss of GFR and were predicted by serum activin, FGF-23 and klotho. 18 subjects had baseline coronary or aortic calcifications: 52% and 65% progressed. 5 subjects had no coronary calcifications at any time. Vascular calcifications were related to serum phosphorus levels. Increases in serum began at 4.0 mg/dl.

Conclusions: Serum markers offer promise as indicators of structural and cellular bone abnormalities accompanying early reduced kidney function. These include reduced bone quantity, quality and turnover abnormalities which are associated with coronary and aortic calcifications. Calcifications occur and progress in most studied subjects. Serum phosphorus levels a 4.0 mg/dl predict vascular calcification progression.

Funding: NIDDK Support, Private Foundation Support

Prospective, Randomized Controlled Pilot Trial to Investigate the Impact of Artificial Intelligence (AI) on Shared Decision Making in Post-Kidney Transplant Care (PRIMA-AI): Study Protocol for a Randomized Controlled Trial
Bilgin Osmanoglu,1 Klemens Budde.1 Charite Universitaetsmedizin Berlin, Berlin, Germany.

Background: Risk prediction models in kidney transplantation are ever increasing. Translation from good metrics to clinical benefit is the upcoming challenge. Another open question is how implementation of AI-based decision support systems (AI-DSS) affects physician-patient relationship in general and shared decision making (SDM) in particular.

Methods: In previous work, we developed risk prediction models for the prediction of infection, rejection and graft loss in kidney transplant recipients (KTR) and showed its superior performance in comparison to experienced physicians in a case-based reader study. Based on these models, we developed an AI-DSS that is implemented into the institutional electronic health record (EHR), and is studied in the PRIMA-AI trial.

Results: A 2-year, prospective, randomized, 2-armed, parallel group, single-center trial. KTR will be recruited in a German transplant center. All patients will receive the same routine care with clinical visits every 3 months. For patients in the intervention arm, physicians will be assisted by an AI-DSS that estimates 1-year risk for rejection, graft loss, or urinary tract infection (UTI). Based on the patients’ risk scores, medical and SDM interventions will be suggested to the physicians per protocol. As primary endpoint, two scores for SDM, the CollaboRATE mean score, and the Control Preference Scale are compared between both groups at baseline and 12 months after randomization. Secondary endpoints address differences in patient and graft survival, rejection episodes, time from suspected rejection to biopsy, hospitalization for UTI, outpatient treatment of UTI, dialysis initiation via catheter or shunt, and patient-reported outcome measures.

Conclusions: First, we investigate the potential benefit of an AI-DSS for the prediction of graft loss, rejection, and UTI in KTR. Additionally, using a mixed-methods approach, we aim to study the influence of AI-DSS on SDM, which can be relevant beyond the use case of kidney transplantation.

Funding: Government Support - Non-U.S.
PUB063
A Systematic Review of Externally Validated Machine Learning Models for Predicting AKI in General Hospital Patients
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1The University of Queensland, Brisbane, QLD, Australia; 2West Moreton Hospital and Health Service, Ipswich, QLD, Australia; 3Princess Alexandra Hospital, Woolloongabba, QLD, Australia.

Background: Acute kidney injury (AKI) is one of the most common and consequential complications among hospitalized patients. Timely AKI risk prediction may allow simple interventions that can minimize or avoid the harm associated with its development. Given the multifactorial and complex etiology of AKI, machine learning (ML) models may be best placed to process the available health data to generate accurate and timely predictions.

Methods: We searched the literature for externally validated ML models developed from general hospital populations using the KDIGO AKI definition. Data extraction was done using the CHARMS and TRIPD checklist and risk of bias was assessed using PROBAST.

Results: Of 889 studies screened, only four were retrieved that fit these criteria (Fig 1). While most models performed well and had a sound methodological approach, the main concerns relate to their development and validation in populations with limited diversity, comparable digital ecosystems, use of a vast number of predictor variables and over-reliance on an easily accessible biomarker of kidney injury.

Conclusions: These are potentially critical limitations to the applicability of ML models in diverse socioeconomic and cultural settings, prompting a need for simpler, more transportable prediction models which can offer a competitive advantage over the current tools used to predict and diagnose AKI.

PRISMA flowchart

PUB064
Implementation of Risk-Stratified CKD Screening Among Patients with Type 2 Diabetes
Camilla Sammut-Powell,1 Rose Sisk,1 Susana Goncalves,2 Shreyash Jain,2 Luong Nguyen Cong,2 Mark P. Edge,3 Thomas D. Motieit,2 Claudia S. Federico,1 Ahmed Hadjadj,1 Rory S. Cameron,1 Gendius Limited, Alderley Edge, United Kingdom; 2AstraZeneca PLC, Cambridge, United Kingdom.

Background: A minimal-resource model to risk-stratify patients with type 2 diabetes for CKD screening has been developed and globally validated. However, it remains to understand how it can be best utilised in practice to support earlier identification of CKD. The CKD Screening Prioritizer (CSP) is a well-accepted and easily integrated risk-stratification tool that can be adopted across several settings. With the last year growing be bested tool during face-to-face consultations on a per-patient basis or by processing entire clinic populations using historic patient records. Using a custom application-programming interface (API) we integrated with electronic health records. Chatbots within healthcare websites allowed direct-to-patient implementation: patients identified as high risk from this method were recommended to consult a healthcare professional on evaluating the next best course of action.

Conclusions: The CSP is a well-accepted and easily integrated risk-stratification tool that can be adopted across several settings. With the last year growing be bested tool during face-to-face consultations on a per-patient basis or by processing entire clinic populations using historic patient records. Using a custom application-programming interface (API) we integrated with electronic health records. Chatbots within healthcare websites allowed direct-to-patient implementation: patients identified as high risk from this method were recommended to consult a healthcare professional on evaluating the next best course of action.

Results: The CSP was implemented across several countries via healthcare professional (HCP)-facing systems and direct to patients. HCPS were able to use the tool during face-to-face consultations on a per-patient basis or by processing entire clinic populations using historic patient records. Using a custom application-programming interface (API) we integrated with electronic health records. Chatbots within healthcare websites allowed direct-to-patient implementation: patients identified as high risk from this method were recommended to consult a healthcare professional on evaluating the next best course of action.

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Funding: Commercial Support - Gendius Limited, AstraZeneca

PUB065
Construction of a Prediction Equation for the Progression and Worsening of CKD Using Artificial Intelligence Algorithms
Koki Ogawa,1 Yasushi Takahashi,2 Seiko Oana,3 Hiroaki Hara,4 Tsukasa Odo,5 Kento Soma,2 Akito Maechima,6 Hajime Hasegawa,6 1Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; 2NEC Solution Innovators, Ltd., Koutouku, Japan.

Background: Clinical studies in the past have focused on specific clinical characteristics (blood pressure, body mass index, renal function, urinary protein, various biochemical test parameters and specific markers, etc.) and analyzed their association with disease severity assessment, prognosis, and prediction of treatment responsiveness, mainly through statistical methods for specific populations. However, there are a wide variety of factors that can influence the above analysis, including age, gender, body size, presence and severity of comorbidities, and presence and type of medications, and so on. To conduct a more accurate and effective analysis, it is necessary to consider the various data above for each individual. Against this backdrop, attempts to use various AI (Artificial intelligence) algorithms to evaluate overall severity and predict future risk have been reported in certain fields in recent years. However, reports in the field of renal disease are limited. To develop a model to predict the risk of CKD progression and exacerbation using AI, and to identify factors that have a significant impact on this exacerbation.

Methods: Data was collected from patients treated in our department from April 1, 2006 to May 31, 2021 with examination intervals of at least one year (3098 cases). The groups with the Green, Yellow and Orange stages of the CKD heatmap were analyzed at a year using AI (rule discovery inference engine) to create a prediction equation. In addition to blood and biochemical test results, 209 factors were used in the analysis, including the name of the disease and drugs administered. A prediction equation was established using 85% of the cases in the population, and the accuracy of the prediction equation was verified by applying the obtained equation to the remaining 15% of cases. The final number of subjects for analysis was 1786 for Green, 824 for Yellow, and 488 for Orange.

Results: When the prediction formula was verified by the above method, the correct answer rate for each group was 76.8% for Green, 75.6% for Yellow, and 70.8% for Orange. Factors influential in CKD exacerbation at each stage were different.

Conclusions: The results of this analysis suggest that the relevant factors may have different priorities for each CKD stage.

PUB066
A New Deep-Learning Analysis Pipeline to Analyze and Quantify Renal Atrophy
Giuseppe L. Spatolatore,1 Alberto Rosati,1 Guido Garosi,1 Noemi La Francesca,1 Clarissa Gambina,1 Simone Cancelli,2 Sergio A. Triponi,2 1Ospedale di San Giovanni di Dio Firenze, Florence, Italy; 2Azienda Ospedaliera Senese, Siena, Italy; 3University of Siena, Department of Medical Biotechnology, Siena, Italy; 4University of Siena, Department of Information Engineering and Mathematical Sciences, Siena, Italy.

Background: Atrophy represents a prognostic factor in many renal diseases and in kidney graft evaluation. Up to date the evaluation of atrophy is made using eyeball methods and has low interobserver agreement. So, there is an urgent need to introduce user-friendly and affordable tools. Digital pathology coupled with AI represents the solution but is challenged by the need of long training of nets through large, annotated datasets. Annotations are manual, time-consuming and need skilled pathologists. Herein we propose a new method to annotate fast and well.

Methods: We have developed two new strategies to perform fast and accurate annotations. The first was the employment of immunostaining with CD10/PAS. CD10 is under expressed in atrophic proximal tubules and absent in the membranes pink. CD10 is under expressed in atrophic proximal tubules and absent in the brush border of proximal tubules, PAS counterstain. CD10 annotations. The first was the employment of immunostaining with CD10/PAS. CD10

Results: The second strategy was to speed up the annotation step using a new workflow (fig1). While most models performed well and had a sound methodological approach, the main concerns relate to their development and validation in populations with limited diversity, comparable digital ecosystems, use of a vast number of predictor variables and over-reliance on an easily accessible biomarker of kidney injury.

Conclusions: These are potentially critical limitations to the applicability of ML models in diverse socioeconomic and cultural settings, prompting a need for simpler, more transportable prediction models which can offer a competitive advantage over the current tools used to predict and diagnose AKI. In kidney graft evaluation. Up to date the evaluation of atrophy is made using eyeball methods and has low interobserver agreement. So, there is an urgent need to introduce user-friendly and affordable tools. Digital pathology coupled with AI represents the solution but is challenged by the need of long training of nets through large, annotated datasets. Annotations are manual, time-consuming and need skilled pathologists. Herein we propose a new method to annotate fast and well.

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Conclusions: These are potentially critical limitations to the applicability of ML models in diverse socioeconomic and cultural settings, prompting a need for simpler, more transportable prediction models which can offer a competitive advantage over the current tools used to predict and diagnose AKI.
Conclusions: we developed an easy fast method, based on AI, that combines morphology and immunophenotype. We wish to improve and standardize the morphofunctional evaluation of kidneys in nephropathology as well as in transplantation.

Funding: Government Support - Non-U.S.

**PUB067**

Improving Outcomes of Patients with CKD by Employing Chronic Care Management Machine Learning Technology

Leigh J. Mack, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.

Introduction: Many patients today struggle with treatment plan adherence due to not understanding the plan or how prescriptions, diet, and exercise are all integral to improved outcomes. By employing personalized messages, two-way communications along with patient education, patients with chronic kidney disease take more interest and ownership in improving their condition. Patient follow-up after a clinical visit is key to improved outcomes. Many times patients do not fully understand the treatment plan and therefore do not follow it as prescribed. Initial contact is made by SMS text that is personalized to the patient from the physician. Patients were then asked to engage in a digitized questionnaire to measure prescription adherence, treatment plan compliance, and lifestyle choices along with specifics on diet and exercise.

Case Description: A total of 521 Medicare patients were enrolled in the service and followed up after 7 days after the last clinical appointment with the physician. Patients had a diagnosis of chronic kidney disease stage 3 through 5. Patients were contacted by SMS text and asked to call in to a service, employing the physician’s digitized voice, asking the patient specific questions related to their condition. Patients were asked 20 questions every two weeks related to observable conditions, prescription adherence, treatment planned adherence, diet, exercise, overall health, and quality of care experience from the provider. Conversations were reviewed by a medical technician for the quality of responses and sentiment. The sentiment was measured using validated machine learning software. Cases were reviewed for 90 days, after which data was compiled with machine learning analytics software to analyze correlations. Specific data shall be presented as it relates to patient engagement and data analysis of all 20 questions.

Discussion: At the time of this submission data is still being gathered and expected to be completed by the beginning of September, 2023. Even though this was a large population, next steps might include lengthening the study to 6 months and enroll a population of over 10,000. A repository might be upwards of 50,000 and might include the patient’s full EMR. As we explore more machine learning processes, we might expect the software systems to detect multifaceted clinical relationships.

**PUB068**

Application and Improvement of Interpretable Artificial Intelligence (AI) Algorithms Using Global Permutation Importance for Intradialytic Hypotension

Jian-An Wang, Hsiang Wei Hu, Kuanyu Chen, Chi Hin Un.

Background: In recent years, machine learning has made significant breakthroughs in the field of smart healthcare. Dialysis has also become part of smart healthcare. In Taiwan, it’s 3,679 people per million undergoing dialysis, whereas the global average prevalence rate of intradialytic hypotension is 11.6% in the past study. Therefore, intradialytic hypotension makes the application of smart healthcare in blood dialysis an important topic. Several articles have used various machine learning algorithms to predict the occurrence of hypotension during dialysis. However, these prediction results often lack proper explanations or are too complex to understand. Therefore, this study aims to improve interpretable AI algorithms and proposes the Global Permutation Importance method as an example, which is the simplest and most interpretable algorithm.

Methods: The core of this method lies in “changing the object of explanation to achieve high interpretability.” Due to the complex feature engineering and mathematical operations, some features in the dataset may have lost readability, and their explanatory results cannot be directly applied to the real world. Therefore, this study transfers the object of explanation to the raw data, namely the dataset without feature engineering. By randomly shuffling the features of this dataset and utilizing the established feature engineering and model, the impact of each feature on the prediction process is evaluated.

Results: The bar plots are used to interpret the results of feature importance. There are some features that are difficult to understand, such as time-related features and difference-related features. For example, the mean and median of the blood flow sequence cannot identify the differences in the world. It’s difficult to interpret how these features impact the prediction. However, all of the features become useful and meaningful using global permutation importance, such as blood flow and body temperature. Additionally, feature engineering can evaluate whether the feature engineering has an effect on the prediction.

Conclusions: Through the aforementioned techniques, our explanatory results not only uncover the model training and feature engineering processes but also enable healthcare professionals to fully understand the explanations, thereby increasing trust in the model and prediction results.

**PUB069**

In Vitro Iohexol Adsorption in Cartridges with Mesoporous Styrene-Divinylbenzene Sorbent

Thango A. Reis,3 Gonzalo Ramirez Guerrero,2 Valentina Corradi,3 Massimo de Cal,7 Anna Lorenzin,7 Claudio Ronco,7 Monica Zanella.7

Background: A strong rationale supports the removal of iodinated contrast media because of its nephrotoxicity. In this experiment, we aimed to investigate the efficacy of iohexol (molecular weight 821 Da) adsorption with a mesoporous styrene-divinylbenzene sorbent using an in vitro model.

Methods: We used a 0.9% NaCl solution spiked with iohexol in a closed-loop circuit. The circuit had a cartridge with adsorbing resin interposed downstream of a peristaltic pump. A glass reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with iohexol. The cartridge was filled with 75 g sorbent resin beads. The concentration of iohexol was assessed by high-performance liquid chromatography with ultraviolet (HPLC-UV) detection. The collection of 2 mL aliquots occurred at eight-time points (0, 5, 10, 15, 20, 30, 40, and 60 minutes).

Results: The reduction ratios after 5, 30, and 60 minutes were 24.5%, 47.5%, and 56.1%, respectively. In the second experiment, the reduction ratios after 5, 30, and 60 minutes were 22.5%, 44.1%, and 50.5%, respectively. After 30 minutes, the adsorption curve plateaued, indicating cartridge saturation.

Conclusions: Removing iohexol via adsorption was effective, with each gram of sorbent removing roughly 105 mg of iohexol (i.e., equilibrium load of 105 mg/g). The use of adsorption has the clinical potential to reduce exposure to nephrotoxic contrast agents.
Vicenza, Italy
Claudio Gonzalo
Vancomycin Adsorption in Cartridges with Mesoporous Styrene-
PUB070
Iohexol concentration during the experiment

Closed-loop circuit

The device was installed in front of the cartridge, specifying the middle segment of the speed at 1800 percussion per minute, amplitude of 10 mm, and frequency of 30 Hz.

15, 20, 25, 30, 40, 60, 80, 100, and 120 minutes. Vibration was implemented with a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from

Transverse vibration induces a substantial amount of radial mixing in the fluid. It creates vorticity contours with the production of vortices; these may enhance contact time between blood and beads. Dynamics studies have shown different local velocities in the cartridge, determining the performance of the sorbent. The packed beads can be approximated as the fluid, represented by vorticity contours with the potential beneficial effects of increasing contact time.

Methods: The circuit had a cartridge with adsorbing resin interposed downstream of a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. For each study point, a sample was drawn at 5, 10, 15, 20, 25, 30, 40, 60, 80, 100, and 120 minutes. Vibration was implemented with a speed at 1800 percussion per minute, amplitude of 10 mm, and frequency of 30 Hz. The device was installed in front of the cartridge, specifying the middle segment of the cartridge as the contact area. The reduction ratio was calculated using the formula: [Initial concentration - Final concentration]/Initial concentration

Results: Reduction ratios after 5, 10, 15, 20, 25, 30, 40, 60, 80, 100, and 120 minutes were 12.5%, 26.3%, 27.6%, 25.8%, 20.4%, 31.4%, 33.1%, 42.1%, 43%, 47.4% and 50%, respectively. A higher vancomycin reduction rate was observed in the first 20 minutes. Subsequently, the obtained curve was similar to a previous experiment without vibration after 20, 40, 60, 80, 100 and 120 minutes.

Conclusions: In this in vitro model, removing vancomycin via adsorption appears to be greater in the first 20 minutes when using vibration to accentuate this technique. Vibration in adsorption to increase performance warrants further investigation.

Funding: Private Foundation Support

Background: Flow distribution inside the cartridge is one of the main issues concerning the performance of the sorbent. The packed beads can be approximated as a bundle of capillary tubes with some wide-diameter channels and gaps in the structure resulting in “channelling of the flow,” avoiding complete contact with the beads. Fluid dynamics studies have shown different local velocities in the cartridge, determining the production of vortices; these may enhance contact time between blood and beads. Transverse vibration induces a substantial amount of radial mixing in the fluid. It creates a swirling or spiraling motion in the fluid, represented by vorticity contours with the potential beneficial effects of increasing contact time.

Methods: The circuit had a cartridge with adsorbing resin interposed downstream of a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from

Results: Reduction ratios after 5, 10, 15, 20, 25, 30, 40, 60, 80, 100 and 120 minutes

Conclusions: These observations strongly suggest combinations of soluble Ca and Mg salts react with Pi differently from Ca or Mg alone. At values of pH characteristic of the small intestine, the two cations rapidly precipitated Pi. However, over half of the Mg ion remained in solution under these conditions. The data suggest that residual Mg ion remains in solution after Pi-binding takes place in the upper intestine. If residual Mg is not absorbed, it acts beneficially in the colon. Conversely, if Mg is absorbed, it acts beneficially in the systemic circulation and intracellularly. Normalization of systemic Mg self-limits further absorption of the ion.

Funding: Commercial Support - BioLink Life Sciences Inc

PUB072
Prevalence and Factors Associated with Renal Hyperparathyroidism Among Dialysis-Require Patients
Bai Ramlyn G. Solaiman, Jennifer Ivy Togonon-Leañó, Jose Paolo P. Panuda. Southern Philippines Medical Center, Davao City, Philippines.

Background: Renal hyperparathyroidism, a CKD complication, is associated with increased parathyroid hormone levels from calcium, phosphate, and Vitamin D imbalances. It is 12-54% prevalent worldwide and associated with significant mortality and morbidity. This study aimed to determine the local prevalence and the factors associated with it among dialysis patients.

Methods: A cross-sectional study was conducted wherein all ESRD patients aged 19-75 years old and on maintenance dialysis ≥3months were included. The mean intact parathyroid hormone (iPTH), Vitamin D, ionized calcium, phosphorus and alkaline phosphatase were recorded. Correlation of age, gender, pre-dialysis co-morbidities, parathyroid hormone (iPTH), Vitamin D, ionized calcium, phosphorus and alkaline phosphatase were recorded. Correlation of age, gender, pre-dialysis co-morbidities,

iPTH, giving an 87.5% prevalence. Age was negatively correlated with iPTH (r=-0.212, p=<0.01, 95%CI0.227,0.512) and the longer they were on dialysis, their predicted iPTH will be higher by 93.637pg/mL (p=<0.01). Dialysis frequency was positively correlated with increased parathyroid hormone levels from calcium, phosphate, and Vitamin D imbalances. It is 12-54% prevalent worldwide and associated with significant mortality and morbidity. This study aimed to determine the local prevalence and the factors associated with it among dialysis patients.

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increase the iPTH significantly [hypertensive nephrosclerosis: \( x^2=9.44; p=0.024 \), diabetic kidney disease: \( x^2=19; p=<0.01 \), chronic glomerulonephritis: \( x^2=12.680; p=<0.01 \)].

**Conclusions:** The 87% prevalence rate supported the high prevalence world-wide. Factors identified were age, presence of pre-dialysis co-morbidities, longer dialysis vintage, and frequent dialysis sessions (3x a week). Shorter dialysis interval stimulates parathyroid gland from increased blood flow triggered during dialysis and altered calcium handling by the kidneys, subsequently leading to hormone secretion.

**PUB073**

**Hypercalcemia as a Solitary Feature of Sarcoidosis**

Amandeep Singh,1 Jon C. Webb,1 Virgilius Cornea,2 Pearl in the Oyster.

1University of Kentucky College of Medicine, Lexington, KY; 2University of Kentucky Medical Center, Lexington, KY.

**Introduction:** In over 90% of cases, sarcoidosis typically manifests initially in the intra-thoracic region, characterized by mediastinal or hilar lymphadenopathy (LAD). It is rare for sarcoidosis to present solely as extra-thoracic, and even rarer for hypercalcemia to be the only initial sign.

**Case Description:** A 70-year-old Caucasian female with history of childhood histoplasmosis, presented with hypercalcemia of 12.2 mg/dl and elevated 1,25 dihydroxy vitamin D3 (1,25(OH)2 D) of 123 pg/ml. A chest CT revealed calcified lymph nodes (LN) in the mediastinum, indicating a previous histoplasmosis. PET-CT showed extensive generalized LAD with increased FDG uptake in the enlarged spleen. Additionally, myocardium showed no abnormal metabolic activity. An inguinal LN biopsy demonstrated non-necrotizing granulomatous inflammation. Staining with Grocott Methenamine Silver (GMS) and AFB was negative for organisms. Histopathology was negative for malignancy or lymphoma. Staining with Grocott Methenamine Silver (GMS) and AFB was negative for organisms. Histopathology was negative for malignancy or lymphoma. Results of Fungitell, QuantiFERON TB gold, antibodies against Histoplasmosis, Blastomycosis, and Coccidiomycosis were all negative. Treatment with prednisone at 0.5 mg per kg led to the normalization of calcium and 1,25(OH)2 D levels within three weeks.

**Discussion:** The measurement of vitamin D metabolites is crucial for diagnosing hypercalcemia mediated by 1,25(OH)2 D. Granulomatous disease can lead to hypercalcemia and elevated 1,25(OH)2 D, therefore, should be considered in the differential diagnosis of hypercalcemia. When diagnosing sarcoidosis, other potential causes of granulomatous inflammation are typically ruled out by clinical features, laboratory findings, imaging, and tissue histopathology (as described under case description). A PET-CT scan is an essential tool in determining an appropriate biopsy site and excluding potential cardiac involvement of sarcoidosis. 1,25(OH)2 D mediated hypercalcemia is responsive to glucocorticoid therapy.

**PUB074**

**Giant Bladder Stone in a Young Male: When Surgery Complements Medicine for Better Outcomes**

Gagan Aulakh,1 Meghan E. Lacovara,1 Arshdeep Singh,2 Khushi Bhatia,2 Yaseen Baseer.1,2

1Jersey City Medical Center, Jersey City, NJ; 2Government Medical College Amritsar, Amritsar, India.

**Introduction:** Bladder stones are extremely rare especially more than 100 grams. This is a case of giant bladder stone in 49 years old male with recurrent UTI and foreign body retention leading to open cystolithotomy.

**Case Description:** 49-year-old male with PMH of recurrent UTI and recurrent nephrolithiasis (lost follow-up with double J stents and nephrostomy tube) evaluated for symptomatic UTI. He denied family history of nephrolithiasis, Crohn’s disease, or consumption of supplements. Blood workup revealed leucocytosis and hyperchloremic normal anion gap metabolic acidosis with normal potassium. Urinalysis showed turbidity with pH of 8.5, moderate trichomycetes in urine, and positive for nitrite and E. coli. Imaging revealed large urinary bladder calculus, bilateral hydronephrosis with encrusted ureteral stents and staghorn calculus in left kidney. ESBL proteus mirabilis grew in blood and urine cultures. General urology and interventional radiology stepped out as extremely encrusted stents made high-risk with usual procedures. As an end resort surgical urology stepped in for multi-modal endourological approach starting with open cystolithotomy. Cystoscopy during surgery was performed which ruled out intravesical obstruction. Stone biochemical showed mixture of struvite and calcium apatite.

**Discussion:** Open cystolithotomy is preferred over transurethral cystolitholapaxy for large stones.
PUB075

Novel Markers of Early CKD-MBD Pathophysiology That Predict CKD Progression and All-Cause Mortality in Patients with Predialysis CKD

Shunsuke Yamada, Shigeru Tanaka, Shumie Matsuda, Takakari Kitazono, Toshiaki Nakano. Kyushu University, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Fukuoka, Japan.

Background: CKD-MBD develops in the early stages of CKD and contributes to the increased risk of end-stage kidney disease and mortality. Thus, it is critical to identify new markers that reflect early events of CKD-MBD and can predict mortality in the pre-dialysis stage of CKD.

Methods: We examined 4,308 patients enrolled in the FKR study, a prospective observational study of patients with pre-dialysis CKD stages G1–G5. We focused on fractional excretion of phosphate (FEP) and estimated phosphate concentration in proximal tubular fluid (ePTFp) as indicators of early CKD-MBD pathogenesis. We compared the onset of change in each indicator with the serum PTH, calcium, and phosphorus levels using baseline data. Additionally, we determined the association of FEP or ePTFp with the risk of all-cause mortality and composite renal event using longitudinal data. The composite renal event was defined as the development of end-stage renal failure and/or 1.5-fold increase in serum creatinine concentrations.

Results: Over 5 years, 1,488 patients developed a composite renal event and 423 died. FEP and ePTFp were elevated as early as an eGFR of 70 mL/min/1.73m² and preceded the changes in serum PTH, calcium, and phosphorus concentrations. Multivariate-adjusted Cox proportional hazard regression analyses revealed a significant association between FEP and ePTFp increase and a heightened risk of developing a composite renal event and all-cause mortality. The hazard ratio (95% confidence interval) for a 1 standard deviation increase in log FEP and log ePTFp was 1.36 (1.20–1.54) and 1.39 (1.21–1.59), respectively. This association was independent of the serum PTH, calcium, and phosphorus concentrations and remained almost unchanged on application of competing risk regression analysis.

Conclusions: FEP and ePTFp may serve as indicators of early CKD-MBD pathophysiology that predict CKD progression and all-cause mortality in patients with pre-dialysis CKD.

PUB076

Beyond Bones: Examining Vascular Calcification in Hemodialysis Patients and Its Association with Bone and Mineral Metabolism


Background: Patients on dialysis are at an increased risk of cardiovascular disease (CVD) and vascular calcification (VC). This study aimed to evaluate the possible relationship between VC and bone and mineral metabolism (BMD) in patients on dialysis.

Methods: This study was conducted in all ambulatory dialysis centers in Qatar from January to December 2022. We retrospectively reviewed dialysis patients’ charts, including patient demographics, comorbidities, BMD parameters (correlated calcium, phosphorus, PTH, and Vitamin D3), and average medication doses per week. In addition, VC was assessed by echocardiography, abdominal and chest X-ray, and abdominal CT.

Results: 842 HD patients were included during the study period. VC was detected in 52.6% of patients (most commonly in the mitral valve with 55.5%). Patients with VC were older age (61.6±14.2 vs. 58.0±16.3 years, p=0.001), had diabetes mellitus (DM) (75% vs. 29%, p=0.006), Higher vitamin D levels (39.0±18.0 vs. 32.1±17.2 p=0.003), and higher 1α-hydroxyvitamin D3 and calcium levels (p<0.001) compared to patients without VC. All other parameters were not different. Regression analysis (univariate and multivariate) for risk factors associated with VC is shown in Table 1. In multivariate analysis, age, and diabetes were significantly associated with risk of VC (OR 1.049, p<0.001 and OR 1.768, P=0.001 respectively). In addition, higher vitamin D levels and higher doses of 1α-hydroxyvitamin D3 were significant risk factors for calcifications (OR 1.017, p= 0.007 and OR 1.178, p<0.0001 respectively).

Conclusions: We found a high prevalence of vascular calcification among our hemodialysis cohort. Risk factors for VC were identified, including old age, DM, high vitamin D level, and high 1α-hydroxyvitamin D3 dose.

Funding: Government Support - Non-U.S.

Table 1: Regression analysis of risk factors for vascular calcifications in hemodialysis patients

<table>
<thead>
<tr>
<th>Uric Acid Analysis</th>
<th>Multivariate Analysis</th>
<th>Uric Acid Analysis</th>
<th>Multivariate Analysis</th>
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</thead>
<tbody>
<tr>
<td>OR</td>
<td>95% CI</td>
<td>P Value</td>
<td>OR</td>
</tr>
<tr>
<td>Age</td>
<td>1.001</td>
<td>1.000–1.002</td>
<td>0.020</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.651</td>
<td>1.945–3.619</td>
<td>&lt;0.0001</td>
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<tr>
<td>Vitamin D Level</td>
<td>1.211</td>
<td>1.004–1.421</td>
<td>0.042</td>
</tr>
<tr>
<td>Oral Calcitriol Dose</td>
<td>1.002</td>
<td>1.000–1.004</td>
<td>0.044</td>
</tr>
<tr>
<td>1α-Hydroxyvitamin D3</td>
<td>1.172</td>
<td>1.083–1.272</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

PUB077

Symptomatic Hypercalcemia Secondary to Hyperthyroidism

Katrina Lamont, Roberto L. Collazo-Maldonado, Victor A. Canelas-Samaniego. Methodist Health System, Dallas, TX.

Introduction: Hypercalcemia is often encountered in clinical medicine. The most common causes of hypercalcemia include primary hyperparathyroidism, iatrogenic causes (medications) and malignancy, while a rare cause is hyperthyroidism. This case highlights a nursing home resident presenting with severe hypercalcemia and undiagnosed thyroïdism.

Case Description: A 58-year-old AA woman with PMHx of CVA on PEG tube feedings presented with sudden onset non-exertional chest pain. The emergency department consulted the Nephrology service for evaluation of severe hypercalcemia and AKI. Medication list included aspirin, statin and citalopram. On exam, her PEG tube was in place, reflexes and vital signs were normal but was hypovolemic. Initial serum chemistries showed a BUN 67 mg/dl, serum Cr was 1.4 mg/dl (SCr baseline <1 mg/dl). ALP 317 U/L, AST 283 and ALT 317 U/L, respectively. CK was normal. Calcium was 13.4 mg/dl, albumin 3.5 g/dl. PTH was suppressed at 17 pg/ml, ionized calcium was 1.67 mmol/L. PTHrP was 5 pmol/L. Vitamin D 25-OH Vitamin D 1.25-OH were normal. SPP and UPE had no signs of mononoclonality. TSH was extremely suppressed at <0.02 UI/ml. T4 was high at 4.12 ng/dl and T3 was 5.13 pg/ml respectively. Thyrotrpin receptor antibody was 3.23 IU/L and thyroid peroxidase antibodies titer was 278.2 IU/L. U/A was normal. Urine drug screen was negative. Renal U/S had normal kidneys. A thyroid ultrasound showed a diffusely heterogenous in echogenicity with abnormal increased vascularularity throughout. EKG had sinus tachycardia. The patient was treated with volume expansion with normal saline, pamidronate and calcitonin. Her serum calcium on discharge decreased to 10.7 mg/dl. She was treated with methimazole and propranolol for newly diagnosed Grave’s thyroiditis. Her symptoms resolved and she returned to her nursing home.

Discussion: causes increased osteoclastic activity leading to bone resorption. Prompt recognition and early treatment of the hyperthyroid state is essential.
**Effect of Magnesium Supplementation on Serum Matrix Gamma-Carboxyglutamate Protein as Biomarkers of Vascular Calcification in Patients with CKD**

Bancha Satirapong, Pavitra Charoensrisakul, Peeraya Permarktjanaro, Naritaya Varothai, Narongrit Siriwattanasit, Naowanit Nata, Theerakasp Sangwonglert, Anmart Chaiprasert, Ooupapatham Supasanyak, Phramongkklao College of Medicine, Bangkok, Thailand.

**Background:** Vascular calcification is a major risk factor of cardiovascular disease and cardiovascular mortality in patients with chronic kidney disease (CKD). Magnesium has pleiotropic potential for interfering with progression of vascular calcification by modulating the expression of anti-calcification proteins including matrix gamma-carboxyglutamate protein (MGP).

**Methods:** This study is double-blinded, randomized, placebo-controlled trial in CKD patients with high risk of vascular calcification. The subjects were randomly assigned (1:1) to receive oral magnesium dioxide (MgO2) 200 mg/day or matching placebo for 12 weeks. The primary endpoint was the between-groups difference in serum MGP level after 12 weeks.

**Results:** A total of 31 CKD patients (19 males and 12 females) were enrolled in the study. At baseline, mean serum magnesium was 2.05±0.23 mg/dL and baseline serum MGP levels did not differ significantly between the two groups. After 12 weeks, the mean MGP concentrations significantly increased in the MgO2 group (mean change, 90.45±102.06 ng/mL; 95%CI 209.45 to 219.80) and also significantly increased in the placebo group (mean change, 73.47±117.73 ng/mL; 95%CI 208.05 to 227.5). However, absolute MGP change was not significantly different between groups (P=0.682). There was no report of serious side effect or hypermagnesemia during the study.

**Conclusions:** Among CKD patients, magnesium supplementation for 12 weeks did not improve serum MGP level as biomarkers for preventing vascular calcification compared with placebo. Larger-scale trials are warranted to confirm these findings.

**Breaking Bad Calcium: The Role of Hemodialysis for Severe Hypercalcemia**


**Introduction:** Hypercalcemic crisis is an emergent medical condition that may lead to serious complications such as acute kidney injury (AKI), muscle flaccidity, neurologic changes including obtundation and coma and cardiac arrhythmias leading to cardiac arrest. Standard treatment for hypercalcemia includes saline hydration, bisphosphonates, steroids, calcitonin and in refractory cases, hemodialysis (HD). HD can effectively lower serum calcium levels but its use is not commonly reported by literature.

**Conclusions:** Among CKD patients, magnesium supplementation for 12 weeks did not improve serum MGP level as biomarkers for preventing vascular calcification compared with placebo. Larger-scale trials are warranted to confirm these findings.

**Bone Mineral Disorder in Patients with CKD Undergoing Hemodialysis Replacement Therapy at a Reference Center**


**Background:** Bone mineral disorder - concomital renal disease is a syndrome that includes calcium, more alterations of calcium, phosphorus, parathormone, vitamin D, remodeling, bone mineralization or volume, vascular or soft tissue calcifications. Generating high cardiovascular risk and fractures. Objective: To determine the prevalence of bone mineral disorder - chronic kidney disease in hemodialysis patients in a reference center.

**Methods:** Descriptive and association study, observational, cross-sectional, protective, which included patients with chronic kidney disease on hemodialysis older than 18 years who agreed to participate. Sample size for prevalence of 60%, with alpha probability of 0.05 and precision factor of 0.1 was 93 patients, however, only 27 patients agreed to participate. Serum values of PTH, calcium, phosphorus, calcidiol, time on hemodialysis, age, sex, and presence of diabetes were obtained. Data processing analyzed with SPSS 22, ORP calculation with 95% CI, Chi square and logistic regression p<0.05.

**Results:** 90% prevalence of bone mineral disorder, prevalence of high turnover bone disease 81.2%. The association of vascular calcifications with age OR 1.324 IC (1.003 to 1.7) p0.04, with PTH OR 1.001 IC (0.9 to 1.04) p0.3 and with time on hemodialysis 3.4 (0.2-40.4) p0.04

**Conclusions:** In our population, the prevalence of bone mineral disorder is consistent with that reported in the literature. Our patients present a high frequency of vascular calcifications and a predominance of high turnover bone disease. The underdiagnosis of this disorder generates complications that have an impact on cardiovascular morbidity and mortality.
PUB083

Investigating Mesenchymal Stem Cell Sources for VEGFA mRNA Transfection and In Vivo Protein Exposure
Robert L. Menzies,1 Cecilia Graneli,1 Alex X. Zhou,1 Xuexong Hong,1 Ulrika Dahlqvist,2 Vijayaganapathy Vaithilingam,3 Mikko Hölttä,2 Neil Henderson,1 Stephanie M. Bates,1 Mick D. Fellows,1 Anna Forslöv,1 Xiuyang Zhu,2 Chiara Ahlström,1 Alessandro Boianelli,1 Ryan Hicks,1 Lilach O. Lerman,2 Perrinelle B. Lærkegaard Hansen,1 AstraZeneca, Gothenburg, Sweden; 2Mayo Clinic Research Rochester, Rochester, MN; 3AstraZeneca R&D Cambridge, Cambridge, United Kingdom.

Background: Cell based therapies offer promising avenues for the treatment of kidney diseases. Among these, mesenchymal stem cells (MSCs) have shown potential due to their immunomodulatory properties. Recent advances in RNA-based technologies have opened up new avenues to enhance MSC functionality. Here we investigate the function of MSCs transfected with RNA encoding vascular endothelial growth factor-a (VEGFA), an important angiogenic protein in the kidney and other organs that is diminished in ischemic diseases.

Methods: Pig (adipose) and human (bone marrow, umbilical, adipose, or induced pluripotent) MSC sources were investigated for reproducible production of VEGFA protein following RNA transfection. VEGFA protein production from MSCs was then investigated in vivo in a mouse pharmacokinetic model and a pig model of renal artery stenosis.

Results: Reproducible and similar post-transfection expression patterns of VEGFA (6-8x10^6 pg/ml) were achieved in human bone marrow MSCs and porcine adipose tissue derived MSCs in vitro, with the prior demonstrating greater expansion potential. Healthy mice injected with VEGFA-MSCs showed transiently increased VEGFA protein levels in kidney. In renal artery stenosis pigs, injection of porcine VEGFA-MSCs produced a peak of VEGFA (3.95 pg/mg renal tissue; 6hrs post injection) which resolved by 10 hours.

Conclusions: These data confirm a transient burst in VEGFA protein is achievable through RNA transfection of MSCs, delivered in a relevant disease setting. The pharmacokinetic parameterisation of MSC-based VEGFA protein production in vivo will inform future cell therapy development.

Funding: Commercial Support - AstraZeneca

PUB084

Hypoxic Preconditioning Alters Micro-RNAs Expression in Mesenchymal Stem Cells from Patients with Hypertensive Kidney Disease

Background: Hypertensive kidney disease (HKD) is a common cause of end-stage kidney disease. Autologous mesenchymal stem cells (MSCs) emerge as a therapeutic option for many kidney diseases, but HKD might alter their regenerative ability. Hypoxic preconditioning (HPC) enhances MSC functionality by modulating global gene expression. We hypothesize that HPC can promote MSCs function by altering their miRNAs expression.

Methods: MSCs were collected from abdominal subcutaneous fat biopsies of healthy controls (HC), hypertensive (HTN), and HKD patients (n=12 each, Fig. 1A). miRNA sequencing (seq) was performed on MSC cultured in normoxic (20% O2) or hypoxic (1% O2) conditions for 24-72h. Differentially expressed (DE) miRNAs (log fold=1.5 or <-1.5; p<0.05) were identified followed by target predictions and gene ontology analysis.

Results: miRNA-seq identified 10 and 16 miRNAs altered by HPC exclusively in HTN and HKD, respectively (Fig. 1B). In HPC MSCs, the upregulated HTN miRNAs target genes were involved in telomere maintenance, DNA damage, and FGFR signaling, whereas downregulated ones were implicated in blood vessel development and growth regulation. Contrarily, upregulated HKD miRNAs target genes participate in TNF-α signaling and response to hormones, whereas downregulated ones were involved in VEGFA-VEGFR2 pathways and regulation of embryonic development.

Conclusions: HPC differentially influences the expression of miRNAs implicated in vascular development and cell senescence in human HKD- and HTN-MSCs and may thereby enhance angiogenesis and MSC regenerative capacity and blunt inflammation. Further studies are needed to explore the unique role of HPC in miRNAs expression and MSCs functionality in HKD.

Funding: Commercial Support - ProKidney LLC.

PUB085

Osteopontin-Associated Reparative Effects of Selected Renal Cells
Andrew T. Bruce, Prakash Narayam, Tim A. Bertram, Deepak Jain. ProKidney, Winston Salem, NC.

Background: Osteopontin (OPN) conveys renal reparative effects. Selected renal cell types (RCCs), a glomerular- and tubular epithelial cell-enriched platform, exhibit reparative and restorative effects in models of CKD. In the present study, we tested the hypothesis that OPN mediates SRC reparative activity.

Methods: Human SRC (National Disease Research Interchange) and renal cortical biopsies (control) monolayers were submitted to a scratch assay in the absence/presence of an OPN neutralizing antibody (ab). Reparative activity was evaluated by imaging (blinded) the number of cells migrating to bridge the wound. Expression of cav1, mmp9, icam1 and cxcr4 was evaluated using qPCR. Genes were seeded into HumanBase for visualization of transcriptome function.

Results: Compared to control, SRCs exhibited increased migration into the wound (p<0.05), an effect reduced by the OPN ab (p<0.05). Expression of migratory markers cav1, mmp9, icam1 and cxcr4 was upregulated in SRCs (p<0.05). Gene ontology confirms that the opn/sap1-cav1-mmp9-icam1-cxcr4 axis regulates migration, adhesion, and wound healing.

Conclusions: These data suggest that SRC associated preservation of renal microarchitecture and maintenance of the renal filtration function, including creatinine clearance, electrolyte balance, fluid homeostasis, urine concentration and Cystatin C metabolism, may be mediated, in part, by an OPN-associated wound healing cascade.

Funding: Commercial Support - ProKidney LLC.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Transmembrane Protein 72, Expressed in the Distal Convoluted Tubule, May Play a Potential Role in Diabetic Kidney Disease

Jian teng Xie, Qiuling Li, Wenjian Wang, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.

**Background:** Transmembrane protein 72 (TMEM72) is highly expressed in tubules of the kidney. This study is designed to explore the role and the potential mechanism of TMEM72 in the development of diabetic tubulopathy.

**Methods:** Serum TMEM72 concentration was tested in health control, patients with diabetes mellitus (DM) and diabetic kidney disease (DKD). The variation trend of TMEM72 could promote the progression of CKD in DM remains to be clarified. In this study, we aimed to investigate whether chronic exposure of melamine could promote progression of kidney injury in DM.

**Results:** We conducted two type 2 diabetic animal models, high-fat diet (HFD) induced model in C57BL/6 mice and db/db diabetic mice, with exposure of melamine at the mimic human tolerable daily intake (TDI) levels (2.5, 6.3 and 50 mg/kg body weight/day). Urine albumin-creatinine ratio (uACR) was used to monitor kidney function. We applied Periodic Acid-Schiff (PAS) staining, Masson trichrome staining, TUNEL assay and Western blotting to observe kidney injury, fibrosis, apoptosis and related protein expression.

**Conclusions:** Taken together, these results suggest that chronic melamine exposure may increase risk to accelerate the development of diabetic nephropathy.

**Funding:** Government Support - Non-U.S.
tubes. To investigate the potential cellular pathway that TMEM72 was involved, an immunofluorescence test was performed with TMEM72, LAMP1, Mito-tracker and Calnexin in cultured distal convoluted tube (DCT) epithelial cells. Western blot was used to detect the activity of TMEM72 in HK2 cells following HG treatment.

Results: The concentration of serum TMEM72 was lower down in DM and DKD group when compared to the health control (p<0.001). The expression of TMEM72 also decreased gradually in human kidney tissue of different stage of DKD following the progression of disease. Co-localization of TMEM72 and NKC2C in immunofluorescence staining indicated that TMEM72 was mainly expressed in DCT. Stimulated by different glucose concentration, cell culture study (mouse DCT cell; human kidney-2, HK-2 cell) in vitro showed that TMEM72 was down-regulated as the glucose concentration gradient rised. In immunofluorescence, the co-localization of TMEM72 and LAMP1 suggested that TMEM72 might be involved in lysosomal metabolic pathways and participate in the progression of DKD.

Conclusions: Our current study has revealed that TMEM72 may act as a novel participant in DKD by being involved in the renal tubular injury.

Funding: Government Support - Non-U.S.

PUB090

Firerene in Chinese Patients with Type 2 Diabetes and CKD: A FIDELITY Analysis

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Background: Neprilysin, a high NLR of ≥3.5 was correlated with increased inflammatory states leading to higher morbidity and mortality. In this study, we aimed to evaluate the relationship between the Neprilysin level and the risk of mortality and morbidity in Chinese patients with type 2 diabetes and chronic kidney disease.

Methods: A total of 63 patients were enrolled in this study. All patients were diagnosed with type 2 diabetes mellitus (T2DM) and were randomized 1:1 to finerenone or placebo. Eligible patients had T2D and CKD (urine albumin-to-creatinine ratio [UACR] ≥30–<300 mg/g and estimated glomerular filtration rate [eGFR] 25–90 mL/min/1.73 m², or UACR ≥30–<5000 mg/g and eGFR ≥25 mL/min/1.73 m²), and were on optimized renin-angiotensin system inhibition. Key emergent adverse events and laboratory evaluations (e.g. serum potassium).

Results: Of the 63 patients evaluated, majority (n=39, 61.9%) had a baseline NLR ≥2, or UACR ≥30–<300 mg/g and estimated glomerular filtration rate (eGFR) 25–90 mL/min/1.73 m², or UACR ≥30–<5000 mg/g and eGFR ≥25 mL/min/1.73 m²), and were on optimized renin-angiotensin system inhibition. Key outcomes were a kidney composite (kidney failure, sustained ≥40% eGFR decrease from baseline over ≥4 weeks, or renal death) and a cardiovascular (CV) composite (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). A secondary kidney composite was kidney failure, sustained ≥40% eGFR decrease from baseline over ≥4 weeks, or renal death. Safety outcomes were assessed by treatment-emergent adverse events and laboratory evaluations (e.g. serum potassium).

Results: Finerenone reduced the risk of the primary and secondary kidney composite in the Chinese subgroup (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.38–0.86; p=0.0066 and HR=0.54; 95% CI 0.40–0.74; p=0.0011, respectively) vs placebo, with consistent effects on components such as kidney failure (HR=0.53; 95% CI 0.33–0.86; p=0.0094). The HR of the CV composite was 0.21 (95% CI 0.12–0.37) with finerenone vs placebo, consistent with that in the overall FIDELITY population. Overall safety outcomes were similar between treatment arms. Hyperkalemia leading to treatment discontinuation was low for finerenone (2.6%) and placebo (0.9%); the difference in mean serum potassium increase from baseline for finerenone and placebo was −0.13 mmol/L from month 1 to 20.

Conclusions: Finerenone had cardiorenal benefits and a favorable safety profile in the FIDELITY Chinese subgroup.

Funding: Commercial Support - Bayer AG

PUB091

Association Between Neutrophil-Lymphocyte Ratio (NLR) and Clinical Outcomes Among Filipino Patients with ESRD Secondary to Diabetic Nephropathy on Maintenance Hemodialysis

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Background: Evidence on the usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic biomarker in diabetes patients with chronic kidney disease is still scarce to date. This study aimed to determine the association between NLR and morbidity among Filipino patients with end-stage renal disease (ESRD) secondary to diabetic nephropathy on maintenance hemodialysis.

Methods: This was an observational descriptive, prospective cohort study that evaluated outpatient Filipino citizens aged ≥18 years diagnosed with ESRD secondary to type 2 diabetes mellitus (T2DM). All patients had good compliance to their hemodialysis regimen (i.e., at least twice weekly dialysis within the past 3 months). The patients were divided into two groups according to the baseline NLR value at a cut-off of 3.5 as the high NLR group (NLR ≥3.5) and the low NLR group (<3.5). The cutoff was based on data that a high NLR of ≥3.5 was correlated with increased inflammatory states leading to higher morbidity. Patients were followed up after 6 months, and data on the primary outcome measure of disease occurrence were collected.

Results: Of the 63 patients evaluated, majority (n=39, 61.9%) had a baseline NLR value of <3.5. The high NLR group included 24 (38.1%) patients; among them, 9 developed disease. In the low NLR group (n=39), only 2 patients developed disease. NLR was significantly correlated with clinical disease outcomes (p=0.05).
Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.

++PUB092++
Dapagliflozin in CKD Patients with Diabetes from a Real-World Study
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Background: Diabetes is one of main causes of chronic kidney disease (CKD), and it increases the risk of adverse outcomes including cardiovascular events, end stage renal disease and mortality. Dapagliflozin (DAPA), as a selective sodium glucose cotransporter 2 inhibitor, has been reported to be beneficial for CKD patients with diabetes in previous clinical trials, however, real-world evidence is limited, especially among Chinese population.

Methods: A total of 803 CKD patients with type 2 diabetes were included in China from January 2011 to December 2021. Eligible participants were adults with estimated glomerular filtration rate (eGFR) ≥20 ml/min/1.73m² and 24-hour urinary protein (24h-UP) of 300 to 3500 mg/24h. Both groups received a stable dose of RASi without immunosuppression therapy or >10 mg prednisolone daily. DAPA group received 10 mg DAPA once daily. Propensity score matching was applied to balance the baseline characteristics, including age, sex, eGFR, 24-UP, and hypertension history. The primary outcome was the change in 24-UP from baseline at 6 months. Nonparametric tests were used to compare differences between groups.

Results: Of the 803 patients, 276 were in the DAPA group (mean age 55.6 yrs, male 66.3%, median eGFR 69.2ml/min/1.73m², median 24h-UP 1214.0mg/24h) and 527 in the control group (mean age 57.4 yrs, male 64.9%, median eGFR 72.1 ml/min/1.73m², median 24h-UP 858.0 mg/24h). After 6 months, DAPA significantly reduced 24-UP compared to the control group (-23.0% vs -4.51%, P<0.05). The reduction in uric acid was 11.6% (vs 4.7%) greater in the DAPA group than in the control group at 6 months (-6.78% vs 0.51%, P<0.001). eGFR decreased significantly in the DAPA group compared to the control group at 3 months (-2.50% vs -0.02%, P<0.05), but no significant between-group differences were observed at 6 months (-2.14% vs -1.89%, P=0.90). Changes in glucose and lipid metabolism during the study did not differ significantly between groups.

Conclusions: In CKD patients with type 2 diabetes, dapagliflozin significantly improves proteinuria with short-term eGFR changes as previously reported. The effectiveness of DAPA in reducing uric acid in the real-world experience was observed, while the underlying mechanisms remain to be investigated.

++PUB093++
Congestive Hepatopathy Caused by Cardiorenal Syndrome Causing Severe Elevations
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Introduction: 80 year old female presenting with a TIA and heart failure exacerbation with AKI on CKD III. Patient was started on ionotrope assisted diuretics to prevent further renal failure. She does not respond to the therapy and also develops sepsis from hospital acquired pneumonia and UTI requiring continuous renal replacement therapy, pressors and intubation for further optimization. The severity of her cardio renal syndrome and cardiogenic shock leads her to develop concomittant congestive hepatopathy leading her to develop severe elevations in her urine enzymes to the level to shock liver or ischemic hepatitis which is a unusual finding.

Case Description: 80 year old female presenting with slurred speech and exertional dyspnea. Admitted for TIA with negative workup of stroke. Patient found to be in a heart failure exacerbation. She has a known medical history of heart failure with reduced ejection fraction with an EF of 20-25% secondary to Takotsubo cardiomyopathy and a clean cardiac cath. She has a CTR-D placed. Patient started on dobutamine assisted diuresis due to severe AKI on CKD III with poor urinary output. Transferred to ICU due to acute metabolic encephalopathy secondary to septic and cardiogenic shock requiring intubation for severe HCAP and a E coli urinary infection. She was required to be placed on a bicarbonate infusion and got CIRR. Due to ongoing cardiogenic shock she developed severe congestive hepatopathy with liver enzymes peaking at AST / ALT 700/900. The patient was thought to have liver failure due to severe AKI in her heart failure. Patient also noted to have lupos workup positive. Renal biopsy to rule out SLE nephritis, remarkable for findings of diabetic nephropathy and ATN. Patient’s renal function subsequently improved and she was discharged with improved renal outcomes and resolution of her amniontransferases.

Discussion: The takeawy from this unique case of cardiorenal syndrome is the severity of congestive hepatopathy causing significant elevations in aminerotransferases. It is very unusual to see such elevations unless it is drug induced, autoimmune or ischemia induced which tells us the severity of her heart failure and her perfusion status. The reason why this happened remains a mystery but it is important to know that it can cause significant elevations in the liver enzymes.

++PUB094++
Effect of Volume Removal by Hemodialysis on Elevated N-Terminal Pro-Brain-Type Natriuretic Peptide (NT-proBNP) Level
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Background: N-Terminal pro-brain-type natriuretic peptide (NT-proBNP) is highly sensitive and specific for the diagnosis of congestive heart failure (CHF). Nearly all end-stage kidney disease (ESKD) patients require replacement therapy have an elevated NT-proBNP plasma level. Measurements of NT-proBNP before and after hemodialysis (HD) in patients who are hospitalized with volume expansion is a common practice. The purpose of this study is to determine the clinical value of repeated NT-proBNP measurements in patients with ESKD or acute kidney injury (AKI) requiring HD, and to study the effect of volume removal via HD on NT-proBNP level.

Methods: We conducted a retrospective analysis of patients admitted to two community hospitals over a 3-year period (Jan/2020-Dec/2022). Patients with AKI requiring HD or ESKD were screened if they had an admission diagnosis of volume expansion including acute CHF or pulmonary edema that was verified radiographically and by physical examination. Patients with an admission NT-proBNP level and a repeat level 2 to 12 hours after HD were included. Over the 3-year period, 36 patients with ESKD and 5 patients with AKI requiring HD fulfilled the inclusion criteria.

Results: Volume removal via HD had no impact on NT-proBNP levels in ESKD or AKI patients (ESKD P= 0.7858; AKI P= 0.6903). Our patients had significantly elevated NT-proBNP due to renal dysfunction and volume expansion. The table below summarizes our main findings.

Conclusions: While identifying acute or chronic HD patients with volume expansion and significant elevation in NT-proBNP to intensify their cardiovascular management may be beneficial, measuring NT-proBNP level after a single HD session to document a positive effect of volume removal is of no clinical value. Our data suggest that NT-proBNP is a useful cardiac biomarker for volume expansion and its elevated level predict high cardiovascular mortality and recurrent hospitalizations in acute and chronic HD patients.

++PUB095++
Cardiac Dysrhythmia Characterization by Intradialytic Holter Monitoring in Patients with Chronic ESRD
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Background: Cardiac dysrhythmias are a common complication in patients with end-stage chronic renal failure undergoing hemodialysis. The intradialytic period, during which patients undergo hemodialysis, is particularly vulnerable to development of cardiac dysrhythmias. Intradialytic Holter monitoring is a non-invasive technique that continuously monitors the heart’s electrical activity during hemodialysis. The study aims to characterize the different types and frequencies of cardiac dysrhythmias during hemodialysis using intradialytic Holter monitoring. This information could help improve the management and treatment of cardiac dysrhythmias in patients with end-stage chronic renal disease.

Methods: This research corresponds to a descriptive, observational, cross-sectional, primary source study from October 2020 to January 2021. The analysis was conducted using a form divided into four sections corresponding to demographic data, clinical data, laboratory tests, and Holter study reports. The same happens after the participant’s agreement and signature of the informed consent.

Results: The results showed that 37.5% of the patients had dysrhythmias recorded on a 24-hour Holter, 55% were between 45 and 64 years of age, and the majority was female, represented by 66.7%. Furthermore, although there was a statistically significant relationship between the duration of dialysis sessions and the number of sessions recorded per week, it is evident that 88.9% of the patients whose Holter recorded dysrhythmia attended three times per week. The most frequent dysrhythmias recorded were tachyarrhythmias in 41.6%, of which 44% were ventricular.

Conclusions: Although no statistically significant differences were observed, age, sex, and the number of hemodialysis sessions per week are regarded as the group with a predisposition for the presence of dysrhythmias in patients on hemodialysis therapy.
PUB096

Hyperkalemia Prevalence and Recurrence in Chinese Patients on Hemodialysis: A Prospective Multicenter Cohort Study (PRECEDE-K)

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Background: Hyperkalemia (HK) is a risk factor for cardiac arrhythmia and death in patients with end-stage renal disease (ESRD) on hemodialysis (HD). PRECEDE-K (NCT04799067) was a prospective cohort study that investigated HK burden in Chinese patients on HD.

Methods: Patients aged ≥18 years on HD (2 sessions/week) were consecutively enrolled from 15 centers in China and followed up for 24 weeks. Primary and secondary endpoints were the occurrence and recurrence of HK (serum potassium [k+] >5.0 mmol/L), respectively. Risk factors associated with HK occurrence and recurrence were exploratory endpoints.

Results: A total of 600 patients were enrolled (median age: 55 years; 67% male). Most had adequate dialysis at baseline (65% had urea reduction ratio >65%; 75% had Kt/V >2). Yet, 453 (76%) patients experienced HK (297 [50%] had k+ >5.5 mmol/L and 171 [29%] had k+ >6.0 mmol/L, Figure). At 6 months, 356 (79%) of these 453 patients had HK recurrence; 203 (45%) recurred in 1 month and 300 (66%) in 3 months (Figure). 366 patients were tested in 306 (68%) patients and 36 times in 84 (16%) patients (Figure). Risk factors for HK occurrence were history of HK, female sex, lower dialysis frequency, and longer dialysis vintage. Risk factors for HK recurrence were history of HK, history of diabetes, and lower dialysis frequency.

Conclusions: HK is common in Chinese patients with ESRD despite standard adequate HD. The high frequency of and short time to recurrence allude to the chronic nature of HK. Effective potassium control on non-dialysis days is recommended in patients on HD, especially those with risk factors, for long-term management of chronic HK.

Funding: Commercial Support - AstraZeneca, Clinical Revenue Support, Government Support - Non-U.S.

PUB098

A Cross-Sectional Study on Outcome of Pro-Brain Natriuretic Peptide (PRO BNP) Levels in Patients on Hemodialysis and Peritoneal Dialysis in a Tertiary Care Hospital

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Background: Mean amino-terminal pro-brain natriuretic peptide (NT-proBNP) level has not been studied well in Saudi hemodialysis population and the effect of high flux hemodialysis membrane in comparison to Peritoneal dialysis patients. We aimed to study the significance of NT-pro BNP level in both hemodialysis and peritoneal dialysis settings.

Methods: This cross-sectional study looked at NT proBNP levels in 50 hemodialysis (HD) patients and 50 patients on Peritoneal dialysis (PD) group in November 2022. Patients in both groups were categorized according to age above and below 70 years. Patients on HD or PD with history of ischemic heart disease or valvular heart disease were excluded from the study.

Results: Among PD patients, 12 patients were above 70 years with mean age of 77.1. while PD patients younger than 70 years comprised of mean age of 41.2 years. We found NT-proBNP 26000 pg/ml in Male patients above 70 years and >12500pg/ml in Females respectively. Similarly those with age less than 70 years had an average NT-proBNP of >17000pg/ml and 25000 pg/ml in male and female subjects respectively. In HD population 26 patients were above 70 years with mean age 73.5 and remaining 24 patients were younger than 70 years of age, with mean age of 50.8. We observed the NT-proBNP levels >5000 pg/ml and >640 pg/ml in Male and female subjects doing PD and HD respectively in older (Above 70) age group. While, younger age group (less than 70 years) had NT-proBNP levels >10000 pg/ml and 8500 pg/ml on PD and HD respectively.

We found that on average NT-proBNP levels were significantly higher in peritoneal dialysis patients in comparison to hemodialysis patients. No significant difference was found across either gender in both groups.

Conclusions: We hereby conclude that NT-proBNP levels in peritoneal dialysis patients in older age group without any ischemic heart disease, volume overload is high and low in hemodialysis patients due to membrane adsorption effect.

PUB099

Adaptive Dialysis: A New Way of Care in Post-Open-Heart Patients

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Background: Automated adaptive dialysis (AAD) is a system shown to improve tolerance, adherence, clinical versatility and is the backbone of our in-house dialysis machine. The purpose of this quality improvement project is to showcase the performance of the AAD system in post open heart patients.

Methods: A retrospective-observational, chart review study. Database was queried from January 01, 2016, thru December 31, 2022, to include post open heart patients undergoing dialysis via the AAD system in the post-operative stage. Patients undergoing Coronary Artery Bypass Surgery (CABG) and Aortic Valve Replacement (AVR), Mitral Valve Replacement (MVR) and Tricuspid Valve Replacement (TVR) were included.

Results: A total of 30 patients between 42 and 79 years of age, were treated with the AAD. 73% underwent strict intermittent hemodialysis (IHD) and 27% received a combination therapy (CmT) of either continuous renal replacement therapy, sustained low-efficiency dialysis or slow continuous ultrafiltration. Average body mass index was 28.9 and hundred percentage of patients received mechanical ventilation and vasopressor support during the post operatory stage. Only patients who received HD were included in the main analysis since patients on combination therapy had insufficient data recorded and had significant critical illness. Patient characteristics per type of surgery in the main...
analysis group consisted of 18 patients post CABG, 1 patient post AVR, 2 patients post MVR and 1 patient with combined CABG/AVR. Ninety percentage of the cohort had history of ESRD and intradialytic complications like clotting only occurred in the CmT group (n:3). Average time of vasopressor support in the main analysis group was less than 24hrs. Key performance indicators are shown on Table 1, while dialyse and blood flow rates ranged between 200-300ml/min and 200-300ml/min respectively. System clotting was prevented by frequent saline flushes instead of heparin flushes except on those patients with complications.

**Conclusions:** Treatment adequacy with the AAD system in this subset of patients was a safe intervention with adequate performance indicators.

| Key Performance Indicators | Avg 2.0% SD 1.19<br>UFR (%)<br>UFR on Therapy per Treatment<br>UFR on Therapy per 1.73m²<br>UFR on Therapy per Treatment (n/74)<br>UFR on Therapy per Treatment (n/74)<br>UFR on Therapy per Treatment (n/74) | Avg 1.0% SD 0.67<br>Roxa Therapy per Treatment (n/74)<br>Roxa Therapy per Treatment (n/74)<br>Roxa Therapy per Treatment (n/74) | Avg 3.5% SD 0.41<br>Roxa Therapy per Treatment (n/74)<br>Roxa Therapy per Treatment (n/74)<br>Roxa Therapy per Treatment (n/74) | Avg 2.0% SD 1.19<br>UFR (%)<br>UFR on Therapy per Treatment<br>UFR on Therapy per 1.73m²<br>UFR on Therapy per Treatment (n/74)<br>UFR on Therapy per Treatment (n/74)<br>UFR on Therapy per Treatment (n/74) |

**PUB100**

**Oral Manifestations, Periodontal Disease, and Need for Dental Treatment in Our Hemodialysis Unit**

Isabel Acosta-Ochoa,1 Manuel Tello-Pellitero,2 Armando Coca,3 María Jesús Rollán,1 Sandra Sanz, Paula Arduña, Carlos L. Merizalde Moscoso,1 María Martinez,2 Kenia P. Cobo Camuzano,3 Alicia Mendiluce.4 Hospital Clínico Universitario de Valladolid, Valladolid, Spain; 2University Europea Miguel de Cervantes, Valladolid, Spain.

**Background:** CKD is associated with specific oral signs and symptoms. Periodontal disease (PDD) is very prevalent in HD individuals, in turn it is related to malnutrition, inflammation, and cardiovascular risk. We evaluated the prevalence of oral manifestations, PDD and need for dental interventions in our HD patients.

**Methods:** Cross-sectional study of individuals in a HD unit. We analyzed dental features, described the prevalence of oral manifestations, PDD and need for odontological interventions. A dentist performed the dental examination and assessment suggested the need for and kind of treatment. All included patients signed an informed consent.

**Results:** We included 34 individuals, age 62±15, 57% HD, vintage 48±6-281. 88% showed absence of dental pieces, 62% had periodontal disease. The frequency of oral manifestations were xerostomia 70%, mucosal pallor, whitish tongue, dysgeusia gingival recession (~40%), least frequent bruxism, dental erosion, halitosis, hypersensitivity 6-15% Table1. We found 64% of EPD (manifested as calculi and dental pockets) Table2 and 24% dental caries. The frequency of brushing per day was sometimes 12%, 1x 41%, 2x 32%, 3x 15% Table3. 24% were active smokers Table4. 65% of patients required some type of treatment, the most frequent being periodontal scaling and dental fillings, >40% required repair or a new prosthesis Table5. The frequency of brushing was not positively nor negatively associated with any parameter of PDD or oral signs.

**Conclusions:** We found a high prevalence of PDD in our HD unit, in accordance with international studies. ~65% of patients require some kind of dental intervention or any action on their prostheses. For this reason, we believe that dental evaluation and treatment should be an integral part of the care of patients in HD. Performing these interventions could improve the parameters of nutrition and inflammation and the quality of life of our patients? Prospective and Interventional studies will be needed to answer this question.

**PUB101**

**Prevalence of Amputations in Hemodialysis Patients: Dialysis Program Without Socks**


**Background:** Dialysis patients are at high risk of ischemia and foot ulcers (14.4%) that frequently precede severe complications, including amputations (5.9%), hospitalizations, and mortality. Critical ischemia in this location accounts for 20% of the annual causes of death in hemodialysis, produces pain that is difficult to control and greatly reduces the quality of life of patients associated with amputations in hemodialysis patients, and to assess the evolution after amputation.

**Methods:** Carrying out a survey by email sent by the SEN (Spanish Society of Nephrology) and SOMANE (Madrid Society of Nephrology). Retrospective, cross-sectional, multicenter study. The survey sent to all hemodialysis units nationwide. Answered by 47 Centers. The exclusion criteria were oncological-traumatic amputations.

**Results:** 50% of the Units have more than 70 patients 40% diabetics In most Units only 5% of dialysis patients have ulcers 70% of the centers answer that 5% have minor amputations and 5% have more serious amputations 63% of the centers answer that 5% of the patients have more than one amputation Risk factors for amputation: > 60 years, male, diabetes, smoking, hyperphosphatemia, malnutrition, ischemic heart disease In most Units <10% of amputees have been prosthethized Annual mortality in patients with chronic ischemia is 20%. Most of the Units use some diagnostic measure to screen for ulcers and/or chronic ischemia of lower limbs.

**Conclusions:** Most dialysis units have patients with ulcers in the lower limbs that precede amputations, mortality and dependency. Having amputee patients in the Unit entails reorganization of work and an effort of human and material resources.
Poly sulfone dialyzer allergy in a Patient on Aquadex Hemofiltration
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Introduction: Poly sulfone dialyzer allergy is a cause of intractable hypotension, usually occurring within the first 20 minutes of hemodialysis. The treatment is to change to a dialyzer made from a different material, such as cellulose triacetate. Hemofiltration membranes for the Aquadex system are made of polysulfone. Here we present a case of polysulfone dialyzer allergy in a patient on Aquadex hemofiltration.

Case Description: An 82 y/o man with CHF, complete heart block, DM, dementia and ESRD was admitted to the CCU for MRSA bacteremia with aortic valve endocarditis and pacemaker lead infection. He was treated with Daptomycin and his pacemaker leads were removed. He received hemodialysis via a new tunneled catheter. On subsequent treatments his BP was noted to be soft, the next treatment he did not tolerate ultrafiltration, and then his dialysis had to be stopped after 50 minutes because of hypotension. The patient was started on Aquadex hemofiltration which was complicated by hypotension with SBP drop from 120 to 70 range within 20 minutes. A clinical diagnosis of polysulfone dialyzer allergy was made and the following day hemodialysis was performed using a cellulose triacetate dialysis. The procedure and UF were tolerated without incident. Subsequent treatments were uneventful and the patient eventually recovered and was discharged.

Discussion: This case shows that polysulfone dialyzer allergy can occur with the Aquadex system, making ultrafiltration impossible despite treatment with steroids, H2-antagonist, epinephrine and vasopressor support. Polysulfone dialyzer allergy is difficult to detect in the critically ill and in patients with heart failure who have multiple possible causes of severe hypotension. This case shows that despite a simpler design, dialysis expertise is valuable for patients using hemofiltration systems.

Magnesium in Dialysis: Is Less More?
Nasreen Samad, Cheryl E. Monte, Barry Health NHS Trust, London, United Kingdom.

Background: Lower Mg++ levels are associated with increased risk of cardiovascular events in CKD. Higher dialyse Mg of 1 mmol has shown 22% increase in T50 which indicates a higher potency of the serum to inhibit calcification. Recently published study with Magnesium supplementation in CKD did not show slower progression of vascular calcification despite increase in plasma magnesium. It would be helpful to know if patients are at higher risk of low Magnesium level with standard dialysate magnesium of 0.5 mmol/L (1 mEq/L).

Methods: To know the impact of currently used dialysate magnesium on serum Magnesium level in haemodialysis patients predialysis Mg was measured in February 2020, October 2021, November 2022 and May 2023 on all prevalent and incident patients. Dialysate Magnesium was 0.5 mmol/L (1 mEq/L) in all patients. We also measured serum potassium, PTH and phosphate and reviewed medicine intake as Proton pump inhibitors, Calcineurin inhibitors and phosphate binders.

Results: In the years 2020, 2021, 2022 and 2023. Mg level was measured in 124, 93, 99 and 96 patients respectively. Mg level average and range in mmol was 0.944 (0.5-1.4), 0.977 (0.7-1.7),1.004 (0.6-2.1), 1.003 (0.6-2.2) in those consecutive years. Number of patients with Mg level 0.7 or below was 13 (10.4%),3 (3.2%), 3 (3.0%) and 3 (3.1%) in the respective years.

Conclusions: With the current use of standard dialysate magnesium a small number of patients were found to have low Mg, 22 out of 412 (5.3%) on data for 4 consecutive years during measurement of predialysis magnesium in single dialysis unit. After first measurement of serum Mg1+ of 2.25% of dialysis patient had died within a year of measurement of Mg level of whom more than half died with COVID-19 in 2020 thus it was difficult to ascertain the impact of serum magnesium on their survival. In following years we found less patients with lower magnesium level. Comparatively more patients on Proton Pump Inhibitors PPI or Calcineurin inhibitors CNI had lower Mg 14/22 (63%) but the numbers were too small to come to a definite conclusion. In general we did not find a significant impact of dialysate magnesium of 0.5 mmol to increase the risk of hypomagnesimia. Whether increasing magnesium dialysate to increase serum magnesium level could improve a survival benefit will need to be ascertained by larger and longer term studies. In the mean time standard dialysate magnesium on 0.5 mmol continues to be a safe and acceptable option.

Evolution of Clinical Characteristics and Prognosis of Maintenance Hemodialysis Population: A Single-Center Retrospective Study
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Background: To analyze the trends of clinical characteristics of the maintenance hemodialysis (MHD) population in a single center, and to explore the risk factors affecting the survival of MHD patients.

Methods: An epidemiological survey of MHD was carried out in a center of a tertiary hospital from January 1,2009 to December 31, 2018. The original medical records were checked through the HIS and LIS systems. The follow-up endpoints were death, replacement of renal replacement therapy, and transfer to other centers. The trend of clinical characteristics of this population for ten years was observed, and the risk factors of survival were analyzed using univariate and multivariate COX regression.

Results: A total of 1,509 MHD patients were included. The average age was 63.66±15.21 years old, including 914 males (60.6%) and 595 females (39.4%), and the median vintage of dialysis was 23 months. With the progress of time, the annual number of MHD patients increased from 200 to 915. Diabetic nephropathy has gradually become the primary cause of end stage renal disease. The annual mortality rate decreased from 51/9/1000 person-years to 38.2/1000 person-years, the main cause of death was cardiovascular events, followed by infection. Hospitalization rate was 302/1000 person-years to 405/1000 person-years. The main cause of hospitalization was cardiovascular complications, followed by vascular access-related complications. The COX univariate study indicated that increasing age, DN, hyperphosphatemia, hyperlipidemia, hyperalboimunemia, and central venous catheter were risk factors for death in MHD patients (p < 0.05). The COX multivariate study analyzed that increasing age, DN, and TCC use were still risk factors (p < 0.05).

Conclusions: The prevalence rate of maintenance hemodialysis in our center increased year by year, and the mortality rate decreased year by year. Aging, diabetic nephropathy, and long-term central venous catheter use were independent risk factors for dialysis patient death.

Funding: Government Support - Non-U.S.
**Case Description:** We assessed the level of itching in 11 ESRD patients, using the Worst Itching Intensity Numerical Rating Scale (WI-NRS) before and after the administration of difelikefalin (0.5 mg/kg/dry wt.). We recorded patients’ baseline characteristics, including age, sex, BMI, time on dialysis, dialysis sessions per week, dialysis duration, and continuation of anti-pruritic treatment. We also documented the quantities of any administered antihistamines, gabapentinoids, topical treatments, narcotics, sedatives, and phosphorus binders and CaXP, Kt/V Urea, PTH and K levels before and during the treatment period. Results: Difelikefalin injection significantly reduced the level of itching as measured by WI-NRS scores in 9 out of 11 patients. No serious adverse events were observed, and the known side effects of difelikefalin injection were recorded with consideration to patients’ pre-existing health conditions.

**Discussion:** Our findings suggest that difelikefalin is a safe and effective treatment for CKD-AP in ESRD patients, with no significant adverse effects. However, limitations include relatively small sample size, lack of a control group and short duration of follow-up. Further large scale studies are needed to confirm our results and to determine the optimal dosing and duration of treatment.

**DFK**

**PUB108**

**Association Between Modified Simple Protein-Energy Wasting (PEW) Score and All-Cause Mortality in Patients Receiving Maintenance Hemodialysis in Phramongkutklao Hospital**

**Narongrit Siriwattanuoti, Phramongkutklao Hospital, Bangkok, Thailand**

**Background:** Protein-energy wasting (PEW) is a frequently observed complication that leads to increased mortality in hemodialysis patients. Many nutritional indexes may be correlated with mortality in these patients. However, a multifaceted assessment of PEW by combined objective nutritional parameters inn Thai population has not yet been established.

**Methods:** We conducted a single-centered, analytical retrospective study that included 28 ESRD patients receiving maintenance hemodialysis at Phramongkutklao Hospital from January 2020 to December 2021. We calculated modified simple protein-energy wasting (mPEW) from four parameters: Serum albumin and Creatinine level, normalised protein catabolic rate and body mass index. The cutoff values of the modified simple PEW score components were based on receiver operating characteristics curves determined by the Youden index. The sensitivity, specificity, accuracy of mPEW were calculated by independent t-test.

**Results:** During the 2-year follow-up period, 11 patients died of any cause. The optimal cutoff values of mPEW score to predict mortality in Thai patients is 2, which provided 100% sensitivity, 58.8% specificity and 75% accuracy.

**Conclusions:** The modified simple PEW score is a useful composite indicator of nutritional status that stratified the risk of all-cause mortality in Thai patients undergoing maintenance hemodialysis.

**Funding:** Private Foundation Support, Clinical Revenue Support

**PUB109**

**Severe Thrombocytopenic Purpura in a Patient Undergoing Hemodialysis**

**Shuqin Mei, Shanghai Changzheng Hospital, Shanghai, China**

**Introduction:** Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection has been a global threat since the end of 2019. Although the main clinical manifestation of coronavirus disease 2019 (COVID-19) are respiratory, its range of clinical manifestation is extensive and may include various systems, including hematological disorders, such as lymphopenia, thrombotic events, thrombocytopenia and immune thrombocytopenic purpura (ITP). A recent meta-analysis and systematic review reported that most of the patients that had developed COVID-19-associated ITP were male and elderly patients. The present paper was the first one that aimed to raise awareness of ITP induced by COVID-19 in patients undergoing maintenance hemodialysis.

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

**PUB110**

**Epidemiology and Outcomes of Endophthalmitis in Maintenance Hemodialysis Patients: A 5-Year Experience**

**Srirlakshmi Gaddam,1 Lakshmi Aishwarya Pavuluri,1 Darshini Kattula,1 Shaih S. Heera,1 Jagritee Gupta,1 Venkata A. Yalamanchili,2 Siva K. Vishnubotla,1 Ram Rupara.1 Sri Venkateswara Institute of Medical Sciences, Tirupati, India; 2Dallas Nephrology Associates, Dallas, TX**

**Background:** Endophthalmitis is a severe eye infection leading to severe impairment of vision. We would like to present the epidemiology and clinical features of endophthalmitis in maintenance hemodialysis patients in a tertiary referral centre.

**Methods:** Our institute is a government run tertiary care centre. The department of nephrology conducts more than 72000 dialysis sessions per annum. The demographic features, clinical manifestations, infection focus and visual outcome of the maintenance hemodialysis patients who suffered endophthalmitis from 2017 to April 2023 were recorded.

**Results:** We observed endophthalmitis in nine patients (0.28%) out of 3206 maintenance hemodialysis patients dialyzed at our institute from 2017 to April 2023. The age range was 17 to 74 years (median: 51 years). Most patients presented with ophthalmalgia, periorbital swelling and redness (n = 9, 100%). Blurred vision was reported by seven patients (77.7%) at admission. There were five diabetics and two patients received immunosuppression in the past. The vascular accesses were: untunneled internal jugular catheter in three, arteriovenous fistula in three, tunneled internal jugular catheter in two and arteriovenous graft in one. Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter were the most frequent causes of bacteria. Intravenous and intravitreal injections of antibiotics and vitrectomy were performed in all. Only one patient had final vision of 6/20.

**Conclusions:** This is a large series of patients of endophthalmitis in maintenance hemodialysis patients. Our study showed different pathogen spectrum, different vascular accesses as source of infection and worse visual outcome.

**PUB111**

**Dialysis Disequilibrium Syndrome: A Case of Rapid Overcorrection**

**Alejandro S. Garcia, Kaltrina Sedalui. Bridgeport Hospital, Bridgeport, CT**

**Introduction:** Dialysis disequilibrium syndrome (DDS) is a rare, but potentially life-threatening, complication of hemodialysis (HD). It presents as an assortment of neurologic signs with varying severity. It may result in seizures, coma, and even death. Major risk factors include severe azotemia and metabolic acidosis.

**Case Description:** A 72-year-old male, with no known past medical history, presented with bilateral leg swelling and mild shortness of breath. On presentation he was alert and oriented, examination was remarkable for some asterixis and lower extremity ophthalmalgia, periorbital swelling and redness (n = 9, 100%). Blurred vision was reported by seven patients (77.7%) at admission. There were five diabetics and two patients received immunosuppression in the past. The vascular accesses were: untunneled internal jugular catheter in three, arteriovenous fistula in three, tunneled internal jugular catheter in two and arteriovenous graft in one. Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter were the most frequent causes of bacteria. Intravenous and intravitreal injections of antibiotics and vitrectomy were performed in all. Only one patient had final vision of 6/20.

**Conclusions:** This is a large series of patients of endophthalmitis in maintenance hemodialysis patients. Our study showed different pathogen spectrum, different vascular accesses as source of infection and worse visual outcome.

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

**Underline represents presenting author.**

**1079**
his BUN dropped another 50% and his acidosis was further corrected. Afterwards he developed progressively worsening encephalopathy requiring evaluation for higher level of care. After extensive work up with imaging and laboratory testing for other causes, the diagnosis of DDS was made.

Discussion: DDS is a rare complication of HD occurring secondary to an osmotic gradient that is created by rapid removal of BUN. Other theories include rapid correction of metabolic acidosis and idiogenic osmoles creation. Our case highlights the changes induced by chronic azotemia facilitate the formation of this osmotic gradient. These include increasing aquaporin channels and decreasing urea transporters, which limits the removal of urea even further than its baseline of its normal coefficient of reflection of 0.45 that the urea has (1). Rapid overcorrection of metabolic acidosis, producing a “paradoxical brain acidosis” may also contribute to the genesis of DDS, as this case highlights (2). Management is supportive until homeostasis is restored. Preventative measures include gentle initiation of HD, gradual clearance of urea, and slow correction of acidosis. Adding active osmoles to the dialysate may reduce gradient formation (3).

**PUB112**

**Indications and Complications Associated with Centrifuge-Based Therapeutic Plasma Exchange: A Nephrologist’s Perspective**

David M. Warner, Manish Anand, Prakash S. Gudsoorkar. University of Cincinnati, Cincinnati, OH.

**Background:** Therapeutic Plasma Exchange (TPE) is an extracorporeal treatment modality used to treat certain diseases, many of which are managed by nephrologists. To investigate the indications and safety of TPE, a retrospective review was conducted to identify the indications and complications of TPE.

**Methods:** This is a single center retrospective review of centrifuge based TPE managed by the division of nephrology at a tertiary care academic center from June 2018 to July 2022. A total of 1219 TPE treatments in 145 patients were reviewed.

**Results:** In total, there were 25 diagnostic indications for TPE as outlined in Table 1 with their category of indication as defined by the American Society for Apheresis (ASFA) 2022 guidelines. There were 14 complications associated with TPE which are documented in Figure 1.

**Conclusions:** Most common being antibody-mediated rejection in kidney transplant recipients (20%), autoimmune encephalitis (16%), and Neuromyelitis optica (11%). 21% of procedures were performed for a condition classified as Category III by the ASFA or not classified. Depletion coagulopathy (48%), hypocalcemia (44%), and hypokalemia (37%) were the most common complications. This study exemplifies the utility of having a systematic audit to review the practice patterns of TPE and supports the inclusion of education on TPE management in nephrology training programs.

**Table 1**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ASFA Category</th>
<th># of Patients</th>
<th># of Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR, kidney transplant</td>
<td>i</td>
<td>25</td>
<td>188</td>
</tr>
<tr>
<td>Autoimmune encephalitis</td>
<td>i</td>
<td>23</td>
<td>132</td>
</tr>
<tr>
<td>Myasthenia gravis</td>
<td>i</td>
<td>14</td>
<td>111</td>
</tr>
<tr>
<td>AIPD</td>
<td>i</td>
<td>7</td>
<td>37</td>
</tr>
<tr>
<td>ANCA Vasculitis</td>
<td>i</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>CDP</td>
<td>i</td>
<td>2</td>
<td>206</td>
</tr>
<tr>
<td>Recurrent PSSG, post-transplant</td>
<td></td>
<td>2</td>
<td>119</td>
</tr>
<tr>
<td>Catabasal in APB, TTP</td>
<td>i</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Neuromyelitis optica</td>
<td>II</td>
<td>16</td>
<td>64</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>III</td>
<td>12</td>
<td>65</td>
</tr>
<tr>
<td>TMA, secondary to ELE</td>
<td>II</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td>Hawelknea’s Encephalitis</td>
<td>II</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Lambert-Eaton Syndrome</td>
<td>II</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>ARM, heart failure transplant</td>
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<td>1</td>
<td>51</td>
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<tr>
<td>Panneumoclasia neurologia</td>
<td>II</td>
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<td>35</td>
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<tr>
<td>FIBS</td>
<td>II</td>
<td>4</td>
<td>73</td>
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<tr>
<td>S/P Person Syndrome</td>
<td>III</td>
<td>3</td>
<td>17</td>
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<tr>
<td>Medication overdose</td>
<td>III</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Multiple myeloma</td>
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<tr>
<td>Central Peritoneal Mydralysis</td>
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<td>5</td>
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<tr>
<td>Ovarian</td>
<td>i</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>ARM, pancreas transplant</td>
<td>i</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Beta-accept removal, COVID-19</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Unexplained immune related</td>
<td>i</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

**Key:** ASFA - American Society for Apheresis; Category - I: life threatening, II: severe, III: mild;^

**PUB113**

**Mortality After Gastrointestinal Bleeding Among Dialysis Patients**

Belen Alejos,1 Yue Jiao,2 Melanie Wolf,2 John W. Larkin,2 Anke Winter,1 Sheetal Chandhuri,2 Manuela Stausa-Grabo,1 Len A. Usuvyat,2 Jeffrey L. Hynes,3 Franklin W. Maddux,3 David C. Wheeler,4 Peter Stenvinkel,4 Jürgen Floege,6 On Behalf of the INSPIRE Core Group. 1Fresenius Medical Care, Bad Homburg, Germany; 2Fresenius Medical Care, Waltham, MA; 3Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany; 4University College London, London, United Kingdom; 5Dept of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; 6University Hospital RWTH Aachen, Division of Nephrology and Clinical Immunology, Aachen, Germany.

**Background:** Gastrointestinal bleeding (GIB) is common in patients on chronic dialysis, yet associated outcomes are uncertain. The INSPIRE group used data on a nationally representative sample of dialysis patients to characterize the mortality rate after a GIB episode.

**Methods:** We used data on adult dialysis patients treated at a provider network in the United States during Jan-2018 to Mar-2021 who had ≥1 GIB episode. GIB episodes were identified from ICD diagnosis codes recorded as a comorbid condition during dialysis care, or as a discharge reason for hospitalization (Zhao et al., AHRQ 2006). Crude mortality rate was calculated considering death anytime, or 365 days, after the first GIB.

**Results:** Among a population of 405,530 patients, 31,084 (7.7%) had ≥1 GIB episode. Mortality rate any time after the first GIB was 43.7% (n=13,573; Figure 1A). Mortality rate after the first GIB comorbidity (40.1%, n=2,435/6,068) was slightly lower than after the first GIB hospitalization (44.5%, n=11,138/25,016). Mortality rate increased with older age and appeared to be highest among patients with an unknown race, followed by a white race (42.3%; Figure 1B). Limiting the analysis to the 365 days after the first GIB, mortality rate was 32.2% after any GIB, 19.2% after a GIB comorbidity, and 36.0% after a GIB hospitalization.

**Conclusions:** Mortality rate after a GIB is high in dialysis patients, with 30% dying within a year and 40% dying anytime during follow-up. Mortality rates were higher after GIB hospitalization versus comorbidity, albeit exceedingly high in both cases. Further analyses are needed and should consider adjustments for age, race, and modality, and comparison to patients who never had a GIB.

**Funding:** Commercial Support - Fresenius Medical Care
Exploring the Management of CKD-Associated Pruritus in Routine Haemodialysis Practice: A Qualitative Content Analysis
Namrata Joshi,1 James Burton,1,2 James Medcalf,1,2 Katherine L. Hull,1,2
1University of Leicester College of Life Sciences, Leicester, United Kingdom; 2University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; 3University of Leicester, Leicester, United Kingdom.

Methods: In a university affiliated dialysis center, a retrospective cohort of ESRD patients with CKD-aP was identified. Baseline data for at least 3 months prior to the cohort was collected on all patients. Patients with previous pulmonary embolism, collagen vascular disease, obstructive sleep apnea, chronic obstructive pulmonary disease (COPD), severe mitral or aortic valve diseases, liver failure and heart failure were excluded from the study. A total of 47 patients were included in the study. E奇妙ocoagrhaphy, C3 and C4, CBC and electrolyte parameters and B-type natriuretic peptide (BNP) and proximal and distal AVF in PH group and and non-PH group were examined and their correlation with PASP (Pulmonary arterial systolic pressure) were analyzed. Univariate and adjusted logistic regression analysis was performed to identify independent factors with PH.

Results: Following adjustments in the regression analysis, internal diameters of the left atrium, right atrium, and LVEF were independently associated with PH. There was a positive correlation between access blood flow and PASP. PASP in patients with proximal AVF was significantly higher compared with those with distal AVF. The only laboratory parameter associated was PH was B-type natriuretic peptide (BNP).

Conclusions: PH has a high incidence in ESRD patients under maintenance hemodialysis. The higher level of inflammatory marker BNP suggests a microinflammatory state as an independent risk factor for PH. Left and right atria diameter and LVEF were independently associated with PH. PASP of patients with proximal AVF was significantly higher compared with those with distal AVF. This study found differences in HD-related factors between the groups with and without PH.

Acute Hemodialysis Rapidly Reverses Cephalin Neurotoxicity
Umair Khan, Sana Fatima, Ann Hinkley, Marat Abdullin, Spencer Hodgins, Gregory L. Braden. University of Massachusetts Chan Medical School Baystate Regional Campus, Springfield, MA.

Introduction: Cefepime-induced neurotoxicity (CIN) is a rare but potentially serious adverse event thought to be due to alterations in γ-aminobutyric acid (GABA) neurotransmission, neurotoxic metabolites, & impaired renal function. S. Lee J of Neurosurgery case Vol 12; 2022. CIN cases presented with atypical symptoms such as confusion and delirium to more severe symptoms such as seizures and encephalopathy. The best treatment for CIN may be renal replacement therapy (RRT).

Case Description: Case 1 A 65-year-old male with a history of ESRD on HD, and gram-negative bacteremia due to AV graft infection on cefepime (2gm post HD), developed obtundation, somnolence and unresponsiveness. Entire work for metabolic encephalopathy was negative. Presumed diagnosis of CIN was made and emergent HD resulted in complete resolution of symptoms within 2.5 hours of dialysis. Case 2 An 85-year-old woman with ESRD and pseudomonas bacteremia on cefepime (2gm post HD), was admitted for myoclonus, somnolence and obtundation. Encephalopathy work up was negative. An electroencephalograms showed findings consistent with non-convulsive status epilepticus (NCSE). She was started on anti-epileptics and benzodiazepine, however with minimal improvement. NCSE was presumed due to cefepine neurotoxicity and patient underwent emergent HD with improvement in 3 hours of dialysis. A repeat EEG at 6 hour post HD showed resolution of NCSE.

Discussion: CIN should always be suspected in patients receiving high dose cefepime in the setting of renal failure and encephalopathy. Treatment for CIN primarily involves drug ceasation and support. However RRT remains a curative intervention for severe CIN symptoms (seizures, encephalopathy). Hemodialysis removes cefepime from blood rapidly and hastens recovery, especially in life-threatening situations. A single 3-hour HD session efficiently removes 70% - 80% of a given dose (S. Lee J of Neurosurgery case Vol 12; 2022). Clinicians should maintain a high index of suspicion in individuals receiving cefepime with diminished renal function. Our cases show that acute hemodialysis effectively reverses CIN. With this we also propose the recommendation for weight based dosing for cefepime to reduce risk of CIN.
liver rejection, one patient with transverse myelitis, one with multiple sclerosis and one with Guillain-Barré syndrome, 56% presented acute renal failure, of these 77% required renal supportive therapy. Regarding the prescription, all were performed by membrane filtration (Prismaflex 2000 filter), with replacement fluid with 3% albumin, with a replacement volume of 1.5 in relation to the patient’s plasma. Among the complications, the most frequent was hypocalcemia. As outcomes we found that 62% presented complete clinical response.

**Conclusions:** We found in plasma exchange therapy a safe and effective tool, with main benefit in alveolar hemorrhage and acute inflammatory demyelizing disease since they presented 100% recovery, no favorable response was found in liver disease, among the most serious complications were the infectious processes. The prognosis was good in patients who received plasma exchange.

**Score Used for Ultrafiltration Titration in a Patient with Fluid Overload**

**Introduction:** The incidence of End Stage Renal Disease (ESRD) is high, with Diabetes Mellitus and Hypertension as the leading causes. Statistics showed that it is the seventh leading cause of death among Filipinos with a 10 to 15 percent increase per year and more than 5,000 on renal replacement therapy. ESRD patients on hemodialysis account for 5%-7% of health care expenditures in developed countries. In this study, we aim to determine the factors influencing emergency department (ED) visits among patients with ESRD on maintenance hemodialysis.

**Methods:** This prospective study included the following: >18 years old and diagnosed ESRD patients on Maintenance hemodialysis.

**Results:** There were 156 patients included; the mean age was 48.42±14.06, most were males (51.93%) and from Davao City, and have their maintenance hemodialysis in a non-hospital based institution (66.6%). Outcome of this study showed that admission rates were at 87.17%. Odds ratio showed that those that are located outside of Davao city (OR=1.685, P=0.471) and those with Economic status Class D (OR=1.914, P=0.573) got the highest risk associated for admission. For the comorbidities, strongest factor is the presence of Diabetes (OR=5.059, P=0.085) and Hypertension (OR=4.972, P=0.099) and number of resident physician visit of at least a year (OR=2.809, P=0.734) and nephrologists visit of more than eight in a year (OR=1.025, P=0.590) also showed to be a risk factor.

**Conclusions:** Overall, among the predictors, the strongest risk factors associated with increased risk of admission are patient related factors. These include those that are not from Davao City, Class D socio economic status, comorbidities such as diabetes, hypertension, and congestive heart failure, and lastly nephrologists visit > 8/year and resident physician visit at least 1/year were all identified to have an increased risk for admission. Considering those risk factors, this study showed that admission rates were high and none resulted to death.

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**Table 1: Demographic characteristics**

**Point-of-Care Ultrasound (POCUS) Venous Excess Ultrasound (VExUS)**

**Introduction:** The efficacy of triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) and non-high-density lipoprotein cholesterol/ high-density lipoprotein cholesterol (non-HDL-C/HDL-C) ratios had been demonstrated as predictor of adverse cardiovascular events and mortality predictors on healthy patients. However, limited studies have been performed to evaluate the efficacy of TG/HDL-C and non-HDL-C/ HDL-C ratios as mortality predictors in hemodialysis patients.

**Methods:** A longitudinal, retrospective, case-control study was developed. A total of 386 patients with treatment of end stage kidney disease on hemodialysis therapy in Hemodialysis Unit of National Medical Center XXI Century in Davao City were enrolled. The medical records, albumin levels, calcium, hemoglobin, para athroid hormone (PTH), total cholesterol, HDL-C, LDL-C, triglyceride, TG/HDL-C and non-HDL-C/HDL-C were registered. The odds ratio was calculated using chi-square and student’s t-test, considering a > 0.05 as a statistically significant value. The prognostic values were accessed by univariate and multivariate COX regression analysis.

**Results:** A total of 386 patients were enrolled. They were distributed as 288 control patients (living) and 98 case patients (dead). The multivariate Cox regression analysis showed that patients over 60 years old (2.19, CI 95%, 1.52-3.17 p <0.001), and a TG/ HDL-C index >3.29 were strongly correlated with increased risk of death (1.648, CI 95%, 1.029-2.638, p =0.038). In contrast, the treatment of dyslipidemia was associated with reduction on the risk of death (0.298, CI 95%, 0.160-0.553, p <0.001).

**Conclusions:** The TG/HDL-C ratio have potential as predictor of mortality in hemodialysis patients. The non-HDL-C/HDL-C ratio failed as prognostic tool, with no statistically significant results in the analysis.
PUB122
Prevalence of Sarcopenia in a UK Haemodialysis Population
Emma L. Watson, Daniel S. March, Matthew Graham-Brown, James Burton.
University of Leicester, Leicester, United Kingdom.

Background: Sarcopenia is a characterised by a loss of muscle wasting, reduced muscle strength and low physical performance. Although often associated with ageing, it is now recognised as a complication of other long term health conditions and associated with worse clinical outcomes including poor quality of life, higher hospitalisation rates and increased mortality. Sarcopenia is cited as a frequent complication of CKD, especially common in people with more advanced disease, but the true prevalence of sarcopenia is unknown. The aim of the study was to determine prevalence of ‘confirmed’ and ‘severe’ sarcopenia in a cohort of UK haemodialysis patients.

Methods: This is a secondary analysis of the CYCLE-HD study cohort, which was a randomised controlled trial assessing the effects of a 6-month intradialytic cycling intervention on cardiovascular health. Presence of sarcopenia was determined using the criteria established by the European Working Group of Sarcopenia in Old People (EWOP) definition. Sit to stand was used to determine muscle strength, fat free mass index was used to determine muscle mass and the short physical performance battery to determine physical function. Individual were classified as either having no evidence of sarcopenia, probable sarcopenia, confirmed sarcopenia, or severe sarcopenia based on the specified cut-offs.

Results: 117 patients (56 ±15 years, 82 [78%] male) were included in the analysis. n=12 patients had probable sarcopenia (10%), n=46 had confirmed sarcopenia (39%) and n=19 (15%) had severe sarcopenia, demonstrating that 63% of our population had some degree of sarcopenia.

Conclusions: The prevalence of sarcopenia that we report here is high. Given the association with poor outcomes and reduced quality of life, it is important to be able to identify patients with, or at risk of developing sarcopenia to be able to implement effective treatment strategies. Unfortunately, the process of diagnosing this disease is multi-factorial and requires the use of tests that can be expensive and require training. This means that patients are rarely screened, and their sarcopenia status is not recorded. Furthermore, there are currently so validated treatments for sarcopenia. Given the high prevalence in our end-stage renal failure population, there is a clear an urgent need for both better detection and treatment strategies.

PUB123
Improving Transition onto Haemodialysis: A Novel Trainee-Led Clinic
Joseph Cairns, Jennifer Widgerdy, Clare I. Castledine, University Hospitals Sussex NHS Foundation Trust, Brighton, United Kingdom; 2Brighton and Sussex Medical School, Brighton, United Kingdom.

Background: Starting haemodialysis (HD) is a precarious time with high mortality and worse outcomes in unplanned starts. An audit of our unit demonstrated median time to first consultant clinic review after HD start was 51 days. Two patients died before review and there were 31 emergency admissions within 60 days of HD start. Running an HD unit is in the UK training curriculum. A 2018 survey of nephrology trainees revealed only 40% within 2 years of completion felt “somewhat/very confident to run an HD unit”.

Methods: A trainee led clinic with 1 hour slots 2-3 weeks following in or outpatient HD start was co-designed with patients and the renal MDT. Consultations focused on background, route onto HD, modality choice, vascular access, transplant prospect, medication review, HD adequacy and fluid status exam. Pre-specified data were collected from hospital records and compared with patients starting HD prior to the clinic start using Mann Whitney U tests.

Results: Between Nov 2022 and May 2023 all patients commencing HD (n=47) were seen in the clinic. Patient characteristics (age, gender, ESKD aetiology), route onto HD, modality choice, vascular access, transplant prospect, medication review, HD adequacy and fluid status exam. Pre-specified data were collected from hospital records and compared with patients starting HD prior to the clinic start using Mann Whitney U tests.

Conclusions: Earlier formal medical review of patients improved time to target weight review, earlier opportunities for referrals to the wider MDT and earlier tailoring of immunosuppression and stop of medications no longer indicated. Trainees gained experience managing HD patients outside a pager-based, trouble-shooting setting. Future data collection is ongoing to explore reduction in hospital admissions and improvements in trainee confidence in managing HD patients.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
system. Our objective was to compare lung ultrasound (LUS), bioimpedance analysis (BIA) and physical examination (PE) in volume assessment status in HD patients.

**Methods:** This is a unicentric, prospective, longitudinal descriptive study. We evaluated volume status by LUS, BIA and PE after the long interdialytic period, predialysis and postdialysis. Data regarding demographics, clinical information, lab tests and complications were reviewed.

**Results:** 9 patients (77.7% male) were included with an average 37±15 months on HD, median age 65±13 years old. Residual renal function was present in 44% of them (> 400 ml only in one), urea-creatinine mean clearance was 3.2±6.6 ml/min, 1.73±2 and 89% had an arterio-venous fistula. Arterial hypertension was present in 78%, diabetes in 33%, ischaemic heart disease in 33%, reduced left ventricle ejection fraction in 22% (transthoracic heart ultrasound ≤6 months) and previous stroke in 22%. Predialysis: 33% showed volume overload signs on PE. Lab test (average): Hemoglobin 11.0±0.6 g/dL, urea 159.4±39.8 mg/dL, serum sodium: 139.9±1.5 mEq/l and serum potassium: 5.0±0.6 mEq/L. BIA: 2.0±1.6 L mean volume overload. LUS: mean Frassi Score was 1.7±1.0 (normal = 0). Postdialysis: After a mean ultraltrallfication of 3.1±1.0 L (which represents 43.±1.1% of the patients’ dry weight) with a sodium conductivity of 139.9±1.0 mEq/L, only 2 patients presented transitory intradialytic hypotension. These 2 patients were the ones that presented higher number of B lines in LUS, with no correlation with BIA. 0% showed volume overload signs on PE. Mean Frassi Score was reduced to 0.7±0.7. No dry weight adjustments were needed.

**Conclusions:** PE showed poor sensitivity for volume status in these patients. LUS was a better predictor of intradialytic hypotension than BIA/PE and constitutes a useful, cheap, innocuous and readily available tool to use in HD patients.

**PUB126**

Skin Biopsy (SB) in Calciphylaxis: A Must?

Victor Maite Sosa Barrios,1 Mario Carlos Gómez González,1,2 '*', Mario Carlos Gómez González,1,2,3 Universidade Federal Fluminense, Niterói, Brazil; 2Universidade de São Paulo, São Paulo, Brazil; 3Hospital Universitario Ramon y Cajal, Madrid, Spain; 4Universidad de Alcalá, Alcalá de Henares, Spain.

**Background:** Calciphylaxis is defined by calcification of cutaneous small blood vessels, resulting in ischemic necrotic lesions. It’s associated with high mortality, being more common in dialysis patients. Although its diagnosis is mainly clinical, SB the gold standard. However, it has limited sensitivity and is associated with complications such as infection. Imaging tests have been suggested as an alternative diagnostic method, without great success.

**Methods:** Patients with calciphylaxis by January 2001-February 2023 were included. We evaluated the performance of SB, SB timing, its diagnostic accuracy and complications.

**Results:** 25 patients were diagnosed, 48% males, mean age of 63.7±14.2 years (range 31-87, median 68). 12 were on hemodialysis, 8 on peritoneal dialysis, 3 were transplanted with functioning grafts and 2 were pre-dialyzed. Dermatologists performed 21 SB: 18 first biopsies and 3 rebiopsies (one patient underwent 2 initial biopsies at the same time). The mean time from symptoms onset to SB was 23.8±16.5 days (median 20). In 8 patients, diagnosis was clinical based on characteristic lesions and risk factors. 17 SB were performed on the lower extremities, 3 on upper extremities and 1 on the abdomen. 76.2% (16) were punch biopsies and 5 were deep spindle-shaped. From first biopsies, 10 (55.5%) were diagnostic, as were the 3 rebiopsies, giving an 61.9% overall diagnostic yield. Time to biopsy was longer in cases where the initial SB was diagnostic (25 vs 22.14 days). All post-SB lesions required wound care, along with calciphylaxis ulcers. Topical sodium thiosulphate, with or without intravenous administration, was used in 4 patients and surgical debridement was performed in 1 patient. Mean wound treatment time was 16.41±13.56 weeks (median 12.14), which was longer in patients with a favorable outcome compared to those who died (21.28 vs 8.84 weeks, p=0.051). Twelve patients developed infectious complications in calciphylaxis lesions (48%), with 8 of them having undergone previous SB (47%). One-year survival rate was 47.8%.

**Conclusions:** SB is the confirmatory test for calciphylaxis, although it can be inconclusive and associated with complications. Further research is needed to expand our knowledge on the usefulness of imaging techniques, particularly ultrasound considering its availability.

**PUB127**

Low Parathyroid Hormone (PTH) Is a Risk Factor for Mortality in Incident Patients on Hemodialysis

Hugo B. de Aquino,1 Maria Eugenia F. Canziani,1 Ana Beatriz L. Barra,1 Jorge P. Strogoff-de-Matos,2 Maria Dalboni,1 Rosa M. Moyaes,2 Rosilene M. Elias.1,2,3,4, 'Universidade Nove de Julho, Sao Paulo, Brazil; 'Universidade Federal de Sao Paulo, Sao Paulo, Brazil; 'Universidade Federal Fluminense, Niteroi, Brazil; 'Universidade de Sao Paulo, Sao Paulo, Brazil.

**Background:** CKD-MBD is a major complication in patients on hemodialysis, contributing to high mortality. We evaluated the role of PTH as a risk factor for mortality in a large cohort of incident patients on hemodialysis.

**Methods:** 4,317 individuals starting therapy between February 1, 2012, and December 31, 2016, were included. Data evaluated included age, sex, diabetes mellitus, body mass index, predialysis systolic blood pressure (Public Health System), predialysis plaques of first dialysis (clinic or hospital), calcium, phosphorus, albumin, urea, alkaline phosphatase and PTH. Patients were divided into 3 groups according to PTH values (<150, 150-600 and >600 pg/mL). Survival analysis was performed using competing risk (kidney transplantation) and causes for diagnosis of dialysis withdrawal (clinical failure, change of method or recovery of renal function).

**Results:** The mean age was 58 ± 16 years, 58.4% men, 43.7% white, 39.7% with diabetes mellitus and 70.9% had their first dialysis session in a hospital, and 59% were financed by the Unified Health System. Median PTH levels were 252 (118-479) pg/mL. The percentage of patients with PTH <150, 150-600 and >600 pg/mL was 32%, 51% and 17%, respectively. Patients with PTH <150 pg/mL were significantly older, mostly white, 47.5% financed by Public Health System, 74% started dialysis in a hospital, had lower BMI, albumin, urea, potassium, phosphorus and alkaline phosphatase, and higher calcium. There were 1,613 deaths in 5 years, of which 423 occurred in the first year. Competing risk analysis revealed that PTH < 150pg/mL was an independent risk factor for mortality (HR 1.14, 95% CI 1.0-1.30, p = 0.044) in a multiple-adjusted model in five years but not in a 1-year follow-up (p = 0.418).

**Conclusions:** One-third of patients initiate dialysis PTH <150pg/mL, a population characterized by a lack of private health insurance and laboratory markers suggesting malnutrition. Public health policies are needed to minimize the risk of mortality.

**PUB128**

Holistic Design Philosophy in Dialysis

Clayton Poppe, Diality, Irvine, CA.

**Background:** Medical care is increasingly being pushed to new settings. As dialysis treatments are increasingly conducted at home, in skilled nursing facilities and transitional care units, the requirements on dialysis machines are changing to meet these needs. A more holistic design philosophy is required to balance sometimes competing or conflicting requirements.

**Methods:** The creation of a design framework starts with a list of the important categories of information. These categories structure information around the challenges we face during product design. For example, how do we think about the tradeoffs between ease of use and flexibility in therapy? The broad categories we capture the main design elements we are trying to optimize. Within the broader categories there are more specific attributes that make up the major user needs the final device should embody. Once we have created the categories, we organize them in a way that helps highlight how the categories relate to each other; are they opposed or do the overlap? This emerging framework is then used to describe the problems we face and focus ideation on those difficult places where our priorities conflict with each other.

**Results:** A simple version of the framework that we developed is outlined in Figure 1. The benefit of this framework was to focus early design exploration on the areas that were most in conflict with each other. An iterative process of design, build, test was able to better show the tradeoffs we would need to make to balance our priorities and optimize the design. We know that we can’t create something that is all things to all people, so properly exposing and evaluating the tradeoffs between desired attributes allows for a design the holistically meets our requirements.

**Conclusions:** A framework for understanding conflicting design elements and guiding design at a high level is the best way to balance the many needs and requirements of a complex device.
short acting ESAs with a longer acting agents provide extended time in circulation to allow the drug to bind to erythropoietin receptors, IV administration of agents with long serum half-life are better choice than Epoetin Alfa.  

Case Description: This is a prospective comparative 3 month study on random 16 adult CKD 5D HD patients, treated by Darbepoetin alfa, Epoetin beta (long-acting ESA) & Epoetin alfa (Short acting ESA) weekly to avoid having the HB concentration fall below (9.0 g/l) were included in this study, average age 58.4 (55-85y), 70.5% male. Etiology of ESRD was DM in 70%, 60% are Anemic. The serum concentration time profile of medication Aranesp (Darbepoetin alfa) following IV route in CRF patients receiving dialysis was biphasic with a mean terminal half-life of 21 hours which was approx. 3-fold longer than that of Epoetin alfa. Another eg. of Mircera – Epoetin Beta, which has long serum half-life of approx. 5.5 days. The preliminary results of treating anemia by Darbepoetin alfa & Epoetin Beta vs Epoetin alfa via IV route in a special cohort of HD patients shown in Graph 1 & 2.  

Discussion: This short study showed, Darbepoetin alfa & Epoetin Beta with long serum half-life via IV route is more efficient in the treatment of anemia than Epoetin alfa thereby eliminating the need for Subcutaneous administration of the drug or increased dose requirement of the medication.

PUB131  
Survey of Peritoneal Dialysis Patients’ Challenges and Experiences During the COVID-19 Pandemic: A Multicenter Study in the United States  
Farah Afifara,1 Dale A. Lee,2 Megan E. Lacovara,3 Tarun Kapoor,4 Rebecca K. Seshasai,5 Shweta Bansal,2 Shuchita Sharma,2 Jaime Urribarri,1 Carol E. Smilyan,3 The Johns Hopkins University School of Medicine, Baltimore, MD; 4Icahn School of Medicine at Mount Sinai, New York, NY; 5University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; 6Vanderbilt University Medical Center, Nashville, TN; 7The University of Texas Health Science Center at San Antonio, San Antonio, TX.  

Background: During the COVID-19 pandemic adjustments were made to peritoneal dialysis (PD) practices in the outpatient units. These unilateral decisions were made by dialysis providers, clinical staff, and governments. The patient perspective regarding these changes during the pandemic has not been explored. We sought to elicit patients’ experiences and perceptions of the challenges they faced, institutional adjustments, as well as their mental health during the height of the COVID-19 pandemic in the United States.  

Methods: We conducted a cross-sectional survey of PD patients across four home dialysis units affiliated with four large academic centers who were on PD between March 2020 and March 2021.  

Results: 98 participants completed the survey across the 4 outpatient PD clinics. Most PD patients did not have to change their home accommodations during the pandemic or have issues getting their dialysis supplies and medications delivered. Most patients felt comfortable coming to the dialysis unit if they needed to during the pandemic. The majority of patients felt supported by their dialysis staff during the peak of the COVID-19 and had modified HQH-2 and GAD-2 scores not consistent with depression or anxiety. Less than 10% of patients considered changing their dialysis modality.  

Conclusions: The adjustments made by the dialysis units during the peak of the pandemic were effective in maneuvering the challenges facing our patients during the COVID-19 pandemic, while providing high quality medical care.

PUB132  
Human Factors Testing of the Quanta Dialysis System for Self-Care Hemodialysis in the United States  
Kathryn Compton,1 Michele Gazella,1 Kelley L. Gorbe,1 Reid Whitlock,2 Lisa Bismarck,1 Paul Komenda,1 Quanta Dialysis Technologies Ltd, Alcester, United Kingdom; 2Seven Oaks General Hospital, Winnipeg, MB, Canada.  

Background: Most hemodialysis (HD) treatments are delivered by healthcare professionals within a facility (in-center HD) but HD is increasingly performed at home via self-care. Uptake of home hemodialysis (HHHD) in the United States (US) remains low despite potential improvements in quality of life, health outcomes and cost savings compared to in-center HD. This may be because patients fear they are unable to manage complex treatments at home. With this in mind, the Quanta™ Dialysis System (Quanta Dialysis System) was designed to be more user-friendly. Human factors testing demonstrated the usability of the Quanta Dialysis System in the United Kingdom but has yet to be validated in a US cohort. Using a human factors testing process, we sought to assess how two lay user groups, patients with kidney failure and caregivers, used the Quanta Dialysis System within a representative, simulated use environment in the US.  

Methods: We recruited patients with kidney failure and caregivers from a dialysis center in California between June and November 2022. Adults who were a patient on dialysis, or a caregiver for a patient on dialysis, within the last 4 years (including the present) were eligible. Participants trained on the Quanta Dialysis System for 4-5 sessions with a Qualified Nurse Trainer followed by a competency sign off session. After a 48-hour decay period, those deemed competent proceeded to 2 test sessions to perform tasks independently. During testing, independent human factors moderators scored patient performance on 11 critical tasks required to effectively set up, operate, and shut down the Quanta Dialysis System. We assessed the number of participants who passed each task.  

Results: A total of 31 individuals (16 patients, 15 caregivers) participated. The mean age was 49 years and 16 (51.6%) participants were female. Of the 16 patients, 9 (56.3%) were from in-center HD. There were 7,200 tasks were tested across all participants. Of these, 96.4% were completed without difficulty, error or assistance.  

Conclusions: The Quanta Dialysis System was easy to use after a small number of training sessions and a 48-hour decay period. These results indicate the Quanta Dialysis System has demonstrated a high level of usability in the US and may help improve HHHD penetration by using a state of the art, compact, easy to use device.  

Funding: Commercial Support - Quanta Dialysis Technologies

PUB133  
Low Albumin May Be a Predictor of Mortality in Patients Transferred from Peritoneal Dialysis to Haemodialysis  
Pranesh Jain, Hari Dukka, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom.  

Background: Peritoneal dialysis(PD) is a preferred modality for many patients needing dialysis treatment. Most patients on PD either get transplanted, switch to haemodialysis(HD) or die. We did a retrospective, observational study to ascertain the outcomes in patients transferred from PD to HD over a 5-year period and determine variables which may predict poor outcomes.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only  
Underline represents presenting author.
Methods: Electronic data base was used to obtain data for all patients transferred from PD to HD from 2014-2018. Variables noted were gender, serum albumin, reason for transfer, PD vintage, whether the transfer was expected (commencement of Haemodialysis using arterio venous fistula), as well as Stoke co-morbidity index score(SCI) at the time of transfer. Observed events were infection(pneumonia, cellulitis, line sepsis, tunnel infection or foot infection), morbidity due to vascular disease(peripheral vascular disease, cardiovascular or cerebrovascular accidents) and mortality, within one year of transfer to HD. COX regression analysis was used to determine the predictor value for each of the variables for these events.

Results: 95 patients (63 male/32 Female) were transferred from PD to HD in the study period. The mean age was 57.03 +/- 14.22 years, mean serum albumin 24.41 +/- 6.64 g/dl, mean PD vintage 1.55 +/- 1.95 years, mean SCI 1.05 +/- 0.63. The events noted within one year of transfer from PD to HD were death(n=11), vascular events(n=28), infection(n=44). The reasons for switch from PD to HD were infection(62.4%), mechanical causes(12.9%), inadequate dialysis(9.8%), patient's choice(8.6%) and not coping on PD(6.5%).32.3% transfers were expected. COX regression analysis (Table 1) indicated low albumin was better predictor of mortality post transfer to HD within 1 year of transfer. None of the variables were statistically significant in predicting cardiovascular morbidity or infections.

Conclusions: Patients with low albumin on PD may have adverse outcomes, when transferred to HD. Further studies with larger patient numbers are needed to determine outcomes.

Cox regression analysis- predictors for mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>0.91 (0.85-0.96)</td>
<td>0.006</td>
</tr>
<tr>
<td>Stroke co-morbidity score</td>
<td>0.56</td>
<td>0.063</td>
</tr>
<tr>
<td>PD Vintage(years)</td>
<td>1.06</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Table 1: Comparing Scores Between Hemodialysis and Peritoneal Dialysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HD (n=80)</th>
<th>PD (n=34)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemodialysis yrs</td>
<td>5.9</td>
<td>7.0</td>
<td>0.062</td>
</tr>
<tr>
<td>Peritoneal Dialysis yrs</td>
<td>5.9</td>
<td>7.0</td>
<td>0.062</td>
</tr>
<tr>
<td>ESRD</td>
<td>25 (30.3%)</td>
<td>42 (61.1%)</td>
<td>0.067</td>
</tr>
<tr>
<td>Reason for kidney disease</td>
<td>66.9% (1.32)</td>
<td>75 (51.6%)</td>
<td>0.162</td>
</tr>
<tr>
<td>SF 12: Physical Component #</td>
<td>88 (52.07+/-0.02)</td>
<td>88 (52.07+/-0.02)</td>
<td>0.730</td>
</tr>
<tr>
<td>SF 12: Mental Component #</td>
<td>88 (52.07+/-0.02)</td>
<td>88 (52.07+/-0.02)</td>
<td>0.730</td>
</tr>
</tbody>
</table>

* Differences in scores were examined using t-test for normal distribution and Mann-Whitney U test for non-normal distribution

PUB134

Who Has A Better Kidney-Related Quality of Life: Peritoneal Dialysis or Hemodialysis Patients? A Cross-Sectional Study from Saudi Arabia

Mohammed Alshehri,1 Abdullah H. Alshehri,2 Khaled M. Asiri,3 Mohamed Q. Alshahab,1 Feras M. Alqahtani,1 Omar A. Asiri.4 King Khalid University College of Medicine, Abha, Saudi Arabia; Saudi Arabia Ministry of Health, Abha, Saudi Arabia.

Background: ESKD substantially impacts different aspects of patients’ lives, including mental and physical health and overall quality of life. The aim of our study is to assess the quality of life (Qol) and the associated predictors in ESKD Saudi Arabian patients receiving either hemodialysis (HD) or peritoneal dialysis (PD). Saudi Ministry of health (MOH) is advancing dialysis care in the country with more focus on patients’ satisfaction and Qol. However, the data regarding Qol in Saudi Arabian dialysis patients is limited.

Methods: A cross sectional study was carried out using Kidney Disease Quality of Life scale (KDQOL-S) to assess the Qol. We disturbed a validated formal arabic version of the questionnaire. Patients older than 18-year-old and attending dialysis clinics in Aseer region, Saudi Arabia, were invited to participate in the study.

Results: A total of 152 responses were analyzed, which were separated into two primary groups: the HD group (98 patients) and the PD group (54 patients). Our results showed no significant differences between the two groups except for the physical composite score at which the PD group had a higher mean than the HD group 37.84 vs 44.75, respectively (p <0.001). However, more PD patients reported feeling depressed compared to HD patients.

Conclusions: KDQOL-S scores were comparable between HD and PD groups except for the physical composite score. On the other hand, PD patients tend to suffer from depression more than HD patients. Interventions to attenuate the physical deconditioning and depressive symptoms in HD and PD patients, respectively, are crucial. Future prospective studies with larger sample sizes are warranted.

Table 1: Comparing Scores Between Hemodialysis and Peritoneal Dialysis

<table>
<thead>
<tr>
<th>n=152</th>
<th>Hemodialysis (n=98)</th>
<th>Peritoneal Dialysis (n=54)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>52.07+/-0.02</td>
<td>52.07+/-0.02</td>
<td>1.000</td>
</tr>
<tr>
<td>Sex</td>
<td>Male (63/35)</td>
<td>Male (42/12)</td>
<td>0.730</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>91.5</td>
<td>90</td>
<td>0.304</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>142.5</td>
<td>143</td>
<td>0.806</td>
</tr>
<tr>
<td>QoL</td>
<td>0.88</td>
<td>0.88</td>
<td>0.999</td>
</tr>
</tbody>
</table>

PUB135

A Review of the Risk Factors and Rates of Peritoneal Dialysis (PD) Peritonitis: A Single-Centre, Retrospective Cohort Study

Stuart R. Decora,1 Ammara Abbas, Bhrigu Raj Sood, Jayakeerthi Rangaiah. Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom.

Background: PD Peritonitis is a frequent and important outcome which contributes to the longevity of the peritoneal membrane and the burden of patient co-morbidities. The existing risk factor data relates to a pool of cohort analyses which are hindered by small numbers of patients included in final analyses. As such, evidence-based indicators against peritoneal dialysis have not been established.

Methods: This single centre retrospective study pooled all patients who accessed peritoneal dialysis from January 2013 to January 2021 and into two separate groups; those who had microbiological evidence of PD peritonitis vs. those with no evidence of PD peritonitis. Demographic and baseline clinical information was compared between the two groups to provide indicators of peritonitis risk.

Results: A total of 631 patients were included in the final analysis, which included 80 patients with a history of PD peritonitis. A total number of 129 infections were reported in the time frame. The organism most commonly reported was staphylococcus aureus, with 37 infections. The mean age of patients at the time of infection was 60, compared to 55, in their non-infected counterparts (mean difference 4.9 years p = 0.0008). The relative risk of male gender resulting in PD peritonitis was 1.03 (CI 0.75-1.14). Within the infected cohort, the relative risk of Asian and Caucasian ethnicity were reported as 0.62 and 0.56 respectively (CI 0.33-1.8 and CI 0.4-0.77). A total of 28 patients reported recurrent infection. The average age for multiple infections was 63, compared to 57 amongst those with a single infection episode (mean difference 5.8 years CI 0.1). An assessment of the role of diabetes status, serum albumin levels, difficulty rating and method of PD catheter insertion, body mass index across with nasal Staphylococcus Aureus Nasal carriage and patient kTV as risk factors for PD peritonitis, is currently underway.

Conclusions: This data demonstrates that in a retrospectively assessed cohort of 631 patients, age was a statistically significant determinant of risk of PD peritonitis, with a predominant staphylococcal organism. Caucasian and Asian ethnicities appeared to have a lower risk of PD peritonitis. Gender was non-significant. Given the retrospective nature of the available data, further investigation is required.

PUB136

Effective Removal of Methylurea by Peritoneal Dialysis

Tanuja Valamurti,1 Tammy L. Sirich,2 Graham E. Abra,3 Margaret K. Yu,1 Timothy W. Meyer,1 Stanford University, Stanford, CA; Palo Alto VAHCS, Palo Alto, CA; 3Satellite Healthcare, San Jose, CA.

Background: Peritoneal dialysis (PD) clears different uremic solutes at different rates. The highest peritoneal clearance known to date is that for urea. Because urea is partially reabsorbed in the native kidney as well as rapidly cleared across the peritoneal membrane, PD can control plasma urea levels as residual function is lost. This study examined whether another low molecular weight uremic solute, methylurea, has clearance characteristics similar to those of urea.

Methods: Measurements were made in 9 patients receiving maintenance PD with a weekly skdK/Vurea of 1.86 ± 0.55 and with variable residual native kidney function (average residual GFR ± 3.1 ± 1.3 mL/min; range 0 to 9 mL/min). Methylurea, urea, and creatinine were measured in plasma, dialysate, and urine with a new LC/MS/MS assay for methylurea and clearances were calculated using standard formulas.

Results: The time-averaged peritoneal dialytic clearance of methylurea was the same as that of urea and significantly greater than that of creatinine. The residual native kidney clearance of methylurea was also the same as that of urea with both solutes having residual clearance values less than that of creatinine. This reflected similar native kidney tubular reabsorption of methylurea and urea (fractional residual clearance < 1) in contrast to native kidney secretion of creatinine (fractional residual clearance > 1). The total clearances of the three solutes were similar but peritoneal clearance accounted for a larger portion of the total clearance of methylurea and urea. Mathematical modeling showed that for methylurea and urea current standard PD can provide a time-average clearance of close to 7 mL/min and, presuming no change in solute generation, maintain plasma levels below those seen at the initiation of dialysis as patients become anuric.

Conclusions: The uremic solute methylurea is cleared as rapidly as urea across the peritoneal membrane and its plasma level can be effectively controlled by PD. Other small uremic solutes which share these characteristics remain to be discovered.

Funding: NIDDK Support
Trends and Outcomes in Open vs. Laparoscopic Peritoneal Dialysis Catheter Placement from 2013 to 2018

Ankur Shah,1,2 Susie L. Hu,1,2 Christina A. Raker,1,2 Brown University Warren Alpert Medical School, Providence, RI; 2Rhode Island Hospital, Providence, RI.

Background: Patients receiving dialysis require a durable access to the bloodstream for hemodialysis or peritoneal cavity for peritoneal dialysis. In peritoneal dialysis, the catheter can be placed via a percutaneous or surgical approach. With the surgical approach being open or laparoscopic. The purpose of our study is to demonstrate in the modern era in a nationwide, US cohort the trends and outcomes associated with laparoscopic versus open PD catheter insertion.

Methods: We conducted a retrospective analysis using NSQIP database from January 1, 2013, to December 31, 2018. Patients undergoing peritoneal dialysis catheter placement were identified using relevant Current Procedural Terminology (CPT) codes. Data on patient characteristics, surgical approach and operative characteristics, and perioperative outcomes were extracted. Trends in the proportion of open versus laparoscopic techniques were analyzed over the study period.

Results: A total of 11,732 patients who underwent peritoneal dialysis catheter placement were included in the analysis. The proportion of laparoscopic techniques increased steadily from 76.1% in 2013 to 86.8% in 2018, while the proportion of open techniques showed a corresponding decline. Statistical analysis revealed a significant temporal trend towards a higher utilization of laparoscopic catheter placement (p<0.001). Mortality was greater for open insertion compared to laparoscopic (odds ratio (OR) 1.56, 95% Confidence Interval (CI) 1.03 – 2.36, p = 0.04). There was no difference in surgical site infection (OR 1.25, 95% CI 0.97 – 1.63, p = 0.18), or sepsis (OR 1.04, 95% CI 0.67 – 1.6, p = 0.87).

Conclusions: This study provides insights into the temporal trends in open versus laparoscopic peritoneal dialysis catheter placement using a large national database. Our findings indicate a substantial shift towards laparoscopic techniques over the study period. While we found open catheter placement to be associated with higher mortality, we believe this is due to confounding by indication and residual confounding. These findings contribute to the growing body of evidence on the evolving trends in peritoneal dialysis catheter placement and have implications for surgical decision-making and healthcare resource planning.

Funding: Clinical Revenue Support

On Growing Home: A Single-Centre Experience with a Dedicated Peritoneal Dialysis Access Clinic

Shabnam Hamidi,1,2 Bourne L. Auguste,1,2 Matthew J. Oliver,1,2 Sunnybrook Health Sciences Centre, Toronto, ON, Canada; 2University of Toronto, Toronto, ON, Canada.

Background: Growing home dialysis programs has been a priority across Canada over the last decade. Initially a rise in home dialysis rates was observed across the country with initiatives targeting predialysis modality education, the use of transitional care units and increased utilization of assisted home dialysis programs. However, this growth has been challenging to sustain with observed attrition during the COVID-19 pandemic. In 2018, our center established a peritoneal dialysis (PD) access clinic as a means to streamline the process of establishing PD access for patients who had chosen PD as their modality of choice. Herein we describe our center’s experience with this dedicated access clinic.

Methods: We reviewed the charts of 29 prevalent predialysis patients who selected PD as their dialysis modality of choice and had an appointment with our PD Access Clinic (PDAC) between March 2021 and November 2022. We collected baseline data including eGFR (mL/min) and risk of progression to ESKD at 2 years’ time (as measured by the Kidney Failure Risk Equation) at the time of their appointment, time to PD catheter access and first dialysis modality. We also collected information on unplanned dialysis starts, defined as hemodialysis access placed during hospital admission.

Results: The mean (SD) patient age was 67 (14) years. Patients had an average eGFR of 10 mL/min and KFRE of 64% at the time of their initial PDAC appointment. There were a median of 3 months to PD catheter insertion from their access clinic appointment. Less than half of patients (45%) ended up on PD as their first dialysis modality and 20% of patients had an unplanned dialysis start. 17% remained predialysis at the time of our review.

Conclusions: Dedicated PD access clinics do not ensure preferred dialysis modality. Unplanned dialysis starts occur with a high degree of frequency despite predialysis clinics. Earlier referral for PD access at higher eGFR may increase likelihood of peritoneal dialysis as the initial modality and would be a future area of study.

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Funding: Commercial Support - Macrotech

Conclusions: This study provides insights into the temporal trends in open versus laparoscopic techniques over the study period. Our findings indicate a substantial shift towards laparoscopic techniques over the study period. While we found open catheter placement to be associated with higher mortality, we believe this is due to confounding by indication and residual confounding. These findings contribute to the growing body of evidence on the evolving trends in peritoneal dialysis catheter placement and have implications for surgical decision-making and healthcare resource planning.

Funding: Clinical Revenue Support

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Table 1
Effects of Thrice Weekly vs. Home Dialysis on Cardiovascular Functional Capacity (ELDEN) Feasibility Study  
Nupur Gupta, Drake Dillman, Gabrielle Kline, Heather Burney, Brent W. Miller, Sharon M. Moe, Kenneth Lim. Indiana University School of Medicine, Indianapolis, IN.

Background: Conventional in-center thrice weekly hemodialysis (ConHD) regimens are associated with unacceptably high cardiovascular (CV) risk. Given the persistently poor prognosis with ConHD, emerging evidence supports an overarching hypothesis that a more physiological approach to administering dialysis through peritonal dialysis (PD) or Home Hemodialysis (HHD) may improve outcomes. Our preliminary work has demonstrated that cardiopulmonary exercise testing (CPET) can be used as a robust quantitative probe of impaired CV functional capacity in dialysis patients. The present ELDEN feasibility study sought to assess the feasibility of recruiting PD and HHD patients for comprehensive CPET.

Methods: The ELDEN feasibility study is an ongoing single-center, nonrandomized 3-arm prospective controlled trial comparing HHD, ConHD and PD. Patients in each group were matched by age, gender, and dialysis vintage. All patients underwent breath-by-breath CPET, physical function testing, echocardiography and bioimpedance testing at baseline and 1-year.

Results: A total of n=84 patients to-date (ConHD n=12; HHD n=24 and PD n=48) were screened to-date. N=48 patients met eligibility criteria (ConHD n=8; HHD n=14 and PD n=26). n=28 were have been enrolled to-date (n=7 ConHD, n=8 HHD and n=13) and n=14 have completed testing (n=6 ConHD, n=8 HHD and n=8 PD patients) to-date(Table 1). There was no difference in age (p=0.7), gender (p=1.0) or dialysis vintage (p=0.2). For CPET, all participants reached a respiratory exchange ratio (RER) > 1.1. No participants experienced an adverse event. Although the study was not powered to detect differences in VO2peak, there was a trend toward higher VO2peak in patients on PD (14.5, 12.2, 19.5) ml/min/kg and HHD (14.6, 12.5, 15.8) compared to ConHD (10.6, 10.0, 4.2) ml/min/kg (P=0.29). Furthermore, VE/VO2 was highest in patients on HHD compared to PD and ConHHD (P<0.01). Additionally, patients on ConHD exhibited reduced peak heart rate compared to those on PD and HHD (P<0.01).

Conclusions: This study depicts the feasibility of recruitment and performance of CPET in home dialysis patients. Patients on HHD exhibited improved ventilatory efficiency while ConHD patients demonstrated chronotropic incompetence compared to the other groups.

Funding: Private Foundation Support

Corynebacterium: Too Sticky to Treat Through Peritonitis?  
Keziva Mathew, Suzanne G. Martin. Saint Vincent Hospital, Worcester, MA.

Introduction: Corynebacterium is an uncommon cause of peritonitis in peritoneal dialysis (PD) with a prevalence of 1.5%. It reportedly responds to antibiotics alone in 60-80% of cases, with a 15% rate of catheter removal (1). We report a case of recurrent Corynebacterium peritonitis ultimately requiring PD catheter removal and transition to hemodialysis.

Case Description: 41M with ESRD on PD developed severe abdominal pain and mild fever. PD catheter exit site and tunnel showed no evidence of infection. WBC was 11,000/uL and PD fluid cell count was 2500 PMN/uL. He was given 2 weeks of IP vancomycin and PD fluid culture was negative. Abdominal pain improved for 6 weeks. Routine post-peritonitis PD fluid WBC count was 143/uL and culture was positive for Corynebacterium species. He was treated with vancomycin for 4 weeks with adequate troughs, but his abdominal pain persisted. PD fluid WBC count was 478 PMN/uL and culture again grew Corynebacterium species. IP vancomycin was restarted but he developed worsening abdominal pain. WBC count rose to 12,300/uL and PD fluid WBC count was 665 PMN/uL. His PD catheter was removed and he began hemodialysis. He completed a 2-week course of IV vancomycin and was transplanted 4 months later.

Discussion: The cure rate of Corynebacterium peritonitis with antibiotics alone was more common compared with S. aureus, Pseudomonas and other gram negatives (2). However, other data suggests that catheter removal may be required more frequently. Delayed infection may be due to biofilm formation, but antibiotic resistance persists in children (3). Notoriously refractory to antibiotic therapy, repeat episodes are common even after prolonged quiescence, likely due to biofilm formation, rather than antibiotic resistance. Corynebacterium causes infective endocarditis, mainly in prosthetic valves (4). Patients with C. jeikeium IE more frequently required valve replacement, again suggesting biofilm formation. The rate of biofilm formation in Corynebacterium bacteremia was 46-62% (5). Another study (6) showed the capacity of C. stigmata to adhere to abiotic surfaces. Biofilms facilitate pathogen adherence to foreign surfaces, impeding successful antibiotic therapy. Given the propensity of Corynebacterium species to form a biofilm, treatment may require PD catheter removal at a higher rate than previously recognized.
a stroke, with an incidence of 2.04 and 0.51 events per 100 person-years, respectively. There were no predictors for PAD or stroke.

Conclusions: Cardiovascular events rates were high in our PD cohort. Hypercalcermia and hyperphosphatemia, associated with vascular and valvular calcification, were risk factors for MACE and CHF. PD-related peritonitis was a predictor of AMI in our population, in line with previous studies.

PUB144
Partnering for Success: Exploring the Relationship Between Task Distribution and Adherence to Home Hemodialysis (HHD)
Waledz Zafar, Maria Bermudez. Geisinger Medical Center, Danville, PA.

Background: Despite several benefits of the more physiologic nature of frequent HHD when compared to in-center hemodialysis, patient and/or care-partner burnout and attrition remains high in HHD with 25 to 40% patients dropping out within the first year (1). Little is known about the degree of patient involvement with specific HHD-related tasks and adherence to therapy. This study aims to assess distribution of HHD-related task burden among patients and care-partners and whether this correlates with adherence to HHD.

Methods: All patients receiving HHD in a tertiary care hospital involved in a single-center HHD program were surveyed using PATH-D (2), an instrument that lists 20 HHD related tasks and asks who performs them. We evaluated association between the proportion of tasks a patient reported self-performing with their age, sex, duration on HHD, depression score using patient health questionnaire-9 (PHQ-9) and the number of missed treatments per month.

Results: All 18 patients currently active in the HHD program were surveyed. 9 (50%) patients were female, mean age was 57.8 years (range 30-79) and 17 patients did HHD with their spouses. Mean duration on HHD was 552 days (range 83-2058). 12 (66.7%) patients had no missed treatments while 5 had missed a mean of 1.5 (range 1-5) treatments per month. PHQ-9 scores were low (mean 1.3; range 0-3). The proportion of 20 PATH-D HHD related tasks that patients reported self-performing ranged from 0%-90% (mean 32.1%). 45% patients self-cannulated their arteriovenous fistulas. No association was found between proportion of self-performed tasks and demographic characteristics or PHQ-9 scores.

Conclusions: Whether there is an association regarding different patient and care-partner task distribution, the type of task and adherence to HHD remains unclear. Even though there is ongoing study and early data shows high adherence with nearly 70% patients having no missed treatments within the past three months as well as low depression scores, we observed significant variation in self-performed tasks. Understanding how HHD task distribution impacts adherence to therapy over time can provide a frontier of opportunity for patient empowerment, consideration for retraining to improve ability to self-care, and thereby reduce attrition and burnout.

References

PUB145
Dialysis-Associated Peritonitis due to Serratia marcescens: A Case Report
Alejandro Toledo Carranza. Instituto Mexicano del Seguro Social, Cuernavaca, Mexico.

Introduction: Serratia marcescens (SM) is a Gram-negative, opportunistic, highly virulent bacterium and a rare pathogen that causes peritonitis Case reports, a Canadian case series, and a systematic review in Hong Kong suggested that peritonitis in PD due to SM was associated with high rates of treatment failure and catheter removal We present a clinical case of peritonitis due to SM that led to catheter loss.

Case Description: A 34-year-old man with a history of end-stage renal disease secondary to diabetes on continuous ambulatory PD for 5 years with a history of 2 previous cases of peritonitis with adequate resolution of these and with peritoneal fluid (PF) cultures without microorganism development Admitted for severe abdominal pain, nausea, vomiting and diarrhea in addition to cloudy PF cytology was requested where (PF) cultures without microorganism development Admitted for severe abdominal pain, nausea, vomiting and diarrhea in addition to cloudy PF cytology was requested where (PF) cultures without microorganism development Admitted for severe abdominal pain, nausea, vomiting and diarrhea in addition to cloudy PF cytology was requested where (PF) cultures without microorganism development. SM was associated with high rates of treatment failure and catheter removal We present a clinical case of peritonitis due to SM that led to catheter loss.

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Discussion: Peritonitis due to SM is a serious complication, so its surveillance should be intensified and appropriate treatment compatible with the antibiogram should be offered. Low socioeconomic status, poor home environment and hygienic conditions increase the rates of peritonitis due to this pathogen, so more frequent and careful patient and family education in such conditions may improve patient care.

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

PUB146
Reduced Rate of Peritonitis in Incremental Peritoneal Dialysis (PD) vs. Standard-Dose PD
Javier De Arteaga,1,2 Peluén Fernández,1,2 Walter Douthat,1,2 Carlos R. Chuichiu,1,2 Jorge de la Fuente,1,2 Hospital Privado Universitario, Cordoba, Argentina; Fundacion Nefrologica de Cordoba, Cordoba, Argentina.

Background: Incremental PD associates with a reduced rates of infection as compared to standard dose PD. may be related to less manipulation of the PD system but there can be other causes like a better local peritoneal defense resulting from less exchanges. Incremental PD is an ailing different from standard dose PD (4 exchanges manual, 2 6lt bags plus a daytime one for APD). Objective: to evaluate our results in a retrospective cohort of adult chronic PD patients in a single center analyzing results of peritonitis in both groups: incremental and standard dose PD.

Methods: Patients: 246 adult patients, 53% men, 71.1 % on manual PD and 34.5% incremental. Study period: December 1994 to December 2022. Inclusion criteria: chronic PD (3 months) in stable patients with a disconnect double bag system. Peritonitis is peritonitis in both groups: incremental and standard dose PD.

Results: See attached tables.

Conclusions: Incremental PD associates to a reduced ner of peritonitis episodes as compared to standard dose PD. Time of followup is significantly lower in Incremental PD. Kaplan meier (time adjusted) although marking a positive tendency couldn’t show a significant reduction in time to the first infection episode for incremental PD. Further prospective studies are needed to answer properly this important question.

RR for peritonitis incremental = 0.48 (IC 95%< 0.31-0.74; p=<0.001), compared with PD full dose

PUB147
Peritoneal Dialysis After Gadolinium-Based Contrast Agent (GBCA) Exposure: A Case Study
Ida A Ayensu, Kara Kaplan, Khaled Boube. The Ohio State University, Columbus, OH.

Introduction: Nephrogenic systemic fibrosis (NSF) is a disorder characterized by thickening and hardening of the skin overlaying extremities and trunk as well as the expansion of fibrosis of the dermis associated with CD34+ fibrocytes. This rare disorder is only seen in patients with advanced CKD. The most common risk factor of NSF is gadolinium-based contrast agent (GBCA). These finding were initially reported in early 2000s when unstable linear GBCAs were given to patients ESKD patients that were dialysis dependent or patients with AKI. Current guidelines recommend dialysis promptly according to the ASPD guide 2016 and causative agents recovered as described previously. We know that 73-78%, 92-95% and 98-99% of free gadolinium is removed after 1, 2, and
PD getting MRI with gadolinium should be tailored to maximize the clearance of GBCA. Peritoneal dialysis (APD) with 10-15 exchanges per day for 24 and 48 hours showed and one would argue that if patient was able to receive 16 exchanges in 48 hours, there is than HD in clearing GBCA. However, this was with a reasonably regular prescription. Further studies on PD and GBCA clearance are needed to establish a better understanding of GBCA clearance.

Impact of Dialysis Modality Selection Clinic

Anupkumar Shetty, Dallas Nephrology Associates, Dallas Nephrology Associates, Dallas, TX

Background: President Trump’s Executive Order on Advancing American Kidney Health has led to ESRD Treatment Choices (ETC) Model taking effect on January 1, 2021, to promote greater use of home dialysis and kidney transplants for Medicare beneficiaries with ESRD in order to preserve or enhance their quality of care while reducing Medicare expenditures. ETC model and other related models have put tremendous pressure to grow home dialysis programs and Dallas Nephrology Associates (DNA) started ‘CKD Modality Selection Clinic’ in 2022 to address this. DNA is a single specialty nephrology practice having 110 nephrologists and 15 nephrology offices in Dallas Fort Worth area.

Methods: DNA's CKD Modality Selection Clinic involves a 40 minute visit offered to patients in late stage CKD 4 and CKD 5 before they commit to a dialysis modality. During the initial 20 minutes, they were given a dialysis modality education booklet and were shown a video on dialysis modality education. Subsequent 20 minutes were dedicated to a physician visit involving history taking, focused examination and discussion of certain key elements shown in the video using the demo manequins with PD catheters, demo PD cyclers and demo NxStage machines. An assessment was made regarding education by the nephrologist and the patient. Patients were asked to choose a dialysis modality before and after the clinic. Patients were followed by the primary nephrologist and the final ESRD treatment selection was noted when they went on dialysis.

Results: The clinic was started in May 2022 and as of April 2023, clinic has been started in 7 offices. 209 patients have attended this clinic so far. In the pre-clinic questionnaire, 47.8% were uncertain about their dialysis modality selection and post-clinic questionnaire showed that 15.8% were uncertain. As of May 2023, among those who attended the modality selection clinic, 12 patients started home dialysis and 3 started in center hemodialysis.

Conclusions: Modality selection helps people make decision about dialysis modality selection. Educated patients chose home dialysis more often than those who do not take advantage of education.

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The Technique Failure Frustrating the Road of Intermittent Dialysis to Continuous Ambulatory Peritoneal Dialysis

Mariela Ibarra, Karina Y. Contreras Torres, Jennifer Esquivel, L. M. Peñarredo, Rafael Valdez-Ortiz. Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.

Background: When starting peritoneal dialysis in patients with end-stage chronic kidney disease, the biggest challenge is the transition from a modality of intermittent peritoneal dialysis to continuous ambulatory peritoneal dialysis (CAPD).

Methods: A cohort study of patients who started PD in an intermittent modality from September 2022 to May 2023 in the Hospital General de Mexico. Those patients were followed until they met one of the outcomes: starting ambulatory PD, migrating to hemodialysis, or death. We defined technique failure as any outcome that included suspending peritoneal dialysis (migrating to hemodialysis and death).

Results: We included 62 patients, 61% (38) were men, the average age was 49 ± 14 years, 74% (46) had a basic educational level and only 21% (13) had a job. The most frequent comorbidities were hypertension in 92% (57) and diabetes in 58% (36). Urgent dialysis start was present in 68% (42) patients and 85% (49) are economically dependent on their families. Technique failure was presented in 42% (26) of the patients. We found an association between technique failure and unemployment (OR 5.2, 95% CI 1.05-26.3, p=0.04), and with presenting at least one event of peritonitis (OR 15.3, 95%CI 3.8-61.4, p=0.001).

Conclusions: There have been a few descriptions about the process faced by patients to achieve an ambulatory PD, especially those who do not have health insurance. In this cohort, we observed that more than 40% of the patients had a failure of the technique before being able to dialyze at home, reflecting a complex adaptation process in patients with limited family support. In addition, it is necessary to facilitate access to replacement therapy that really improves the quality of life and long-term prognosis.
Nontunneled Hemodialysis Catheter Survival in Uninsured Population in Yucatan, Mexico

Background: In Mexico, the access to renal replacement therapy (RRT) is unequal, especially for the uninsured. Yucatan has a high prevalence of obesity, diabetes, hypertension, and nephrolithiasis which implies a high burden of chronic kidney disease (CKD). The Hospital Agustin O’Horan receives uninsured patients with CKD from southeast Mexico. In patients who are not candidates for peritoneal dialysis but require RRT with hemodialysis (HD), a non-tunneled hemodialysis catheter (NTHC) is placed. NTHC has a higher rate of infectious complications compared to tunneled hemodialysis catheter (THC) or arteriovenous fistulas (AVF). Our objective was to determine the infection-free survival of NTHC related to catheter related bloodstream infections (CRBSI).

Methods: This is an observational study in patients ≥18 years with CKD, who started HD with NTHC in our center from January to December 2022 and evaluated the survival rate of the NTHC related to catheter related bloodstream infections (CRBSI).

Results: 93 NTHC were placed, 63.4% in women, mean age was 49.5 years. Most of the NTHC were non-ultrasound guided (74.2%) and the internal jugular vein was the main insertion site (87.1%). The median survival time until the development of CRBSI was 134 days (95% CI 105.79-162.20). There were no significant differences in catheter survival with respect to sex, age, and insertion site. Compared to the first 30 days after catheter placement, the relative risk for CRBSI was 7.00 (95% CI 2.14-22.87, p= 0.001) within 31-60 days and 7.63 (95% CI 2.36-24.65, p= 0.0007) within 61-90 days.

Conclusions: Long-term catheterization with NTHC is a reality in our center despite the evidence that it poses a high risk for CRBSI. Unfortunately, the lack of a vascular access team for the creation of AVF and placement of THC prevents us to use a more permanent access with less complications. In that sense, we need to engage our policymakers in order to guarantee better vascular access care, especially for the uninsured population.

Arteriovenous Fistula Creation Affects the Von Willebrand Factor
Suzanne Laboviwie,1 Laura M. van der Linden,2 Roel Bijkerc,1 Zhiuao Xiao,1 Laisel Martinez2 Roberto I. Vazquez-Padron,3 Joris I. Rotmans,4 Leids Universitair Medisch Centrum, Leiden, Netherlands; 1University of Miami School of Medicine, Miami, FL.

Background: Von Willebrand Factor (vWF) is a glycoprotein secreted by endothelial cells as high molecular weight multimers (HMWM). vWF mediates hemostasis by platelet binding and factor VIII stabilization. When HMWMs are cleaved to low molecular weight multimers (LMWMs), the capacity to bind platelets is lost. Cleavage of HMWMs is dependent on shear stress and blood flow patterns, such as laminar to turbulent flow transition. Loss of HMWMs can result in increased bleeding tendencies. An arteriovenous fistula (AVF) is the gold standard for hemodialysis access, whereby there is a transition from laminar into turbulent flow at the anastomosis between the artery and vein. In this study, we investigated the effect of AVF flow on the composition of vWF multimers.

Methods: Patient matched plasma samples of two-stage brachiobasilic AVF surgeries were obtained from the Jackson Memorial Hospital and the University of Miami Hospital, according to the hospitals regulatory requirements. ELISAs were performed to determine total plasma vWF concentrations and vWF's collagen-binding capacity. vWF multimers were separated based on molecular weight in a multimer assay and quantified with
Gunshot Wound in an Arteriovenous Fistula in Hemodialysis Patient

Robertó Ramirez Marmolejo,1,2,3 Angelica M. Delgado,1 Sofia Ramirez Isaza,4 Carlos Mejia,2,4 Provenral Group.1 Universidad del Valle, Cali, Colombia;2 Fundación Prevenral, Cali, Colombia;3 Hospital Mario Correa Rengifo, Cali, Colombia;4 Pontificia Universidad Javeriana Facultad de Medicina, Cali, Colombia.

Introduction: The violence in Cali Colombia has put the medical team in interesting and difficult challenges. The city is in position #2 of the most dangerous in the world. A patient is presented who received an impact from a firearm projectile precisely in his left antebrachial arteriovenous fistula, he was immediately taken to vascular surgery. No articles were found in the literature that presented similar wounds.

Case Description: A 23-year-old male patient, on hemodialysis, was admitted to the emergency, after receiving the impact of a firearm projectile precisely in his left antebrachial arteriovenous fistula. He lost a lot of blood, which was controlled with a tourniquet. He was immediately taken to surgery, finding an aneurysmal degeneration and multiple endoheal lesions proximal to the anastomosis of the projectile. Image 1. A spindle incision is made over aneurysmal degeneration, Image 2. The fistula is closed and medium-caliber vessels are repaired using the Carrel technique.

Discussion: No articles were found that presented wounds in an arteriovenous fistula for hemodialysis and only one was found where a self-inflicted stab wound by the patient himself was described as a suicide attempt. The blood flow from an arteriovenous fistula for hemodialysis is greater than 600ml/min, any injury is potentially lethal if not handled properly.

Epidemiology of Hemodialysis Vascular Catheter-Related Blood Stream Infections: A Clinical Audit

Dinith P. Galabada, Upali Kaushalya. Nephrology Dialysis Transplant Unit, North Colombo Teaching Hospital, Ragama, Sri Lanka.

Background: Central venous catheters (CVC) are commonly used as a temporary access method for hemodialysis among patients with End Stage Renal Disease (ESRD). Catheter related blood stream infections (CRBSI) are a frequent complication of CVCs. Acceptable incidence rate for CRBSI is <1.5/1000 catheter days according to KDOQI clinical practice guideline for vascular access -2019 update. Therefore, this clinical audit aimed to assess the incidence of CRBSI and associated risk factors.

Methods: Records of ESRD patients undergoing hemodialysis via a CVC at a tertiary care hemodialysis center in Sri Lanka from April 2022 to March 2023 were considered for this audit. Data regarding demographics, medical history, hemodialysis access type (tunneled or non-tunneled central venous catheter), access site (internal jugular or femoral vein), duration of CVC, co-morbidities, development of CRBSI and responsible microorganisms were collected. Age, gender, CVC type, access site, CVC duration and presence of Diabetes mellitus were analyzed to determine the association with CRBSIs.

Results: A total of 76 ESRD patients were analyzed. The mean age was 54.7 (±11.5) years. Majority were male (63.2%). Common co-morbidities were Diabetes mellitus (72.4%) and hypertension (73.8%). In most patients, (81.6%) diagnosis of chronic kidney disease was made after ESRD developed. No previous nephrology clinic follow up, before initiation of hemodialysis, was observed in 44 (57.9%) patients. Median catheter duration of non-tunneled CVCs (NTCVC) (n=49) was 16 days and tunneled CVCs (TCVC) (n=71) was 144 days. NTCVCs had a CRBSI incidence rate of 7.07/1000 catheter days while TCVCs had a considerably low-rate of 0.58/1000 catheter days. Causative microorganisms were Staphylococcus aureus (31.6%) including Methicillin resistant variant, Coagulase negative Staphylococcus (23.07%) and Klebsiella pneumoniae (15.3%). Age, gender, Diabetes mellitus, site of CVC and duration of CVC showed no significant associations with CRBSIs.

Conclusions: Tunneled CVCs CRBSI incidence is within the acceptable range despite having longer catheter durations, while NTCVCs show a higher CRBSI incidence than the target value. Our analysis did not discover any significant associations with CRBSI incidence. Therefore, we recommend changing access from NTCVC to TCVC or arteriovenous fistula at earliest convenience to prevent CRBSI.
Unconventional Ultrasound (US)-Guided CVC Placement
Madeline S. Chung, Marie Fouad, Khaled Boubees. The Ohio State University Wexner Medical Center, Columbus, OH.

Introduction: Percutaneous cannulation of central veins is used for both short and long-term vascular access (VA). VA is an area of difficulty among KRT patients who have had multiple procedures involving the central veins. These patients are prone to vascular calcification, stenosis and thrombosis related to their VA, complicating further VA planning and procedures. This is especially true in emergencies when expedient bedside placement of dialysis access is necessary, but difficult using conventional methods.

Case Description: 60 yo man with ESKD on HD via LUE A VF who presented with worsening dyspnea admitted for CHF and pulmonary hypertension management. The CVC tip overlying the right brachiocephalic vein (BCV) near the superior vena cava (SVC) confluence. Two further attempts at placement in the LIJ vein resulted in similar positioning. He was unstable for transport to IR. We placed a guidewire into the malpositioned LIJ catheter and retracted it. The ultrasound (US) probe was placed at the base of the right neck to visualize the right subclavian arch, leaving the SVC as the default location, since its location deep in the thoracic cavity, precludes visualization of the SVC by US.

Discussion: CVC can be a difficult procedure especially when approached via the LIJ vein due to its tortuous path. It is further complicated in patients with difficult anatomy. At most institutions, bedside resources for image guidance are still largely limited to US and CXR, and are generally the only option in patients too ill for transport to the radiology department where more advanced options are available. It is therefore important to utilize the bedside US to its full capacity and learn different windows to visualize VA options beyond the conventional approach.

Malpositioned LIJ CVC in the right BCV
PUB161

Minimally Invasive Guidewire Exchange Technique for Tunneled Hemodialysis Catheters: Preservation of Venous Insertion Site in Chronic Hemodialysis Patients

Fernando A. Cuellar-Gonzalez,1,2 Sebastian Consuegra-Flores,1,2 Néstor H. Cruz Mendoza,1 Mauricio Arvizu Hernández,1,2 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; Tecnologico de Monterrey - Campus Ciudad de Mexico, Ciudad de Mexico, Mexico.

Background: Tunneled hemodialysis catheter (THC) has become an acceptable form of vascular access (VA) when an arterio-venous fistula is not feasible or available. Dysfunction of THC is associated with removal and replacement of THC. Few techniques of guidewire exchange of THC have been reported. We aim to present the experience of our center in guidewire exchange of THC, with preservation of the same venous insertion site with only one incision at the jugular site, without fluoroscopy and local anesthesia performed by interventional nephrologist.

Methods: Retrospective, single-center study conducted between Jan/2018-May/2023. Guidewire exchange of THC due to dysfunction in 15 pts on chronic HD performed by interventional nephrologist.

Results: 15 procedures were performed in same number of patients, mean age 41.2 +/- 13.6 years, 53% were female, mean duration of HD was 3.2 years; 12 (80%) have one previous VA, all THC were located in right internal jugular vein. The success rate of the procedure was 100%. At 3 months, 12 cases remained functional, two catheters had not completed three months of follow-up, one catheter was removed earlier due to infection. Only mild complications, such as bleeding requiring sutures, were reported in two cases, with no major complications recorded.

Conclusions: Our study shows that the guidewire exchange of THC, with preservation of the same venous insertion site with only one incision at the jugular site is a reliable method in patients with dysfunction of THC and with low risk of complications.

PUB162

Patient’s Navigator for Lupus Nephritis: Pilot Evaluation


Background: Systemic Lupus Erythematosus (SLE) is an autoimmune condition that disproportionately affects women, racial and ethnic minorities, and individuals of lower socioeconomic status1. Patients with SLE often face social determinants of health challenges that are barriers to care and influence health outcomes2. To improve outcomes, we implemented a patient’s navigator program focused on addressing the medical and social needs of patients with lupus nephritis (LN).

Methods: In this pilot phase, we included 13 patients with LN that were identified by their treating physician with high medical needs (newly diagnosed or flare of LN; recent hospitalization or emergency room visit; transitioning from pediatric to adult care) and/or high social needs (food and economic insecurity, uninsured; complex family situation with childcare or elderly care needs, high no-show rate, limited health literacy, mental health challenges). Initial screening was performed by college volunteers connected to the medical team who reviewed the results and implemented interventions aiming patient’s specific needs. Follow-up assessments were arranged to modify the social determinants of health that negatively affected patients.

Results: The demographic and screening results are summarized in Table 1. Financial help with medication and physician visit copays were reported as the most pressing need followed by transportation, disease education and assistance with medication compliance. Based on the initial screening, we started an intervention plan tailored to individual needs such as financial support for transportation, social services, blood pressure machine, pill box and lupus education.

Conclusions: The pilot phase of our patient navigator program successfully identified additional medical and social needs for patients with LN. We plan to expand this program by identifying more patients and arranging for follow-up assessments to modify social determinants of health that negatively affect our patients. Our program can serve as a model for other institutions to improve outcomes for patients with SLE.

Funding: Private Foundation Support

Table 1

<table>
<thead>
<tr>
<th>Age (median range)</th>
<th>36 (20-55)</th>
</tr>
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<tbody>
<tr>
<td>Gender</td>
<td>Female: 11 Male: 2</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Black: 11 White: 1 Hispanic: 1</td>
</tr>
<tr>
<td>Lupus stage</td>
<td>Acute flare: 8 Partial remission: 2</td>
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BP: Blood pressure

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
An International Public-Private Partnership Model for Renal Replacement Therapy in Uzbekistan: Lessons and Challenges
Suresh Sankarasubbbaiyan, Botir Damirov, Savitha Kasiviswanathan, Dilshod Sobirov, Ravshanbek Raximov, Khurshid U. Dosimbergenovich, Shiva Chaudhary, Kamal D. Shah. Nephrocare Health Services Pvt Ltd, Hyderabad, India.

Background: Uzbekistan is part of New Independent States region in Europe with 35.6 million population and GDP/capita of 2254.9 dollars with an acute need for RRT availability and accessibility.

Methods: The Uzbekistan government chose a dialysis provider from India to initiate a public-private partnership model of RRT. Our objectives are 1. Describe the model for hemodialysis by roles, resources and service provided 2. Present demography, dialysis practice and clinical outcome from April-December 2022.

Results: Under the model, the government funded and governed while the private provider ensured leadership, human resources, technology, HD delivery and information capture (paper based & digital). HD facilities were at: Bogot (pop:10600), Nukus (pop:330,000) and Urgench (105,000) with machine capacity of 25, 34, and 31 respectively at 65% utilization (Image 1). B Braun dialog machines and Wego F18 Polysulfone 1.8m2 dialyzers were used. Staff patient ratio of 1:3 with oversight by physicians with nephrology training. Image 2 presents patient, practice and outcome characteristics. Proximal public health facilities provided support for acute care and biochemical monitoring.

Conclusions: We demonstrate an emerging model of knowledge and skill transfer between LMIC in RRT with profound delivery challenges in access to care, manpower and HD delivery in Uzbekistan.

Patient characteristics N=430

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</tr>
<tr>
<td></td>
<td>18 - 40</td>
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<td>41 - 60</td>
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<tr>
<td></td>
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</tr>
<tr>
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<td>4</td>
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<td></td>
<td>GN</td>
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<td>8 - 9.9</td>
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<td></td>
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<td></td>
<td>&gt;12</td>
<td>33(11.66)</td>
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<td></td>
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<td>10 to 30</td>
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<tr>
<td></td>
<td>31 to 60</td>
<td>103(23.95)</td>
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<tr>
<td></td>
<td>&gt;60</td>
<td>83(19.3)</td>
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<tr>
<td>9</td>
<td>Outcome</td>
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<td></td>
<td>Continue</td>
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<td>Died</td>
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<td></td>
<td>Shifted elsewhere</td>
<td>12(2.79)</td>
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<tr>
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<td>Txp</td>
<td>24(5.58)</td>
</tr>
</tbody>
</table>

Language Barrier and Abdominal Compartment Syndrome with Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)
Alvin G. Kwon, Melissa Baker, Hanny Sawaf. Cleveland Clinic, Cleveland, OH.

Introduction: In the US, using a primary language other than English is a known barrier to adequate healthcare utilization and patients’ comprehension of diagnosis and treatment. Adverse events were more prominent in limited English-proficient patients at 46.8% compared to 24.4% in English-proficient patients. Abdominal compartment syndrome (ACS) is commonly diagnosed with intra-abdominal pressure over 20mmHg and related organ failure such as AKI. However, ACS has nonspecific symptoms and poor physical exam sensitivity as low as 40-50% making it challenging for physicians to diagnose it promptly. We present patient with intra-bladder pressure proven ACS complicated by AKI required hemodialysis.

Case Description: Patient is a 25-year-old Spanish-only speaking male diagnosed with necrotizing pancreatitis after being found with septic shock requiring two vasopressors for blood pressure support. Patient was also found to have generalized weakness, abdominal distension, hypotension, and jaundice. The patient tested positive...
for Confusion Assessment Method and needed to rely on a landline interpreter service. He had no family or social support to assist with his history. After rigorous intravenous fluid resuscitation for pancreatitis, patient remained anuric with lower extremities edema and was initiated on continuous veno-venous hemodialysis. Given his severe abdominal distention and tenderness on physical examination, intra-bladder pressure was measured at 29 mmHg while patient was still systemically hypotensive. Surgical intervention was not performed, given comorbidities and concerns that it caused more harm than benefit. Decompression via nasogastric tube and scheduled enema were continued and bladder pressure was decreased at 5 mmHg three days later. Unfortunately remained dialysis-dependent and passed away from worsening septic shock.

Discussion: Poor socioeconomic status and language barriers and confusion from encephalopathy are previously unreported risk factors for ACS that may contribute to mortality in vulnerable populations; additional barriers to communication with providers may make reporting patient changes difficult. Therefore, physicians should pay extra attention to vulnerable people. Future studies between language barriers, socioeconomic status, and ACS should be followed.

PUB165
What Does Justice Require of Us in Kidney Health?
Unini Odang, Harvard University, Cambridge, MA.

Background: Thirty-seven million Americans live with chronic kidney disease, while over 800,000 have end-stage kidney disease (ESKD), a devastating life-altering condition. Unfortunately, kidney health disparities and inequities abound, and the current literature does not integrate a comprehensive view of justice in kidney health. Justice, the fair distribution of fundamental rights, duties, socio-economic, health, and healthcare opportunities, is linked to wellbeing. The overarching goal of this paper was to demonstrate how kidney health, health equity, and justice are inextricably linked.

Methods: This work used a wide justice lens to explore the moral question of variances in kidney health metrics (disparities) and outcomes (inequities). Relevant peer-reviewed scientific journals and seminal justice articles were reviewed. Information was gleaned from discussion with Justice experts. Justice principles and relevant ethical principles were linked to create a Kidney Health justice-based framework.

Results: Findings unveiled widespread inequities in kidney disease risk, care, and outcomes. Common kidney disease risk factors—diabetes and hypertension—are 12-13 times more prevalent in Blacks; ESKD prevalence in Blacks (29.8 %) is quadruple that of Whites. Blacks and Hispanics are 53% and 65%, and 79% and 53%, less likely to receive home dialysis and kidney transplantation than Whites. Also, racism, poverty, and oppression are unique determinants of kidney health inequities.

Conclusions: This project illustrated the link between kidney health and justice with a novel justice-based kidney health framework, connecting normative justice theories to bioethical principles of dignity, care, virtue, and solidarity. An infographic highlighted the necessity for collaboration among the individual, community, organizational, and governmental socio-ecological levels. Justice requires policymakers and kidney care stakeholders to adopt a far-reaching, transparent, accountable, sustainable, and just kidney health plan.

PUB167
Assessing the Current Evidence on Environmental Sustainability in Nephrology: Protocol for a Scoping Review by the International Society of Nephrology, Emerging Leaders Program Catalog 2022-2024
Isabelle Ethis,1,2 Divya P. Bajpai,3 Brendan Smyth,4 Winston W. Fung,5 Maria Pippas,6,8 Peace Bagash,6,10 Letizia De Chiara,6 Ehab Hafiz,11 Dearbhlia M. Kelly,12 Ugochi C. Onu,12 Shaifali Sandal,4 Workagegnehu H. Bilchut.10 International Society of Nephrology – Emerging Leaders Program Catalog 2022-2024, 1Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada; 2Centre de Recherche du Centre Hospitalier de l’Universite de Montreal, Montreal, QC, Canada; 3Mater Misericordiae University Hospital, Dublin, Ireland; 4King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Mumbai, India; 5NHRMC Clinical Trials Centre, Camperdown, NSW, Australia; 6St George Hospital, Kogarah, NSW, Australia; 7The Chinese University of Hong Kong, Hong Kong, Hong Kong; 8McGill University Health Centre, Montreal, QC, Canada; 9University of Bristol Faculty of Health Sciences, Bristol, United Kingdom; 10Southmead Hospital, Bristol, United Kingdom; 11Theodor Bilharz Research Institute, Giza, Egypt; 12University of Nigeria, Nsukka, Nigeria; 13Università degli Studi di Firenze, Firenze, Italy; 14Mulago National Referral Hospital, Kampala, Uganda; 15Makerere University, Kampala, Uganda; 16University of Gondar, Gondar, Ethiopia.

Background: Human-induced climate change is a significant threat to global public health. The healthcare sector contributes significantly to environmental damage through resource depletion and greenhouse gas emissions. Furthermore, nephrology practices have a disproportionately higher share in the carbon footprint produced by medical therapies (e.g. dialysis). This review aims to map the available evidence of green/sustainable nephrology in the literature to better understand the current lacunae in the evidence and challenges faced while adopting eco-friendly practices.

Methods: A search strategy, developed in collaboration with a medical librarian to be used in Medline, and adapted for other databases (PubMed, Embase, Cochrane Library, CINAHL), will be used to retrieve references. A secondary manual search of all references from included studies will be undertaken (snowballing approach). All publications (including original studies, case reports, editorials, review articles, editorial letters, positional statements from professional societies, and conference abstracts) addressing any environmental impact of activity in kidney care; current knowledge or awareness of environmental impact of kidney care impact; any activity, strategy or effort focused on environmental sustainability of kidney care activity; or any barrier or challenge faced in adopting environmentally sustainable kidney care activity will be included. A data extraction table will be used to record the key components and information from the retrieved papers. Extracted data will be analyzed qualitatively using preidentified and newly identified themes.

Conclusions: The use of social media platforms accessed by cell/smartphone technology should be explored to find better means of education and communication in HD patients.

Demographics of study population

<table>
<thead>
<tr>
<th>Gender (%)</th>
<th>Male (n=49)</th>
<th>Female (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61 (7-134)</td>
<td>61 (7-134)</td>
</tr>
<tr>
<td>Self-reported Disability (N=75)</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>African American – 95%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Asian – 4%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Caucasian – 1%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Landmark at home (%)</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Intern at home (%)</td>
<td>71%</td>
<td>71%</td>
</tr>
<tr>
<td>Own car in last 6 months (%)</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Food security risk score (N=75)</td>
<td>Moderate-risk score – 97%</td>
<td>Moderate-risk score – 97%</td>
</tr>
<tr>
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<td>3%</td>
</tr>
<tr>
<td>Low risk score</td>
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<td>0%</td>
</tr>
<tr>
<td>Dialysis access (%)</td>
<td>AVF: 90% (75)</td>
<td>AVG: 10% (75)</td>
</tr>
<tr>
<td>AVG: 10% (75)</td>
<td>AVG: 10% (75)</td>
<td></td>
</tr>
<tr>
<td>PC: 8 (25)</td>
<td>PC: 8 (25)</td>
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</table>

Utilization of smart phone for various activities in our dialysis cohort

PUB166
Use of Cell/smartphone Technology in an Urban Free-Standing Hemodialysis Facility in the United States: A Single Center Study
Sunit K. Palleti,1 Kavitha Vellanki,1 Judith Beto,2 Vinod K. Bansal.1 Loyola University Medical Center Department of Nephrology, Maywood, IL; 2Loyola University Health System, Maywood, IL.

Background: Cell/smartphone has become a basic necessary commodity in the 21st century and can provide knowledge to be a valuable means for patient education when used appropriately. Data on cell/smartphone technology usage in the hemodialysis (HD) population is non-existent. We proposed to study the utilization of cell/smartphone technology in selected activities to better understand our patient population and identify new means of communication.

Methods: All patients receiving in-center dialysis were approached to complete a 2-page paper survey. Data collected included age, sex, self-reported ethnicity, presence of landline/internet at home, and ability to drive. The food security risk score was assessed using the USDA validated 2-question format.

Results: Of the 110 HD patients, 77 agreed to participate (70% response rate), and 70 of the 77 had a cell/smartphone. The baseline demographics of the study population are shown in Table 1. Image 1 demonstrates the various activities smartphone is used in our HD cohort. Interestingly, women used text messaging more frequently than men (82% vs. 68%), and those who used text messaging were found to be younger than those who did not (58.1 and 71.2; age in years). 64% reported active browsing on their phones while receiving HD. We did not find any association between the ability to drive and the food security risk score.

Conclusions: The use of social media platforms accessed by cell/smartphone technology should be explored to find better means of education and communication in HD patients.
Reproductive Health Perceptions and Priorities of Males Living with Chronic Kidney Disease (CKD)

**Background:** Chronic Kidney Disease (CKD) affects 1 in 10 Canadian males, and up to 80% of males living with CKD experience complications related to their reproductive health (sexual function and fertility). Despite its importance to overall health and quality of life, reproductive health is often overlooked during the management of CKD in males. This study aims to identify the reproductive health perceptions and priorities of males living with CKD.

**Methods:** An exploratory web-based survey will be designed through a comprehensive literature review and in consultation with experts in the field of nephrology, urology, and reproductive health. The survey will assess reproductive health perceptions and priorities of males living with CKD.

**Data collection:** Snowball sampling will be employed to recruit self-identified adult males living with CKD, with invitations disseminated through national and international CKD patient organizations, social media platforms, and CKD clinics in Calgary, Alberta, Canada.

**Results:** Descriptive statistics will be employed to analyze numeric and Likert-scale data, while conventional content analysis will be utilized to analyze open-ended data.

**Conclusions:** Reproductive health perceptions and priorities of males living with CKD are poorly understood. Our findings will guide future patient-directed research and encourage the development of targeted interventions to address the reproductive health needs of males living with CKD.

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

Underline represents presenting author.

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Hind H. Alnouri, Fakhriya J. Alalawi, DAHC, Dubai, United Arab Emirates.

**Background:** For patients with end-stage renal disease (ESRD), renal replacement therapy (RRT) is necessary to sustain life. However, many pre-dialysis CKD patients lack the information to make wise healthcare decisions regarding their future management. We have a model program named Renal School, launched in 2008 and still working to date, and consists of a multispecialty team (including nephrologists, clinical dieticians, haemodialysis and PD nurses, psychologist, and social worker). We provide comprehensive education about various modalities of renal replacement therapy to patients with CKD stages 4 and 5 (GFR<30 ml/min), aiming at reducing the need for emergency dialysis and catastrophic complications associated with delayed RRT.

**Methods:** Since 2008 until date, 1021 patients attended renal school and were explained various modalities of RRT. Patients received a number of learning resources, and their preference for a particular modality was considered.

**Results:** Among 1021 patients, 315 selected haemodialyses, 217 opted for peritoneal dialysis, 119 were referred for pre-emptive kidney transplantation, and 321 remained undecided. Educated patients were prepared with access at the start of dialysis, which reduced complications associated with delayed dialysis therapy, had fewer hospital days of stay and had significant cost savings. Moreover, they received better care, enjoy better clinical outcomes, and cope better with the stresses of RRT. Although the majority (32.5%) could not decide regarding the type of RRT, they yet became more compliant with medication and dietary regimen, and they were able to plan healthy lifestyles and cope with their chronic illness.

**Conclusions:** By offering comprehensive information, fostering shared decision-making, providing psychosocial support, and addressing lifestyle management, these programs empower patients to actively participate in their healthcare decisions. Through their involvement, patients can select the most suitable RRT modality based on their preferences, leading to improved treatment outcomes and a higher quality of life.
Online Continuing Medical Education (CME) Improves Knowledge of Gaps in CKD-Anemia Management in Practice

**Amy Larkin, Linda Ritter. Medscape Education, New York, NY.**

**Background:** We sought to determine if online continuing medical education (CME) could improve the clinical knowledge and confidence of nephrologists and hematologists related to current gaps in care for patients with CKD-anemia.

**Methods:** The CME intervention comprised a 30-min online video-based roundtable discussion among 3 expert faculty with downloadable slides. The effects of education were assessed for learners completing both knowledge pre- and post-assessment questions using a matched pre-/post-assessment design, with participants serving as their own controls. A paired samples t-test was conducted for significance testing on overall average number of correct responses and for confidence rating, and a McNemar test was conducted at the question level (5% significance level, P < .05). Confidence was assessed in a 4° question using a 5-point Likert scale. The activity posted September 16, 2022, and data were collected through December 21, 2022.

**Results:** In total, 59 nephrologists and 35 hematologists answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation: Overall, 39% of nephrologists and 29% of hematologists improved their knowledge 27% of nephrologists and 14% of hematologists demonstrated improvements at recognizing disparities in the management of CKD-anemia (P < .01 for both groups). Continued educational gaps: 39% of nephrologists and 40% of PCPs need additional education related to managing DD-CKD-aP (P < .01 for both groups). 59% of nephrologists and 49% of PCPs demonstrated improvements at providing patient education related to DD-CKD-aP (P < .01 for both groups). 41% of nephrologists and 40% of PCPs had a measurable improvement in confidence in providing team-based management of CKD-aP (P < .01 for both groups).

**Conclusions:** This study demonstrates the success of online, text-based, interactive continuing medical education on improving clinical knowledge and confidence of nephrologists and PCPs related to managing patients with DD-CKD-aP. Continued knowledge gaps were identified for future educational targets.

**Funding:** Commercial Support - Developed through an independent educational grant from CSL ViFor

**PUB175**

Online Patient Education Improves Understanding of CKD-Associated Pruritus

**Amy Larkin, Donald Blatherwick. Medscape Education, New York, NY.**

**Background:** This study assessed the impact of online patient education on knowledge, confidence and intent to act regarding chronic kidney disease-associated pruritus (CKD-aP).

**Methods:** The educational intervention consisted of 2 activities comprised of text, integrated visuals, and patient video commentary published on WebMD Education in 2022. Demographic questions were asked prior to each activity. Knowledge questions were asked both before and after to assess learning gains. Intent to change and confidence questions were asked at the end of each activity. Absolute improvements were calculated for pre-/post questions.

**Results:** Activity 1: Dialysis: Talking to Your Doctor About Your Skin 9,355 learners; 327 completers of all questions 56% female; 53% white, non-Hispanic; 65% over 54 years of age. After the education, 80% intend to talk to HCP about CKD-aP; 81% confident in understanding changes that can happen to skin while on dialysis Activity 2: Ways to Manage the Itch When You’re On Dialysis 938 learners; 213 completers of all questions 62% female; 64% white, non-Hispanic; 81% over 54 years of age 20% improvement in knowledge regarding ways to treat CKD-aP; 85% intend to talk to HCP about ways to help manage the itch while on dialysis; 80% confident in talking to HCPs about their skin and if itching happens [LA1] Data missing from dashboard, waiting on data.

**Conclusions:** The metrics and outcomes gathered in this assessment are a strong indicator that online patient activities on WebMD Education improved knowledge and confidence and prompted intent to act related to CKD-aP.

**Funding:** Commercial Support - This education was supported by an independent educational grant from CSL ViFor

**PUB176**

Virtual Nephron: A Qualitative Assessment of a Virtual Reality (VR) Educational Tool

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**Background:** The proliferation of VR technology has led to the creation of innovative educational tools. Using funding from the ASN, we developed a 3D VR renal physiology course. We present a qualitative analysis of its perceived utility.

**Methods:** Internal medicine PGY1 residents were randomly assigned into 2 groups: a VR group (exposed to the VR session) and a conventional group (received a printed script of the VR learning course). The VR session consisted of a 3D review of water and electrolyte transport and on diuretic mechanism of action. Within a week of the intervention, both groups underwent a 2-hour seminar on physiology of solute/water transport and diuretics. The VR group was asked to rate their VR experience at the end of the seminar. This was performed using a RedCAP-based survey consisting of a 4-point Likert scale. Residents randomized to the VR group were also asked to participate in a focus group. Sessions were recorded and transcribed verbatim. Data was analyzed through the content analysis approach by two independent reviewers who met to compare coding and reach consensus on emerging themes.

**Results:** Of the 64 PGY1 residents who were randomized to VR group, sixty-two completed the PCPs educational assessment. Overall, > 90% of the residents rated the platform positively in all parameters, and 77% preferred it as a teaching method (Table 1A). Three focus groups met for one hour. Each group respectively comprised 9, 8, and 15 interns from each academic years 2020-2023. Several recurring themes emerged in our analysis (Table 1B).

**Conclusions:** The feedback of the VR course was overwhelmingly positive and was perceived to be a helpful educational adjunct. Educational institutions should consider supporting the development of interactive educational tools to enhance learner experience.

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

Underline represents presenting author.

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Underline represents presenting author.

PUB177

Assessing ChatGPT’s Reliability as a Novel Educational Resource for Interventional Nephrology
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Background: Interventional Nephrology is a new subspecialty of Nephrology that focuses on ultrasound guided renal biopsy, insertion of peritoneal and tunneled dialysis catheters, and endovascular procedures for managing arteriovenous fistulas in dialysis patients. Additional educational resources are necessary to support its growth as a developing field. ChatGPT is an state-of-the-art language model with exceptional proficiency in natural language processing tasks, raising questions about its potential as an educational resource for interventional nephrology. However, its performance in this field has not yet been evaluated.

Methods: The Nephrology Self-Assessment Program (NephSAP) was utilized to evaluate the accuracy of ChatGPT in answering questions related to Interventional Nephrology. There was a total of 55 questions on NephSAP related to Interventional Nephrology. The question bank was executed twice using ChatGPT, and the level of concordance between the initial and subsequent runs was determined. Questions containing images were excluded from the assessment due to current limitations in ChatGPT’s image processing capabilities.

Results: ChatGPT achieved an accuracy of 52% on the initial run and 60% on the subsequent run. The overall concordance between the initial and subsequent runs was 73%, with the same responses on 40 questions (73%) and different responses on 15 questions (27%). Correct concordance was 63%, while incorrect concordance was 38%. Among the 15 questions with different responses, ChatGPT revised 7 incorrect responses to correct responses on the subsequent run. Conversely, it also switched 5 correct responses to incorrect responses on the subsequent run. There were 3 questions on which ChatGPT’s responses remained incorrect on both runs.

Conclusions: ChatGPT’s accuracy in answering questions related to Interventional Nephrology was suboptimal with an overall accuracy of 56%. The concordance between the initial and subsequent runs also suggested that ChatGPT may be unreliable. Based on these findings, the current version of ChatGPT is not a dependable educational resource for nephrologists, nephrology professionals, or medical staff in this subspecialty. Further development would be necessary to enhance ChatGPT’s performance in the field of Interventional Nephrology.

PUB178

Enhancing Patient Education Through Artificial Intelligence (AI): Evaluating ChatGPT’s Accuracy in Providing Information on Living Kidney Donation
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Background: Living kidney donation is a complex process and individuals seeking reliable information often turn to Frequently Asked Questions (FAQs) websites, such as Donate Life America. ChatGPT is an AI language model with the potential to offer accurate and comprehensive information on living kidney donation. However, its effectiveness in addressing patient queries specific to this topic has not been assessed. We aimed to evaluate ChatGPT’s performance in providing accurate information on living kidney donation by comparing its responses with those provided by nephrologists and a widely accessible FAQs website.

Methods: The study collected 27 questions on living kidney donation from the Donate Life America’s website and divided into four steps: original questions, paraphrased questions with different interrogative adverbs, paraphrased questions with verbs and prepositions removed, and questions with misspelled words. ChatGPT’s answers to each question were compared with those provided by the FAQs website and nephrologists to evaluate its accuracy.

Results: ChatGPT’s accuracy varied depending on the question type. ChatGPT provided correct answers for 85.2% of the original questions. Questions were paraphrased with different interrogative adverbs or with verbs and prepositions removed, and correct answers were provided by ChatGPT in 96.3% and 92.6% of the cases, respectively. The accuracy decreased to 85.2% when the questions contained misspelled words. Overall, the concordance between the initial and subsequent runs was tested and found to be 85.2% with an accuracy of 85.2%. The overall concordance in correct answers between the 1st and 2nd run of the original questions was 85.2%.

Conclusions: This study highlights ChatGPT’s promising accuracy, in providing reliable information on living kidney donation. ChatGPT consistently demonstrated accuracy rates >85% across a range of question formulations, including original questions and paraphrased versions. However, caution should be exercised when relying on ChatGPT’s responses to questions with misspelled words. The study suggests that further advancements are needed to enhance ChatGPT’s performance and ultimately improve patient education.

PUB179

Nephrology Program Director Protected Time for Training Program Administration: A Follow-Up Survey
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Background: In 2022-23, the Accreditation Council for Graduate Medical Education (ACGME) reduced minimum required program director (PD) protected time from 0.25 (10 hrs/week) to 0.2 FTE (8 hrs/week) for programs with <7 approved fellow positions. A survey of nephrology PDs in April 2022 found that 48% were not receiving the minimum 10 hrs/week.

Methods: A 22-question, anonymous follow-up survey was sent to all US adult nephrology PDs (March 2023) on how much protected time they received in 2022-23 and how much they needed to effectively administer their programs. We compared results with 2021-22, asked how PDs would use extra time if provided and assessed PD potential for burnout.

Results: Response was 62% (92/149) with 88% completion. Geographical distribution and number of approved positions was similar to the national profile. 61% had <7 approved fellowship positions for 2022-23 compared to 69% in ACGME’s data (IQR 6.25;12); 8 hrs/week (IQR 4.10) for programs with <7 fellows. 40% of programs were not in compliance with protected time requirements, regardless of approved fellow number. 37% (30/81) of PDs agreed they had “enough protected time to effectively administer my program.” PDs at smaller programs (< 4 and 5-6 fellows) estimated needing a minimum 10 hrs/week for effective program administration (16 hrs/week for <10 fellow programs). The top 3 tasks PDs would focus on if they had more time were 1) improve didactic curriculum (60%); 2) develop individualized fellow learning pathways (48%); 3) mentor fellow scholarly work (46%). 51% indicated they would prefer defined protected time in hrs/week for each program leadership member. Only 15% would prefer a block of time divided between faculty as they saw fit. 22% (18/81) were at high risk for emotional exhaustion, reporting feeling “burned out from my work” daily or a few times a week.

Conclusions: PDs report needing more protected time to complete necessary administrative and didactic tasks—a minimum 10 hrs/week regardless of program size. This would allow PDs to focus on improving fellow didactics and developing individualized fellow learning pathways, as recommended by the 2022 ASN Taskforce on the Future of Nephrology. The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.

PUB180

Surveying the Nephrology Landscape: A Targeted Needs Assessment Among Resident Learners
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Background: Interest in a nephrology career has waned among residents. Knowledge gaps and lack of exposure may contribute to this. Survey-based needs assessments have identified educational needs among nephrology fellows, but research targeting internal medicine residents is limited.

Methods: We distributed an electronic survey to internal medicine and medicine-pediatric residents at two academic teaching hospitals in Maryland in fall 2022. It included four sections: demographics, training, kidney disease topics, and educational resources. We analyzed responses using mixed methods including descriptive statistics, Spearman correlations, and inductive thematic analysis.

Results: Forty-nine of 208 residents completed the survey (24% completion rate). Those who had completed an internship or nephrology rotations were more likely to have considered a nephrology career (P = 0.006). The resources residents used most frequently and deemed most helpful are displayed in Figure 1. Residents felt most knowledgeable about hypertension (average 3.8 on a 5-point scale) and least knowledgeable about transplant topics (average 1.8 on 5-point scale).
about transplant nephrology (1.5/5). They most desired additional instruction on tubulointerstitial disease (51%). Suggestions for improvement in nephrology education centered around increased exposure to nephrology faculty, additional clinical rotations in nephrology, more nephrology teaching, and greater availability of nephrology resources.

Conclusions: Residents are interested in learning about nephrology topics and having nephrology incorporated more consistently into the internal medicine residency curriculum. These findings will help guide the creation of educational interventions to increase residents’ knowledge of and interest in nephrology.

Figure 1. Value of educational resources reported by internal medicine residents.

PUB181
Does an Online Curriculum for Continuous Renal Replacement Therapy Affect Internal Medicine Trainee Knowledge?
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Background: Current online resources of continuous renal replacement therapy (CRRT) do not focus on its clinical application at the resident level. We developed an interactive, video-based online curriculum on CRRT with learning objectives specifically designed for internal medicine residents. We aimed to improve resident fluency with CRRT using a stand-alone educational resource.

Methods: We sent an online needs assessment survey to internal medicine residents at our institution. This was followed by voluntary study participation. Our study included two arms. The control arm completed a 10-question knowledge assessment. The intervention arm participated in an interactive 20-minute online curriculum module prior to completing the same knowledge assessment. Participants in the intervention arm also completed a post-curriculum survey.

Results: Our needs assessment showed that residents had minimal instruction on CRRT but were interested in learning. Baseline characteristics and results can be seen in Table 1. Participants in the intervention arm scored higher on the knowledge assessment than the control. There was no difference based on PGY level or prior nephrology rotation experience. All (100%) of those who completed the curriculum recommended the module to their peers and thought the length was appropriate. An important limitation was low participation rate: 188 participants were surveyed, and 36 (19%) responded.

Conclusions: This study demonstrates a stand-alone module can improve resident knowledge in CRRT. Participants in the intervention arm performed better on an assessment irrespective of PGY level and prior nephrology rotation experience. Further studies will aim to optimize trainee participation.

Results of survey after training program

PUB182
Improving Dialysis Nursing Burnout with Innovative Technology Training
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Background: Nursing burnout is prevalent due to both rising shortages and increased workload. Studies cite dialysis nurses lack time and resources necessary for patient care. Furthermore, nurses in public hospitals are at higher risk for compassion fatigue, creating a greater need for change. Many owe the burnout to frequent complex patient interactions, high levels of depersonalization in poor work environments and complex technology. With respect to technology, a newer dialysis device, cleared in 2018 produces dialysate on demand for use in the acute, chronic, and home settings. The Tablo system offers a coordinator training program to ease implementation of this innovative technology. This report findsings from the training program.

Methods: An electronic survey was distributed to trainees enrolled in the Tablo coordinator program from May 2020-April 2023 (n=459). Questions included demographic hospital setting, dialysis experience, comfort with troubleshooting alarms and net promoter scores.

Results: Results from 399 respondents (90.88% overall response rate), from 187 unique facilities were analyzed. Most were dialysis or critical care nurses (24.56% and 25.81% respectively), worked in a hospital (82.20%) and greater than 5 years dialysis experience (53.38%). Many have never managed or managed less than 5 treatments on Tablo before training (58.16%), over 87% were extremely satisfied with the Tablo learning curve and 77.2% felt prepared for survey readiness. 88.97% of participants would highly recommend the Tablo Coordinator program to their friends and colleagues. 130 participants reported being either satisfied or very satisfied after training, see Table 1.

Conclusions: In summary, most nurses trained on this innovative technology feel they can perform tasks successfully and are looking forward to working with the device. This Tablo training program will help combat the stressors that dialysis nurses are faced with daily, leading to burnout. More research is needed to address the burnout issue in the dialysis sector.

Funding: Commercial Support - Outset Medical

Impact of the Preclinical Renal Block on Medical Students’ Attitudes Toward Nephrology
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Background: Teaching during the medical students’ (MS) clinical years is critical in deciding what specialty they pursue. Previous research in nephrology and other fields (e.g. psychiatry, general surgery) has explored the impact of clinical rotations on a medical student’s attitudes and preference for that specialty as a future career. Per our literature review, this is the first study to evaluate the impact of education in the pre-clinical years on a medical student’s preference towards nephrology. We present the impact of the Renal Block (4-week pre-clinical nephrology curriculum for first-year MS) on students’ attitudes towards nephrology and their desires to pursue nephrology as a specialty.

Methods: We administered a survey to first-year MS at the University of North Carolina School of Medicine (Chapel Hill, NC) for the 2022-2023 academic year [n=194]. This survey was distributed before and after the Renal Block and consisted of attitude-based questions that aimed to evaluate students’ perceptions and preferences.

Results: Pre-survey response rate was 51.5% (100/194) and post-survey response rate was 40.2% (78/194). Not all questions were answered by every student. 92% of the students found the field interesting after Renal Block as compared to 76% before the block. 90% felt that the block increased their interest in nephrology. Work-Life Balance, intellectual curiosity and long-term patient relationships were the top 3 factors affecting choice of specialty amongst MS (Table 1).

Conclusions: The three key findings were: 1) More students became interested in nephrology as a subject and/or career choice post-Renal Block; 2) Work-life harmony is an extremely important factor to students when choosing a specialty to pursue; and 3) Per students’ responses on short answer, the individual teaching the Renal Block had a major impact on student experience. Thus, pre-clinical nephrology teaching has a huge impact on MS attitudes towards nephrology.

Results of survey on MS attitudes towards nephrology
PUB184
Creation of a Comprehensive List of Interventional Nephrology Training Centers in the United States
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Background: Interventional Nephrology practice in the United States (US) began in the private sector in the 1990s. Unlike other nephrology sub-specialties, the training of Interventional Nephrology in the US is available in both academic and private practice centers. There needs to be a comprehensive resource that outlines the details of the Interventional Nephrology training programs in the US. This lack of resource has created a barrier for nephrology trainees interested in pursuing Interventional Nephrology training. The Training and Workforce Committee of the American Society of Diagnostic and Interventional Nephrology (ASDIN) aimed to develop a comprehensive list of Interventional Nephrology training programs in the US.

Methods: The Training and Workforce Committee of the ASDIN sent an electronic survey to all ASDIN members. The survey questionnaire focused on the type of Interventional Nephrology training center (academic/hospital-based or private practice), type of Interventional Nephrology procedure training, duration of training, and eligibility for Interventional Nephrology training for trainees on Visitors International Stay Admission (VISA).

Results: We received survey responses from the Medical Directors of 27 Interventional Nephrology training centers. Of these 27 centers, 14 were academic or hospital-based, and 13 were private practice centers. 17 of these centers were accredited by ASDIN. All centers provide hemodialysis vascular access procedure training, 10 centers provide peritoneal dialysis catheter placement training, and 13 centers provide endovascular arteriovenous fistula creation training. The duration of Interventional Nephrology training varied across the centers, and in majority of the centers, the training duration was either 3-6 months (9 centers) or 6-12 months (9 centers). Eligibility for Interventional Nephrology training based on the trainees’ VISA status was variable, with 5 centers offering training to J-1 Visa holders.

Conclusions: To date, this is the most comprehensive list of the Interventional Nephrology training programs in the US. The list is available on the ASDIN website: https://www.asdinn.org/page/trainingcenters. This list will be an invaluable resource for nephrology trainees interested in pursuing Interventional Nephrology training.

PUB185
Increasing Attitudes Toward the Field of Nephrology Using Interactive Dialysis Modules for Trainees
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Background: End-stage kidney disease and dialysis-dependent patients form a significant portion of the hospital population encountered by resident physicians. However, these trainees often lack formal education and confidence in managing dialysis-related care. Previous studies have indicated that trainees find kidney disease complex, contributing to decreased interest in nephrology. Additionally, there is a need for interactive educational tools to facilitate learning. This study aimed to assess the impact of interactive online modules on dialysis knowledge acquisition and attitudes towards nephrology.

Methods: We created five case-based interactive online modules, each focusing on an indication for acute dialysis initiation (acidosis, electrolyte abnormality, intoxication, volume overload, uremia) and linking these to fundamental dialysis principles (diffusion, convention, ultrafiltration, adsorption). The modules were designed to be completed within 10-20 minutes. Learner responses guided the progression of cases, providing detailed explanations for incorrect responses and concise summaries for correct responses. Modules were distributed among internal medicine resident physicians and medical students for voluntary completion. Pre- and post-module assessments included a 5-point knowledge questionnaire and a 4-point Likert scale survey measuring attitudes towards nephrology concepts and careers.

Results: 27 participants responded (16 pre-curriculum, 11 post-curriculum), including one medical student. Post-curriculum knowledge assessment scores showed improvement compared to pre-curriculum scores (3.3 vs. 4.5, p < 0.01), driven primarily by responses (2.9 vs. 4.5, p < 0.01). While attitudes towards nephrology did not improve significantly, there was a decrease in participants who found dialysis intimidating (3.2 vs. 2.7, p = 0.03).

Conclusions: The study demonstrated that interactive online modules enhanced participants’ knowledge of dialysis concepts and increased their comfort in managing dialysis patients, particularly among internal medicine trainees. Although attitudes towards nephrology careers were unchanged, this would not be expected from a single intervention. These modules could be combined with other strategies to improve nephrology knowledge and generate greater interest in the field.

PUB186
A Successful Resuscitation: Bedside Native Kidney Biopsies Performed by Nephrology Fellows at an Academic Tertiary Care Center
Eily Hayes, Blaithin A. McMahon, Natalie T. Friedin. Medical University of South Carolina, Charleston, SC.

Background: Biopsy is the gold standard for diagnosing renal pathology, and performing percutaneous kidney biopsy is a core clinical task taught in all graduate medical education in nephrology. The growth of interventional radiology and COVID-19 pandemic-related department restructuring and staffing turnover significantly decreased fellows’ opportunity to perform and gain clinical competency in kidney biopsies at our academic tertiary care center. Faculty and fellows developed a new protocol for performing low-risk ultrasound guided biopsies bedside, resulting in a significant increase in kidney biopsies performed by nephrology.

Methods: A protocol for low-risk kidney biopsies performed at bedside was developed and implemented. The protocol included indications and contraindications for biopsy, characteristics of low-risk biopsy patients, pre-biopsy clinical management guidelines, the biopsy procedure, standardized post-biopsy orders, and templates for related documentation. The protocol was revised to address institution-specific challenges as they arose. Data regarding the number of biopsies, complications, and diagnoses were recorded and analyzed.

Results: From June of 2020 through December 2021, two bedside kidney biopsies were performed by nephrology fellows (1.26 biopsies per year). The new protocol was implemented at the start of the 2022-2023 academic year. In the subsequent 11-month period, ten biopsies were performed bedside by nephrology fellows (10.91 per year), an 864-percent increase. One of the ten biopsies (10%) was complicated by subcapsular hematoma; though our sample size is small, this rate comparable to that in a systemic review and meta-analysis of over 118,000 renal biopsies published in CJASN in 2020 (11%). Data collection is ongoing, but an additional benefit at our institution has been that patients can be biopsied, and diagnosis obtained, earlier in the clinical course.

Conclusions: At our tertiary academic center, a protocolized approach to low-risk kidney biopsies at bedside has significantly increased the number of kidney biopsies performed by nephrology. An unanticipated benefit is that low-risk patients have had shorter wait-times for biopsy, allowing for tissue diagnoses and initiation of treatment earlier in the clinical course.

PUB187
Observations from the POCUS Precourse at the NKF 2023 Spring Clinical Meetings
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Background: In April 2023, a POCUS precourse was conducted at the National Kidney Foundation (NKF) Spring Clinical Meetings with the intent of providing foundational knowledge and practical skills necessary to perform basic scans pertinent to nephrology.

Methods: To maximize the time for hands-on learning, a set of 5 recorded lectures was provided to the registrants as pre-reading material. The workshop structure consisted of two identical 4-hour sessions (AM & PM) accommodating 16 and 23 learners respectively. See Figure 1 for the layout. An anonymous post-course survey was sent out, answered by 25 unique respondents (response rate 64%).

Results: The respondents were asked to rate their perceived confidence in acquiring and interpreting POCUS images on a scale of 0-10. The confidence in acquiring kidney images increased significantly from 2.6 ± 2.3 (mean ± SD) before to 7.8 ± 1.5 after the workshop (p<0.001). Confidence in acquiring lung and cardiac images showed a remarkable improvement (1.8 ± 2.4 to 7.7 ± 1.5 [p<0.001] and 1.5 ± 2.2 to 7.2 ± 1.3 [p<0.001] respectively). In addition, the respondents reported a substantial improvement in their confidence in interpreting kidney, lung, and cardiac ultrasound images (4.5 ± 2.2 to 7.7 ± 1.1 [p<0.001], 2.3 ± 2.4 to 7.6 ± 1.5 [p<0.001] and 2 ± 2 to 7.3 ± 1.5 [p<0.001] respectively) [Figure 2].

Conclusions: The NKF POCUS precourse was successful in improving confidence of participants in acquiring and interpreting basic scans. While confidence does not necessarily imply competence, it serves as a motivating factor for continued practice. It is not realistic to expect improvement in competence via a half-day workshop.
Nomophobia: Phone-Lessness Phobia Among Kidney Professionals

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Background: The nature of healthcare providers’ work demands continuous connectivity and accessibility to digital resources eg. quick access to medical references, patient information and teleconsultations. Nomophobia, also known as “No-Mobile Phone Phobia”, refers to anxiety, or nervousness caused by not being in contact with a mobile phone. There is paucity of literature to explore the prevalence and severity of nomophobia among kidney professionals.

Methods: A cross-sectional pilot study was conducted among healthcare professionals from April-May 2023. This abstract includes responses from attending physicians, fellows, nurses, advanced care providers (APP) and dialysis technicians. A web-based validated survey was shared using emails and social media applications such as whatsapp, linkedin and twitter. The study was IRB-exempt.

Results: A total of 100 responses were recorded from 10 countries in this ongoing survey. There were 49% females, with the highest representation in the age (in years) between 35-45(35%) and 25-35(25%). Approximately 50% of the respondents were Asians, 36% were White, 5% were Hispanics, and 2% were Black. The kidney professionals included attending physicians (38%), nurses (23%), fellows (11%), and APP (8%). The majority years of experience was of 6-10 (28%). Nearly 50% kidney professionals reported using their smartphones for more than 2 hours at work, and 64% reported using them for personal activities for up to 4 hours (Fig. 1). A vast majority (74%) was an I-phone user. The nomophobia prevalence of mild, moderate, and severe nomophobia was 13%, 52%, and 34%, respectively.

Conclusions: This pilot study denotes that the 2/3rd kidney professionals have self-reported nomophobia. Early recognition and management of nomophobia are crucial for improving work-life balance, and ensuring their wellbeing in the evolving digital era.
stable patients however CVVHD could be substituted in patients in shock. Education of signoous patients and providers to avoid metformin when there is a risk of renal failure, particularly with hypovolemia, is crucial to prevent MALA.

**TREATMENT OF SEVERE HYPOXENATREMIA WITH UREA IN LIVER CIRRHOSIS**

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**Introduction:** Treating severe hypernatremia in liver cirrhosis is challenging. Hypertonic saline and vaptans can be unsafe and cost prohibitive. It needs ICU for close monitoring. Urea given orally can be safe in treating patients with hypernatremia with SIAH. Its role in treating hypernatremia in liver cirrhosis is not established. We present our experience in treating one such patient successfully.

**Case Description:** A 58-yr-old female with liver cirrhosis from alcoholism and hepatitis C infection was admitted with hypotension, tense ascites and shortness of breath. Her chemistry revealed a sodium of 120 mmol/L, total protein 7g/dl and albumin 2.5 g/dl. BUN 3 mg/dl and creatinine of 0.4 mg/dl. AST 146 U/L, ALT 57 U/L and a bilirubin of 2.8 mg/dl. Urine sodium was <5 mmol/L and osmolality was 366 mOsm/kg. Therapeutic paracentesis of 6 liters performed on the day of admission and 4.25 L on 3rd day and was started on urea15 grams bid. Her sodium level was monitored frequently. On day 3 her sodium was 126 mmol/L and she was discharged on day 5 when it was 128 mmols/L.

**Discussion:** Hypernatremia can be caused by several conditions. The treatment in most conditions includes elimination of free water, free water restriction or deficient hormones replacement in adrenal insufficiency and hyponatremid. Hypernatremia is frequently seen in patients with ascites secondary to advanced cirrhosis and portal hypertension. The development of ascites in patients with cirrhosis with portal hypertension and systemic vasodilation leads to activation of the sodium-retaining neurohumoral mechanisms, which include the renin-angiotensin-aldosterone system, sympathetic nervous system, and release of antidiuretic hormone (ADH). The net effect is the avid retention of sodium and water to compensate for the low effective circulatory volume resulting in worsening ascites and release of antidiuretic hormone (ADH). The net effect is the avid retention of sodium and water to compensate for the low effective circulatory volume resulting in worsening ascites. Salt and water restriction alone may not be effective and hypertonic saline and vasopressin receptor (V2R) agonists use can be costly and potentially lethal from osmotic demyelination. We conclude that urea is a novel option for treating hypernatremia. It may eliminate the risk of osmotic demyelination unlike with hypertonic saline and V2R. It is an endogenous product of amino acid metabolism, is cost effective in treating hypernatremia of liver cirrhosis and hence should be utilized more frequently. Controlled trials are needed.

**SLC34A3 MUTATION: A “NON-GARDEN VARIETY” OF HYPERCALCEMIA**

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**Introduction:** Hypercalcemia is a common reason for renal consultation. Measuraments of parathyroid hormone (PTH), PTH-related peptide, 1,25(OH)D, and serum phosphorus are typically ordered. 1,25 hypervitaminosis prompts routine investigation for ingestion, granulomatous disease, or lymphoproliferative disorders. When a source is not obvious, further genetic testing should be considered.

**Case Description:** 60-year-old woman with diabetes mellitus type 2, hypertension, hyperlipidemia, chronic atrial fibrillation, chronic pelvic pain, and history of rheumatic heart fever was referred for intermittent hypercalcemia, ranging between 9.9-11.2 mg/dL. Medications: amlodipine, atorvastatin, magnesium oxide, loratidine Vital signs: height 160 cm, weight 85.5 kg, blood pressure 145/62 mmHg, pulse 72 bpm, 36.2°C. Physical exam with no clinical signs of hypercalcemia. 24-hour urine study: calcium 924 mg, phosphorus 310 mg, hydroxypropion 0.5 mg. Serum 1,25(OH)D and PTH were normal. Renal ultrasound without stones or structural abnormality. Hypercalcemia was suspected and genetic testing was ordered. Mutations in all 11 known genes for hypercalcemia were excluded. Genetic testing showed a novel heterozygous mutation in SLC34A3 gene, c.769G>A. Mutation was present in the patient and her mother.

**Discussion:** Genetic testing was positive for heterozygous mutation of SLC34A3, a gene encoding the renal sodium-dependent phosphate cotransporter 2c (NPT2c). In this condition, phosphaturia is thought to increase 1,25D synthesis to increase gastrointestinal (GI) absorption of phosphorus. The high 1,25D level simultaneously enhances GI absorption of calcium, causing hypercalcermia and corresponding hypercalciuria. At the time of this writing, urine studies for phosphaturia is pending. Presence of hyperparathyroidism will confirm the etiology of hypercalcemia as hereditary hypophosphatemic rickets with hypercalcermia, in which case, treatment would be phosphorus supplementation. In current era, genetic testing, patient only develops abnormal calcium and phosphorus profile without associated bone involvement. Hypercalcemia has a wide differential diagnosis. A thorough search for its cause is warranted for direct and specific therapy.
When History Repeats Itself: Metformin-Associated Lactic Acidosis
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Introduction: Metformin associated lactic acidosis (MALA) is a fatal phenomenon that clinicians often overlook. However, predisposing comorbidities such as CKD can make the patient more vulnerable to MALA, especially if the metformin dose is not appropriately adjusted. We present a patient with a suspected history of CKD, prior admission for suspected MALA, on high dose metformin who presented with severe lactic acidosis and acute kidney injury requiring dialysis.

Case Description: A 70-year old female with a history significant for diabetes and hypertension presented with nausea, vomiting, fatigue, and confusion. Chart review showed that she had several hospitalizations before that were complicated by AKI requiring dialysis, including one in which MALA was suspected. Unfortunately, her home metformin dose (1000 mg BID) was never adjusted. Her GFR the previous year ranged from 60 to 90 mL/min/1.73m² in several squared, and her average GFR was maintained around 51 mL/min/1.73m². Vitals on admission were 113/55 mmHg, heart rate of 111 bpm, respiratory rate of 28, and temperature of 97.1 F. On physical exam she was alert and oriented, appeared uncomfortable and had tachycardia. Creatinine was 6.2 mg/dL, with blood urea nitrogen of 40 mg/dL, Lactic acid of 18 mmol/L, beta-hydroxybutyrate of 1.8 mmol/L, bicarbonate of 6 mmol/L, anion gap of 37 mmol/L, and initial pH of 6.63. She was initiated on maintenance fluids and sodium bicarbonate infusion, but continued to deteriorate, with lactic acid peaking at 40 mmol/L and she was intubated and transferred to the ICU. Her hospitalization was further complicated by shock requiring pressors and steroids. She was started on continuous renal replacement therapy. Within 24 hours her lactic acid resolved, her mentation improved, and she was liberated from the mechanical ventilator. Her home metformin was discontinued.

Discussion: While MALA was not officially diagnosed with CKD, there are several factors that raise suspicion for her having this chronic illness. Her average GFR the previous year, history of hypertension, diabetes, as well as prior episodes of AKI requiring hemodialysis warranted an evaluation for CKD. Patients who survive AKI have been shown to have an association with developing CKD. In the setting of recurrent admissions for AKI and CKD risk factors, providers should have a lower threshold for investigating potentially nephrotoxic medications.

Drug-Induced Fanconi Syndrome Presenting as Chronic Constipation: A Well-Known but Forgotten Entity
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Introduction: Fanconi syndrome is a proximal renal tubular dysfunction characterized by renal wasting of electrolytes and solutes. Acquired Fanconi Syndrome is described in the context of various exogenous toxins, drugs, and systemic diseases. We present a case of long-standing constipation treated with a seemingly simple solution by identifying an often-ignored underlying etiology.

Case Description: This is a 59-year-old South Asian female with history of hypertension, diabetes, stage 3a chronic kidney disease, and chronic hepatitis B and C infection who presented to the hospital with complaint of persistent abdominal discomfort due to constipation for 3 weeks. She had prior hospitalizations for the same complaint. Her home medications included tenofivir disoproxil fumarate (TDF) which she had been taking for 10 years amongst others. Lisinopril and metformin were recently discontinued owing to a previous hospitalization for acute kidney injury. At presentation, labs were significant for hyperkalemia (K 2.3), unresponsive to aggressive oral and intravenous potassium supplementation, mild hypotension (Na 131), hypophosphatemia (PO4 1.9), hyperchloremia (Cl 113), and acute on chronic renal dysfunction with BUN/ Creatinine 20.2/17.2 mg/dL. Urinalysis showed a glucose of >1000 mg/dL and protein of 100 mg/dL. Further work-up of hypokalemia revealed a trans-tubular potassium gradient (TTG) of 5.6, indicating renal wasting. Tenofovir was suspected to be the culprit causing renal tubular acidosis and electrolyte derangements precipitating chronic constipation. Patient was switched to Entecavir after consultation with infectious disease. Follow-up during subsequent months showed correction of electrolyte abnormalities without the need for supplementation and resolution of constipation.

Discussion: Fanconi syndrome is a well-established entity, with a known association with Tenovif. Clinicians often overlook the pathology leading to unnecessary work-up and prolongation of symptoms. In our case, simply discontinuing the drug helped correct the electrolyte derangement and prevent subsequent hospitalizations due to constipation. Physicians should closely monitor patients on medications known to induce Fanconi and keep this syndrome in the differential when dealing with multiple electrolyte imbalances and disproportionate glucosuria. Early identification can prevent progression of disease.

Anion Gap Metabolic Acidosis in Chronic Acetaminophen Use: An Ongoing Conversation
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Introduction: In the inpatient setting high anion gap metabolic acidosis (HAGMA) is a common finding. Clinical approach to address HAGMA tends to focus on common etiologies such as lactic acidosis, diabetic ketoacidosis, uremia and others, with electrolyte checking and acetaminophen toxicity as the underlying problem. Accumulation of 5-oxopropionate has been described as causing HAGMA in cases of acute acetaminophen overdose. However, a case of chronic acetaminophen use and chronic kidney disease with acute exacerbation of chronic renal dysfunction due to hypokalemia leading to development of HAGMA is described.

Case Description: 74yo female with medical history of HTN, SLE, DM2, end-stage renal disease (ESRD) on hemodialysis (HD) Admitted for CABG and severe aortic stenosis repair. Last HD had been a day prior to surgery and resumed on POD1 as continuous veno-venous hemofiltration (CVVH). Scheduled medications included aspirin, heparin, hydroxychloroquine, pantoprazole, polyethylene glycol. On laboratory values Na 135 mEq/L, K 4.6 mEq/L, Cl 99 mEq/L, HCO3 25 mEq/L, BUN 22 mg/dL, creatinine 3.02 mg/dL, glucose 88 mg/dL, Ca 9.6 mg/dL and PO4 4.5 mg/dL. Post-op complicated with metabolic acidosis from apparent bacterial meningitis with constant requirement of pressors. Started on ampicillin and cefepime antibiotic therapy, CVVH continued for 26 days. Transitioned to accelerated veno-venous hemofiltration (AVVH) thrice weekly. After AVVH was completed the patient developed metabolic acidosis with a bicarbonate of 16 mmol/L, arterial blood gases pH 7.29, paO2 183 mmHg, pCO2 level 34 mmHg and bicarbonate level 16 mmol/L. Lactic acid level 0.8 mmol/L and D-lactic acid undetected. Due to acidosis CVVH was restarted on POD28. The following day bicarbonate was 24 mmol/L.

Discussion: Medication review showed scheduled APAP since prior to admission. This was low concern for lactic acidosis as the exogenous source of anions as insulin continued throughout the tube feeds. We inferred the increased HAGMA likely resulted from 5-oxopropionate accumulation. APAP was discontinued on POD29, CVVH was discontinued the next day with intermittent HD provided on POD31 three weekly schedule. Holding HD for greater than 48 hours, bicarbonate was maintained at >24 mmol/L. Chronic acetaminophen use and 5-oxopropionate should be considered in HAGMA when more common etiologies have been addressed. The use of RRT complicated the picture and delayed diagnosis. Most reported cases have been females with chronic medical conditions including renal insufficiency, malnutrition, sepsis, and pregnancy.

Unsettling Lactate Levels: A Hint Toward Metformin Toxicity
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Introduction: Metformin is a common and safe antidiabetic agent to treat diabetes mellitus (DM). Metformin-associated lactic acidosis (MALA) is a rare condition yet has high clinical deterioration and mortality rates. The following case illustrated a patient presenting with encephalopathy, found to have metabolic acidosis due to metformin toxicity.

Case Description: A 51-year-old male with a past medical history of atrial fibrillation, congestive heart failure, DM type II, hypertension, hyperlipidemia, and obesity presents with encephalopathy and respiratory distress. Physical exam was remarkable for somnolence, scleral icterus, bilateral lower limed edema and venous stasis distention. His baseline serum creatinine levels were in the 1.10-1.2mg/dL range. Relevant labs at presentation revealed serum creatinine 2.77 mg/dL, blood urea nitrogen 34 mg/dL, potassium 8.3 mmol/L, bicarbonate 8 mmol/L, anion gap 39 mmol/L, and lactate 22.3 mmol/L. Metformin level was at 9.00 mg/dL. Radiological workup was unremarkable. Patient went into circulatory shock requiring vasopressor support and mechanical ventilation. Continuous renal replacement therapy (CRRT) was initiated for severe hyperkalemia and acidosis. Sodium bicarbonate infusion was started to improve acid-base dyscrasia. He was transitioned to hemodialysis after hemodynamic stability was achieved. According to literature, therapeutic plasma metformin level ranges between 0.1 and 4 mg/ml, higher metformin levels are proposed to be a cause of lactic acidosis. Risk factors include individuals with decreased renal function, impaired hepatic metabolism and cirulatory abnormality. Metformin stimulates lactate conversion and promotes substrates for lactate production, owing to unsettling lactate levels when it accumulates. MALA presents with nonspecific symptoms which can lead to delays in diagnosis. It is imperative that dialysis is promptly initiated for treatment, clearing metformin accumulation. Early suspicion and metformin levels in specific patients can lead to favorable outcomes.

Hypokalemia-Induced Nephrogenic Diabetes Insipidus in an Adult with Severe Hyponatremia: A Case Report
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Introduction: Acquired nephrogenic diabetes insipidus (DI) can be due to kidney disease, medication adverse effects, or electrolyte derangements, such as hypokalemia. We report a case of acquired nephrogenic DI due to hypokalemia leading to hyponatremia.

Case Description: A 54-year-old man with hypertension and bipolar disorder on lithium therapy presented with nausea, vomiting, and fatigue for several days. Initial electrolyte workup revealed metabolic alkalosis with blood pH of 7.51, serum bicarbonate of 41 mmol/L, serum sodium of 102 mmol/L, serum potassium of 2.0 mmol/L, and serum chloride of 60 mmol/L. Urinalysis showed low osmolality of 60 mOsm/kg and sodium of <20 mmol/L. The hyponatremia was attributed to a combination of psychogenic polydipsia and decreased solute intake and was treated.
with fluid restriction. Subsequent hyponatremia overcorrection (>12 mmol/L per day) with a continued urine output of 7-8 L/day was managed with dextrose 5% in water and desmopressin. Interestingly, urine osmolality remained at 63 mOsm/kg and did not increase after several doses of desmopressin, consistent with the diagnosis of nephrogenic DI, initially attributed to lithium use. However, after normalization of serum potassium, spontaneous urinary concentration to 360 mOsm/kg was observed (Figure 1), suggesting hypokalaemia-induced nephrogenic DI.

Discussion: This case illustrates the critical role that potassium plays in the urine concentrating ability of the kidney. Adequate serum potassium levels are necessary for the kidney to respond to desmopressin, which is an essential tool in treating hypotonic DI. Rapid potassium repletion is often initially delayed to avoid hyponatremia overcorrection and its dramatic complications. However, hypokalaemia can lead to acquired nephrogenic DI which can worsen hypotonia overcorrection.

Figure 1. Serum sodium and urine osmolality trend over the course of the treatment. The urine osmolality did not increase with desmopressin administration. However, with potassium repletion, the urine osmolality started rising, suggesting a diagnosis of hypokalaemia-induced nephrogenic diabetes insipidus.

PUB200

A Rare Case of Zonisamide-Induced Distal Renal Tubular Acidosis (RTA)
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Introduction: Zonisamide is a commonly used anti-epileptic drug which has been associated with side effects such as constipation and nausea. It has also been reported to cause distal renal tubular acidosis in the past but this is an exceedingly rare occurrence. Upon review of literature, only one documented case report has been published showing the association between zonisamide use and RTA. In this case, we aim to further the knowledge of this seldom seen side effect.

Case Description: A 28 year old male with history of autoimmune limbic epilepsy and temporal lobectomy on zonisamide was admitted to our institution after being referred by PCP for hyponatremia and rhabdomyolysis. Prior to admission, he noted a myriad of symptoms such as myalgias, unsteady gait, and nausea. BMP on admission revealed potassium level of 1.6, serum chloride 115 and serum bicarbonate 2. EKG changes associated with severe hyponatremia were noted. He was started on continuous potassium replacement with IV as well as oral supplements. Despite adequate correction, his potassium level continued to drop and remained under 2 mmol/L. Workup showed normal serum aldosterone level. Serum and urine electrophoresis showed no evidence of monoclonal gammopathy. Renal ultrasound, CT abdomen and CT chest were all normal with no anatomical abnormalities or masses. Urine anion gap was inconclusive- neither significantly positive nor negative. Spot urine protein/creatinine ratio was 37.6 mg/g which was suggestive of urinary potassium losses. After ruling out other causes of potassium depletion, his medication list was reviewed and zonisamide was identified as a potential cause of hyponatremia. He was tapered off zonisamide and started on alternate therapy. He was eventually stabilized and discharged to home. Upon follow up labs in 6 weeks, his potassium had normalized and he was asymptomatic which further proved that zonisamide was the cause of distal RTA and severe hypokalaemia.

Discussion: This case highlights the importance of thorough history and medication review which aids in diagnosing such challenging presentations. Although there is not much literature to support, zonisamide can cause RTA as shown in our case. Other anti-epileptic agents have been studied such as topiramate which are implicated in RTAs, suggesting that agents previously which have not been studied might also have the potential for such side effects.

PUB201

Pseudonormokalemia
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Introduction: Thrombocytosis is a well known cause of “pseudohypokalemia”, whereby measured serum potassium is falsely elevated due to release from platelets after clotting time collected, which can be overcome by the addition of heparin. In clinical practice, heparinized tubes are used after identification of hyperkalemia to rule out pseudohypokalemia. Rarely is this considered in the setting of normal serum potassium, but is still an important consideration in patients with thrombocytosis as a normal value may represent a total body deficit in potassium, known as “pseudonormokalemia”. We present the case of a patient with thrombocytosis and normal measured serum potassium who developed metabolic alkalosis during diuresis, though found to have significant hypokalemia after heparinizing the collection tube.

Case Description: Our patient was a 53 yo man with HTN admitted to the cardiothoracic service for CABG after admission for STEMI. His course was complicated by AKI for which the nephrology consultation service was involved. His kidney function recovered during his admission, though with hypervolaemia for which he was diuresed with IV furosemide. During his course he developed reactive thrombocytosis, and rising serum bicarbonate with apparent normal serum potassium (Figure 1). After heparinizing potassium collection, significant hypokalemia (2.9 MEq/L) was revealed in a patient with sensitive myocardium.

Discussion: We report the case of “pseudonormokalemia” in a patient diuresed with furosemide with concomitant reactive thrombocytosis. We believe this case highlights an important consideration in the evaluation of patients at risk for hypokalemia, and to consider use of heparinized collections in those with thrombocytosis regardless of their serum potassium level.

Figure 1. Trend in platelet count and basic metabolic profile during hospital admission. T represents day of heparinizing sample.

PUB202

Trimethoprim-Sulfamethoxazole-Associated Severe Hyponatremia
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Introduction: Trimethoprim-Sulfamethoxazole (TMP-SMX) is recommended as first line therapy for the treatment of Pneumocystis Jirovecii pneumonia. Although described in the literature, hyponatremia remains a rare complication of TMP-SMX treatment. Here, we present a case of severe hyponatremia in a hospitalized patient following treatment with high-dose intravenous TMP-SMX.

Case Description: 65-year-old female with metastatic lung cancer presented to our hospital for shortness of breath and fatigue. Pt. received a course of chemotherapy 4 days prior to presentation. Pt. was found to have Pneumocystis Jirovecii pneumonia and was initiated on high-dose intravenous TMP-SMX (430 mg trimethoprim and 86 mg SMX twice daily). SNa was 137 mmol/L (normal range 135-145 mmol/L) prior to initiation of TMP-SMX treatment. SNa subsequently decreased to 129 mmol/L the day after initiation of TMP-SMX and decreased further to 118 mmol/L 2 days later. CT chest showed diffuse bilateral ground glass opacities concerning for infectious process vs pulmonary edema. Patient received intravenous furosemide therapy. SNa however decreased further to 114 mmol/L. Hyponatremia work up revealed low serum osmolality of 250 mosm/kg, elevated urine osmolality of 481 mosm/kg, and inappropriately elevated urine sodium of 45 mmol/L. Patient was initiated on 3% hypertonic saline infusion. SNa improved but remained stable at 121 for the next 2 days. Intravenous TMP-SMX was subsequently discontinued. SNa gradually improved to 129 mmol/L, 2 days after discontinuation of TMP-SMX. Over the next few days, patient clinical condition worsened and died during the hospital stay.

Discussion: Patients receiving chemotherapy are at an increased risk for serious bacterial, fungal, and viral infections. Our patient was found to have Pneumocystis Jirovecii pneumonia. Treatment with high dose intravenous TMP-SMX resulted in severe acute hypo-osmolar hyponatremia. While the exact mechanism of hyponatremia secondary to TMP-SMX use remains unclear, inappropriate secretion of anti-diuretic hormone and renal salt wasting have been proposed in the past. Hyponatremia improved significantly in our patient soon following the discontinuation of TMP-SMX treatment. Clinicians should be aware of this potential and reversible adverse effect of this agent.

PUB203

Oxcarbazepine-Induced Hyponatremia
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Introduction: Antiepileptic medications are well known to induce hypoosmotic hyponatremia, however, the precise mechanism of action remains under debate, ranging from SIADH induction to psychogenic polydipsia. Unfortunately, these agents are often overlooked and continued upon hospital admission. We describe a patient who developed hypoosmotic hyponatremia in setting of recently started oxcarbazepine.

Case Description: 54 yr female seizure disorder, hypertension, and COPD presented with the chief complaint of progressive shortness of breadth and refractory nausea due to community acquired pneumonia and viral gastroenteritis, respectively. Chemistry panel...
showed serum sodium 121 mmol/L (138 mmol/L one month prior), serum osmolality 262 mOsm/kg, potassium 4.1 mEq/dL, BUN 17 mg/dL, and serum creatinine 0.9 mg/dL. Vital signs showed blood pressure 128/73 mmHg and heart rate 72 BPM. Physical exam revealed euvolemic volume status with lack of altered mentation. U/S showed bilaterally increased echogenicity and simple renal cysts. After obtaining prior fluid administration, revealed urine sodium 24 and urine osmolality 500 suggesting ADH attributed to pneumonia and nausea. She was started on a 1 L/day free water restriction and urea 15 mg BID and admitted to ICU for sodium monitoring. Home medications, including osacarbazeine, were continued upon admission. The serum sodium failed to improve over the first 36 hours despite increasing urea powder to 400 mg BID and fluid restriction. Medication hold was used to prevent the continuation of home osacarbazeine which, per patient history, was initiated three weeks prior to hospitalization. Osacarbazeine, urea powder, and fluid restriction were stopped and neurology service consulted for implementing an alternative anti-epileptic agent. The serum sodium continued to worsen, with additional intervention, from 121 mmol/L to 138 mmol/L, over the proceeding 72 hour time interval.

Discussion: Osacarbazeine can result in hyponatremia refractory to the common therapeutic strategies used to treat SIADH. Our case illustrates the importance of reviewing the outpatient medication list as many pharmacologic agents can be continued upon admission, without discretion, ultimately contributing to refractory electrolyte abnormalities. Additionally, we must consider alternative etiologies, even in the setting of known SIADH stimuli, when common clinical practices fail to result in hyponatremia improvement as an unidentifiable etiology may be present.

PUB204 Salt Is Good: Correction of Hyponatremia in Heart Failure with Dietary Sodium

Introduction: Hyponatremia is the most common electrolyte imbalance in patients with acute decompensated heart failure. It is associated with increased mortality, hospitalizations and readmissions with management of volume overload. The mechanisms of hyponatremia in heart failure are high levels of antidiuretic hormone coupled with low glomerular filtration rate and the use of loop and thiazide diuretics. We present a case highlighting the complexity of sodium balance in acute decompensated heart failure.

Case Description: A 65-year-old female with CHF with preserved EF (60-65%), pulmonary hypertension, CAD, Type II diabetes, atrial fibrillation, CKD, presented with acute decompensated heart failure and volume overload. Diuresis was started with bumetanide on day 1 of the hospitalization. Chlorothalidone was added on day 5. This was switched to Metolazone on Day 7. On admission, sodium was 134 mEq/L and down trended to a low of 121 mEq/L on hospital day 13. This was accompanied by significant nausea and vomiting. Despite strict free water restriction and a diuretic holiday, hyponatremia persisted. She was then encouraged to eat ramen (2167 mg Na per serving) and given salt tablets in addition. Free water restriction was continued as well and so were the loop diuretics. Thiazide diuretics were held. Serum sodium subsequently improved to 131 mmol/L with improvement in symptoms. She was discharged in a euvolemic state on a home regimen of bumetanide and oral salt.

Discussion: We present a case of hypotonic hyponatremia in acute decompensated heart failure. The first line management of hyponatremia in heart failure is diuresis and dietary sodium restriction. However, hyponatremia may be induced or worsened in these patients by multiple mechanisms including SIADH, like physiology and use of thiazide diuretics. In such cases, adherence to a sodium restricted diet while on diuretics may worsen hyponatremia. Increased access to dietary salt with concomitant free water restriction may correct this problem as demonstrated in our patient. Using dietary sources of sodium chloride as little as 1770 mg Na or 760 mEq Cl per day to raise the sodium level to at least 130 mEq/L for the patient to undergo surgery for his fractures, a trial of tolvaptan 7.5 mg PO daily was initiated, resulting in a rise in serum sodium to 127 mEq/L in the first 24 hours, and a level of 130 mEq/L in 72 hours. Diuretic therapy was discontinued and tolvaptan was continued for the remainder of the hospitalization, 700 mg PO BID, with a sodium level reaching 134 mEq/L by day 26 of therapy. He was able to undergo surgery, tolvaptan was discontinued, and the patient was discharged home with normal sodium levels.

Discussion: Tolvaptan is a breakthrough in the treatment of hyponatremia, particularly in patients with SIADH, but its use in patients with HF has also been of great support. This case is an example of its effectiveness in this population.

PUB206 Hypo-Hyperalactemia of Rhabdomyolysis
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Introduction: Rhabdomyolysis (RD) is the breakdown of skeletal muscle, with release of intracellular contents including electrolytes and enzymes, which can result in AKI. Hyponatremia is commonly associated; however, hyperalactemia after initial hypotonic hyponatremia has been reported. The pathogenesis of hyperalactemia remains unclear with multiple theories. We report a case of hypo-hyperalactemia associated with cocaine induced rhabdomyolysis.

Case Description: A 42-year-old male with a history of polysubstance abuse presented with septic shock along with cocaine intoxication leading to severe muscle damage, AKI, and requiring intubation. On admission, the Na level was 1035±10 U/L, BUN 28 mg/dL, Creati 2.8 mg/dL, and Corrected Ca 6.7±.1 mg/dL. A week after the admission, his Ca level started to normalize; However, after 20 days he developed hyperalactemia with Ca values ranging from 10.3 to 12.8 mg/dL with PTH 16.3 mg/mL and Na level of 108±3 mg/dL. This did not show any response to 15 mEq/L of Na or 0.9% NS. After 1 month, his clinical condition started to deteriorate, and he passed away.

Discussion: Disturbance in Ca homeostasis has been observed in cases of rhabdomyolysis-induced AKI. Initial Hypocalcem is due to sequestration of Ca associated with hyperphosphatemia in the destroyed muscle. Subsequent hyperalactemia may occur during the recovery phase of AKI caused by RD. The pathophysiology of hyperalactemia in this case was a subject of debate. Some believed that the pathophysiology of hyperalactemia occurring in the recovery phase of RD induced AKI, was from resorption of Ca from injured muscle and transient hyperpar. However, others believed that the mechanism of hyperalactemia is the dissolution of deposited CaPO4 from the damaged muscles, in which the deposits were shown in the technuim pyrophosphate scan. This case supports the hypothesis that remobilization of calcium deposits from damaged muscle is the main element of delayed hyperalactemia, as the PTH and 1,25(OH)2 D levels were suppressed during the period of hyperalactemia. However, our patient was unique in presentation as his hyperalactemia occurred while on HD as opposed to during renal recovery. We want to increase awareness of this phenomenon with case report.

PUB207 Oxtreotide-Induced Hyperkalaeimia
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Introduction: Sulphonylurea agents are widely used in the treatment of type II diabetes. Hyperglycemia is a major side effect with renal impairment and long acting SUAs as risk factors. Oxtreotide is a synthetic somatostatin analog that is a potent inhibitor of growth hormone, glucagon, and insulin and used to treat relapsing or refractory glyicyemia induced by SUAs.

Case Description: 43-year-old male with obesity, hypertension, diabetes, sleep apnea, heart failure, hyperlipidemia, recent hospitalization for hyperglycemia, CKD 5 nearing dialysis. Present with asymptomatic hyperglycemia with BS ranging 20-50s for two weeks. He had diabetes for 10 years, he was on Semaglutide since last admission and on Glipizide at admission. Vitals were BP 138/80mmHg, Pulse 93 bpm. Temp 97.8 F, Resp 21/min, sat 96% on 3L of NC(85% on RA), BMI 48 kg/m2. Labs significant for K 3.6 Meq, BUN 52 mg/dL, Creat 8.06 mg/dL, Glucose 45mg/dL. Insulin 0.75 units, TG 7.24, TC 206 mmol/L, Lactate 1.3mmol/L, UA had Protein 300, large blood, trace leukocyte esterase, RBC 73, Glucose, ketone, bilirubin, nitrite, WBC, cast were neg. U/S showed bilaterally increased echogenicity and simple renal cysts. After hyperglycemia did not resolve with DSW. He was transferred to ICU for D10 infusion and started on Oxtreotide SQ. His hyperglycemia resolved but he developed severe hyperkalaeimia at 7.3 Meq without EKG changes, which did not resolve with medical therapy. He required HD. His potassium improved but continued HD for CKD5.

Discussion: Oxtreotide, similar to somatostatin, directly inhibits the release of insulin from the pancreatic endocrine gland, glycagone, as compared to dextrose infusions for SUAs overuses. The mechanism of oxtreotide induced hyperkalaeimia is most likely due to the suppression of insulin release, which impairs cellular potassium uptake resulting in an increased extracellular potassium concentration. While oxtreotide is primarily metabolized in the liver, some experts suggest that dosage modification may be necessary due to reduced clearance. Although there have been only a few reported cases in the literature, we suspect that hyperkalaeimia induced by oxtreotide may be more common than previously recognized.
underline represents presenting author.

PUB208
The Alkaline Tube: A Dangerous Tide
Javeda Bhat,1,2 Sabah M. Khan,1 Ann Hinckley,1 Spencer Hodgins,1
1Baystate Medical Center, Springfield, MA; 2University of Massachusetts Chan Medical School, Worcester, MA; 2Kidney Care and Transplant Services of New England, West Springfield, MA.

Introduction: Metabolic alkalosis is the most common acid-base disorder in critically ill patients. When severe (pH>7.55) it is associated with significantly increased mortality. Here, we have a critically ill patient in the setting of severe metabolic alkalosis who was treated successfully with hemodialysis (HD). The case highlights the importance of recognizing nasogastric tube (NGT) suction as a source of severe metabolic alkalosis, as well as rapid intervention.

Case Description: An 83-year-old man with HTN, CAD, HFrEF, DM, and CKD IV (baseline Cr 2.6 mg/dL) presented with nausea, vomiting, and abdominal pain. He was found to have SBO and was treated with NGT decompression at an outside hospital. NGT output increased over 4 days up to 7L in 24 hours. Bicarbonate increased to >50mmol/L on day 4 with ABG showing pH 7.63; bicarbonate was estimated at 78mmol/L based on Henderson-Hasselbach equation. He only received NS at 100 mL/h for 4 days despite rising NGT output. He developed anuric AKI with a creatinine of 6.7mg/dL with fatigue, muscle twitching, and tremors. He was sent to the ICU due to recurrent ventricular arrhythmias, then was transferred to our institution for HD due to severe metabolic alkalosis and anuric AKI. Despite the ICU team’s attempt to place a dialysis catheter, adequate blood flow for dialysis was not achieved. A new catheter was not placed until the following morning delaying HD for around 12h. Post-HD ABG showed a pH of 7.45 and bicarbonate 33mmol/L. The patient was eventually able to stop dialysis and was discharged.

Discussion: This patient developed severe metabolic alkalosis due to loss of gut HCl. The underlying physiology is a chloride-sensitive alkalosis that may be treated with NS and repletion of potassium, however in the setting of his oliguric AKI, he was unable to secrete adequate bicarbonate. His case illustrates a few important pitfalls; first, high NGT output should have prompted major adjustments to therapy; receiving NS at 100mL/h led to gross undertreatment of his chloride losses. Second was underestimating his acidosis upon arrival in the ICU; he had been experiencing significant ventricular arrhythmias and was at high risk for seizures and death, however, the malfunctioning dialysis catheter took more than 12h to replace. This patient ultimately had a good outcome but illustrates common pitfalls that many providers could make in the management of severe metabolic alkalosis.

PUB209
Linezolid-Induced Lactic Acidosis
Gilda M. Portalatin, Natalie N. McCall. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Linezolid is used to treat many gram-positive bacterial infections. Its use has increased with the emergence of many multi-drug resistance organisms. Lactic acidosis is a rare but potentially fatal adverse effect of linezolid. Here we discuss a case highlighting the importance of prompt recognition of Linezolid-induced severe lactic acidosis.

Case Description: A 41-year-old woman with ovarian cancer complicated by severe lower extremity lymphedema presented to the emergency department with worsening bilateral lower extremity swelling and pain after failed outpatient antibiotic therapy. Initial workup included a CT scan of the lower extremities concerning for necrotizing fasciitis. Her course was complicated by septic shock, temporarily requiring pressor support, bilateral lower extremity swelling and pain after failed outpatient antibiotic therapy. Initial labs confirmed BUN of 166 mg/dL, Creatinine of 27 mg/dl and eGFR of 2 (ref range: 60-89). CT scan of the abdomen showed bilateral retroperitoneal abscesses. Fundoscopy confirmed findings of optic neuropathy. Inflammatory and autoimmune work up was sent for his glomerulonephritis. Per his labs, he met criteria for CKD stage 5 and was started on peritoneal dialysis; vision improved after 3 sessions and was discharged in stable condition.

Discussion: Uremia can be caused by retention of waste products in the blood due to kidney dysfunction. Accumulation of uremic toxins in the optic nerve can lead to ischemia and optic nerve damage causing visual disturbances; from blurriness to complete loss. In one study, out of 276 patients studied with CKD, 4.7% were found to have uremic optic neuropathy with prevalence proportional to the extent of renal dysfunction [1]. Another study of 93 patients with end stage renal disease found that incidence of 7.5%; risk factors included age, longer duration of renal failure, and higher serum levels [2]. Cataracts are also common uremic patients. Retinopathy in uremic patients can be caused by various mechanisms including ischemia, hypertension, and diabetic nephropathy [3].


PUB210
A Case of Uremic Optic Neuropathy
Ali Shah, Peter Iskander, Chilisa Shafi, Khadijah Sajid. Wright Center for Graduate Medical Education, Scranton, PA.

Introduction: Uremia is the accumulation of urea in the blood; typically secondary to retention due to kidney dysfunction. Damage to the optic nerve due to its toxicity can lead to visual defects and eventual blindness. Initial management is treating the underlying cause but may require emergent hemodialysis to rapidly filter out the excess urea.

Case Description: 29 year old male with unknown past medical history presents with bilateral blury vision. Initial labs confirmed BUN of 166 mg/dL, Creatinine of 27 mg/dL and eGFR of 2 (ref range: 60-89). CT scan of the abdomen showed bilateral retroperitoneal abscesses. Fundoscopy confirmed findings of optic neuropathy. Inflammatory and autoimmune work up was sent for his glomerulonephritis. Per his labs, he met criteria for CKD stage 5 and was started on peritoneal dialysis; vision improved after 3 sessions and was discharged in stable condition.

Discussion: Uremia can be caused by retention of waste products in the blood due to kidney dysfunction. Accumulation of uremic toxins in the optic nerve can lead to ischemia and optic nerve damage causing visual disturbances; from blurriness to complete loss. In one study, out of 276 patients studied with CKD, 4.7% were found to have uremic optic neuropathy with prevalence proportional to the extent of renal dysfunction [1]. Another study of 93 patients with end stage renal disease found that incidence of 7.5%; risk factors included age, longer duration of renal failure, and higher serum levels [2]. Cataracts are also common uremic patients. Retinopathy in uremic patients can be caused by various mechanisms including ischemia, hypertension, and diabetic nephropathy [3].


PUB211
Renal/Cerebral Salt Wasting in a Patient with COVID-19
Rohini Singla,1,2 Adrian J. Baudry,1,3 Tulane Kidney Beans. Tulane University School of Medicine, New Orleans, LA; 2New Orleans VA Medical Center, New Orleans, LA.

Introduction: Renal salt wasting (RSW), commonly known as cerebral salt wasting (CSW), a less recognized cause of hyponatremia, which has mostly been reported in patients with CNS disease, can also be associated with other medical conditions. Hyponatremia has been reported with COVID-19 infection, mostly multifactorial due to loss of sodium ions in the digestive tract, SIADH, and poor intake. It has only rarely been reported with COVID-19. We report a case of COVID-19 infection-associated hyponatremia due to renal/cerebral salt wasting.

Case Description: A 95-year-old male with a history of dementia, hypertension, hyperlipidemia, stage 3a chronic kidney disease, and prostate cancer presented to the emergency department with anorexia, cough, sore throat, and positive home COVID-19 test. Initial workup revealed normal chest X-ray, WBC count of 8,0, serum sodium of 121 mmol/L, potassium of 4.6 mmol/L, chloride of 87 mmol/L, BUN of 20 mg/dL, creatinine of 1.1 mg/dL, serum osmolality of 252 mOsm/kg, urine osmolality of 460 mOsm/kg, urine sodium of 132 mmol/L, urine chloride of 17 mg/dL. TSH and FT4 were normal. The sodium decreased to 115 mmol/L, initially expected to improve over several days with the re-initiation of IVF, reaching a level of 133 mmol/L. Repeat FEUric acid remained elevated at 11.97%, and serum uric acid remained low at 3.35 mg/dL. He was discharged with improved laboratory results and remained stable during follow-up visits.

Discussion: Differentiating RSW/CSW from other causes of hyponatremia is important due to different treatment approaches. Both RSW/CSW and SIADH have similar clinical parameters like high urine osmolality and sodium, low serum uric acid, and high FEUric acid particularly. However, the FEUric acid improves in SIADH after an improvement in urine sodium. Both RSW/CSW and SIADH have an improvement in sodium levels but not in CSW. SIADH is usually treated with fluid restriction in addition to other measures. While RSW/CSW is treated with volume repletion as patients have intravascular volume depletion. This case signifies that RSW/CSW should be in the differential diagnosis of patients with COVID-19 and hyponatremia.

PUB212
Hyponatremia Causing Confusion, or Confusion Causing Hyponatremia?
Jaspreet Saini, Creighton School District 14, Phoenix, AZ.

Introduction: Hyponatremia can present with vomiting, confusion and seizures. This case discusses hyponatremia caused by LGI Associated Limbic Encephalitis.

Case Description: 75 year old female presents after having tonic clonic movements of upper and lower extremities. Physical examination shows a laceration at her temple and alert to self only. Labs show WBC of 14.2 K/uL, Na of 117mmol/L, K of 2.8 mmol/L,
osmolality of 248 Osm/kg H2O, Urine osmolality of 726 Osm/kg H2O and urine Na of 74 mmol/L, demonstrating severe acute intravascular dehydration. Serum pyruvate was elevated to hypotonicity; normal saline at 100 mL/hr was started and patient’s Na decreased to 113 mmol/L and she had multiple seizures. Hyperpotonic saline is started but Na is unchanged. Lumbar puncture is normal. EEG monitoring showed numerous clinical epileptiform discharges, consistent with a subdural space occupying lesion (SOL) vs. idiopathic cortical dysplasia and subtle EEG dysfunction. MRI brain showed subtle right lentiform nucleus enhancement. CSF is sent out for vital and autoantibody screening and there is anti-levine-rich glioma 1 protein (anti-LGI1) present. Solumdroler and plasmapheresis for 5 days is started. Na increases from 130mmol/L to 136mmol/L and patient’s neurological symptoms resolve.

Discussion: Limbic Encephalitis affects the amygdala, thalamus hypothalamicus and medial temporal lobes of the brain causing behavioral disturbances, changes in personality and cognitive behavior; seizures, and psychiatric symptoms. It is a paraneoplastic syndrome associated with small cell lung cancers, pancreatic tumors, cell tumors of the testis and ovaries of the ovaries. It can be associated with infections, immunosuppression and autoimmune encephalitis. Auto-antibodies associated with the autoimmune encephalitis include N-methyl-D-aspartate receptor, glutamate 1 and glutamate 2 receptors, and leucine-rich anti glioma 1 protein (LGI1). The severe hypotonicity is because it is expressed in the hypothalamus. It has been shown that ADH, which correlates with our patient leading to a picture of syndrome of inappropriate ADH. Additionally, LGI1 is also expressed in the tubules of the kidneys. Treatment is high dose steroids, IVIG, and plasmapheresis. Many develop malignancies and require frequent screening. In conclusion, although confusion and seizures are symptoms of hypotonicity, if it does not resolve with traditional fluids, the confusion can cause hypotonicity and encephalitis needs to be considered.

PUB213 Successful Treatment of a Rare Profound Lactic Acidosis and Anuric AKI due to Metformin-Associated Lactic Acidosis Ao Wang, Arty Kremer, Subodh J. Saggi, Moro O. Salifu.

Introduction: Metformin therapy in patients with reduced kidney function can generate toxic levels since these drugs are almost entirely removed by kidney, resulting in lactic acidosis. We report a case of metformin induced lactic acidosis in a patient with AKI.

Case Description: A 73-year-old female with a past medical history of Type 2 Diabetes, Hypertension, seizure, cardiovascular disease sent from Nursing home for hyper tension, hypoglycemia and altered mental status. Her medications included metformin 500mg bid, metoclopramide, risperidone, ondansetron. On exam, blood pressure 92/42mmHg, and O2 saturation 96% on 3L nasal cannula, 20 respiratory mins, Heart rate 53 beats/min, and temperature 35.6 °C. Initial lab workup showed VBG PH 6.9 with Pco2 32mmHg, HCO3 6 mmol/L acute lactic acidosis, Lactate 27.7mmol/L, glucose 163 mmol/L, bicarb 11 mmol/L. Serum Na 130/Cl 105. We repeated hemodialysis next day and patient’s Na decreased to 14.2 mmol/L and patient’s mental status improved. We present a case of possible toxic alcohol exposure, turned out to be BD overdose.

Discussion: Butanediol (BD) is an industrial solvent, used for plastic manufacture. Illicit recreational use is associated with central nervous system (CNS) depressant effects (“date-rape drug”). BD ingestion may cause hepatic shock and multiorgan failure. BD has a long half-life, but often unknown. We present a case of possible toxic alcohol exposure, turned out to be BD overdose.

Take away lesson: 1,4-Butanediol Overdose: An Unrecognized Toxidrome Rachel Pinto, Mario Bernaba, Scott Mullaney, Bethany E. Karl, Cynthia Miracle. University of California San Diego, San Diego, CA.

Introduction: Butanediol (BD) is an industrial solvent, used for plastic manufacture. Illicit recreational use is associated with central nervous system (CNS) depressant effects (“date-rape drug”). BD ingestion may cause hepatic shock and multiorgan failure. BD has a long half-life, but often unknown. We present a case of possible toxic alcohol exposure, turned out to be BD overdose.

Discussion: Butanediol (BD) is an industrial solvent, used for plastic manufacture. Illicit recreational use is associated with central nervous system (CNS) depressant effects (“date-rape drug”). BD ingestion may cause hepatic shock and multiorgan failure. BD has a long half-life, but often unknown. We present a case of possible toxic alcohol exposure, turned out to be BD overdose.

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

Underlines represent presenting author.
Symptomatic Uremia Without Significant Azotemia


Introduction: Uremia is a clinical syndrome encompassing many non-specific symptoms such as anorexia, nausea, and fatigue. Typically, uremia occurs once the glomerular filtration rate (GFR) dips below 50% of average normal GFR, and overt uremia is usually observed in patients with GFR greater than 10 mL/min and BUN lower than 100 mg/dL. In addition, the BUN represents one of many organic waste products that accumulate with decline in GFR and does not appear to contribute much to the uremic illness.

Case Description: A 61-year-old woman with CKD stage 3b secondary to diabetic nephropathy presented to the emergency department from nephrology clinic for acute kidney injury. Over the past year she had been losing weight due to intractable nausea, vomiting, diarrhea, and decreased appetite. During this time, she was at CKD stage 3b with baseline GFR (BUN) ranging 28-39 mg/dL. Due to hyperbilirubinemia and elevated transaminases, she underwent extensive GI workup including gastric emptying study, abdominal CT and MRI, EGD, and liver biopsy. She was diagnosed with gastritis due to Helicobacter pylori infection which was treated without resolution of her symptoms. The liver biopsy showed hepatic steatosis and congestive hepatopathy. Nephrology was consulted and, though the BUN was only mildly elevated with a peak of 53 mg/dL, the patient was started on inpatient hemodialysis (HD) with marked improvement in her symptoms. After her second day of HD, she ate an entire personal pizza with no nausea when two days prior there were discussions regarding whether she should be started on total parental nutrition (TPN) due to significant malnutrition.

Discussion: Uremia represents a constellation of symptoms related to accumulation of organic waste products as the GFR falls. The often-subjective nature of the diagnosis of uremia poses a great diagnostic challenge in patients such as this with rather unremarkable BUN levels. Diagnosis of uremia in the absence of significant azotemia represents an important gap in the extant literature because patients with symptoms impacting their overall quality of life would benefit from earlier initiation of renal replacement therapy (RRT) and may be spared expensive and invasive testing as a result. This case is an excellent reminder not only on the BUN level when considering whether a patient has overt uremia requiring initiation of RRT.

Drug-Induced Fanconi Syndrome with Hyperphosphatemia
Navneet Kaur, Muhammad W. Bajwa. North Alabama Medical Center, Florence, AL.

Introduction: Fanconi syndrome is characterised by proximal renal tubular dysfunction leading to hypophosphataemia, hypokalaemia, hyperchloremic metabolic acidosis, glycosuria, and aminoaciduria. It is usually an inherited condition diagnosed in children, but can be acquired in adults as well, commonly due to drugs such as antimicrobials, antivirals, anticancer drugs, and valproate.

Case Description: An 81-year-old male presented from a nursing home with complaints of severe generalized weakness, and was found to have significant volume depletion, along with a potassium of 1.7, metabolic acidosis, acute kidney injury, and rhabdomyolysis. During the hospitalization, despite aggressive supplementation, he continued to have severe refractory hypokalaemia and hyperchloremic metabolic acidosis. However, interestingly, the patient initially had hyperphosphatemia. Urine studies revealed glycosuria, proteinuria, and inappropriate sodium, potassium and phosphate wasting along with increased excretion of these electrolytes. After extensive work up ruled out other causes of these metabolic derangements, the leading differential was Fanconi syndrome. The patient had been recently started on valproate for bipolar disorder which is a known cause of Fanconi syndrome. However, one of the defining features of Fanconi syndrome is hypophosphatemia, whereas our patient had hyperphosphatemia. This was likely secondary to rhabdomyolysis, which might have been caused either by hypokalemia itself or prolonged immobility due to hypokalemia induced weakness.

Another possible contributor was transcellular phosphate shift secondary to Fanconi syndrome induced metabolic acidosis. The patient’s valproate was held and all electrolyte levels started improving. As expected in Fanconi syndrome, the initial hyperphosphatemia transitioned towards hypophosphatemia as the rhabdomyolysis and metabolic acidosis improved, and eventually normalized.

Discussion: Patients with Fanconi syndrome may have incongruous lab findings due to the many causes, especially those with hyperphosphatemia due to rhabdomyolysis despite increased urinary phosphate excretion. It is thus important to critically examine every part of the clinical picture, in order to avoid erroneously ruling out the diagnosis. Urinalysis and electrolytes should be regularly checked in patients on valproate therapy as it is a known cause of Fanconi syndrome.

Idiopathic Recurrent Serositis After Bilateral Nephrectomy in ADPKD
N. Chandrasekaran, M. Topf, 2 Heather L. Henderson, 1 Keith A. Hilliard. 1 Ascension St. John Hospital, Detroit, MI; 2 Oakland University William Beaumont School of Medicine, Rochester, MI.

Introduction: Nephrectomy in autosomal dominant polycystic kidney disease (ADPKD) is performed in up to 40% of patients being evaluated for renal transplant. Indications are recurrent or hemorrhagic cysts, urinary tract infections, large size of native kidneys or intractable pain. The most common complications are blood loss, iatrogenic bowel injury, and death due to sepsis. Few case reports have described recurrent ascites as a postoperative complication, usually of hepatic origin. This case describes recurrent serositis following bilateral nephrectomy with no apparent liver pathology.

Case Description: GP is a 72-year-old male with advanced CKD due to ADPKD. He underwent bilateral nephrectomy prior to a living unrelated donor transplant with hemodialysis planned as a maintenance modality. In 2022 he was noted to have bilateral nephrectomy complicated by a liver laceration. Coagulation and liver function tests remained normal. He returned to the hospital 2 months later with complaints of worsening abdominal distention. CT showed new large bilateral pleural effusions, a pericardial effusion, and ascites. The pericardial effusion was drained, and pericardial biopsy showed no histologic abnormality or evidence of malignancy. Pleural fluid was transudative. Cytology and cultures were unremarkable. Initial ascitic fluid was indicative of portal hypertension, yet several repeats were not suggestive of portal hypertension. He was evaluated for heperculosis, leptospirosis B and C, legionella, and PsA, all of which were negative. An echocardiogram showed a newly reduced ejection fraction 30-35%, which recovered after CABG in June 2022. Transjugular liver biopsy in December 2022 was negative for cirrhosis or portal hypertension. He required biweekly paracentesis with removal of 6-8 L until the fluid tapered and resolved by January 2023. In February 2023 he received a deceased donor renal transplant. At 3 month follow up creatinine was 0.97 mg/dL with no further serositis.

Discussion: Bilateral nephrectomy for ADPKD has rarely been associated with recurrent ascites. Iatrogenic chylous ascites and ascites due to hepatic venous outflow obstruction or polycystic liver have been described. Neither hepatic venous pleural nor pericardial effusions following nephrectomy in ADPKD were seen in literature review. This case highlights serositis after nephrectomy, a yet undefined complication.

Significance of Genetic Testing in APO L1 Nephropathy
Ananthamadilida Adisag, Ramanakumar Adisa, Ramanakumar Gupta,1 Manjula Balasubramanian.1 Albert Einstein Medical Center, Philadelphia, PA, 2Lugans’kij derzhavnij medichnij universitet, Lugansk, Ukraine.

Introduction: Gitelman syndrome (GS), also known as familial hypomagnesemia-hypokalemia is an inherited salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. Mutations in SLCL2A3 gene is the underlying cause which results in defects in the apical sodium chloride cotransporter also known as the thiazide sensitive cotransporter in the distal convoluted tubule. GS is rare and inherited in autosomal recessive fashion with an estimated incidence of 1 in 40,000.

Case Description: We present a 26-year-old woman referred to the nephrology clinic for evaluation of chronic hypokalemia. It was first noticed at the age of 14, she reported several hospital admissions requiring treatment for hypokalemia. She was once admitted to the ICU after developing temporary paralysis which resolved with K+ replacement. She was subsequently prescribed 40mg of KCL. Her previous lab work showed K+ in range of 2.5-2.5 mmol/L and metabolic alkalosis. She denied any cramps, palpitations, weakness, polydipsia, salt cravings, vomiting, use of laxatives or diuretics. She reported taking OTC Mg supplements daily. Clinical examination was unremarkable. Her weight was 50kg with BMI 17.9 and BP was 116/79. Lab work showed aldosterone 24.7ng/dL and renin 14 ng/mL/h with a normal ARR of 1.76, other labs are shown in Table 1. She was counseled on likely diagnosis and informed consent was obtained to perform genetic testing which confirmed GS.

Discussion: The criteria for suspecting diagnosis of GS include; chronic hypokalemia with inappropriate renal K wasting (FeK > 9%); Metabolic alkalosis; Hypomagnesemia with inappropriate renal Mg wasting (FeMg > 4%); Hypocalciuria (spot urine Ca:Cr < 0.07mg/mg) 0.05mg/mg in this patient; High plasma renin activity (normal levels 0.2-2.0 ng/mL); Fractional excretion of CI < 0.5%, Low or normal-low BP and normal renal US. Clinical diagnosis can be challenging due to substantial number of mimics. Demonstrating biallelic mutations in SLCL2A3 achieves a molecular genetic diagnosis of GS.

<table>
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<th>Urine value (meq/L)</th>
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Importance of Genetic Testing in APO L1 Nephropathy
Ananthamadilida Adisag, Ramanakumar Adisa, Ramanakumar Gupta,1 Manjula Balasubramanian.1 Albert Einstein Medical Center, Philadelphia, PA; 2Lugans’kij derzhavnij medichnij universitet, Lugansk, Ukraine.

Introduction: A-28-year-old non-diabetic, non-hypertensive female from West Africa Malian with pertinent history of pulmonary embolism, latent TB, recently diagnosed with Pneumonia on triple therapy, came to nephrology office for evaluation of proteinuria. Pertenent family history of ESRD on dialysis in 2 first degrees relatives. No h/o smoking or alcohol use. Physical exam grossly normal.

Case Description: Initial labs showed creatinine 1 mg/dL, GFR 58. UA 1+ protein. UPCR of 2.3 g. Renal ultrasound showed irregular echotexture, normal size and cortical thickness. Serologic work up for proteinuria including hepatitis B/C, HIV, ANA, SPEP

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Underline represents presenting author.
and UPEF was negative. Renal biopsy was performed for proteinuria. Pathology showed FSGS. Genetic testing was performed remarkable for homoygous APOL1 gene. She was on CKD stage 3b/4 at the time of diagnosis of APOL1 nephropathy. Then progressed to ESRD now on hemodialysis.

**Discussion:** In 2010, genetic variants were discovered in the apolipoprotein L1 [APOL1] gene that explained a surprisingly large fraction of this major health disparity. Understanding the biology of APOL1 gene risk variance has been advancing at a molecular level [1] [2]. APOL1 gene is 1 of the 6 members of the APOL gene family on human chromosome 22. It is a naturally occurring gene that can be found in many organs of the body, including the podocytes of the kidneys [3]. Approximately 13% of African-Americans carry two APOL1 risk alleles. These variants termed G1 and G2, are a frequent cause of kidney disease termed APOL1 nephropathy [2]. Spectrum of APOL1 nephropathy include HIV associated nephropathy [HIVAN], primary focal segmental glomerulosclerosis (FSGS), Lupus collapsing glomerulopathy, sickle cell disease, nephropathy, and hypertension-associated arterionephrosclerosis [6]. KDIGO 2021 guidelines for the management of glomerular diseases updated classification of FSGS into 4 types. One of them is genetic cause which includes APOL1 nephropathy leading to ESRD [3]. APOL1 kidney disease tends to be progressive, and current standard therapies are generally ineffective [2]. Multiple studies have demonstrated that APOL1 high risk donor kidneys fail at higher rates than non-risk kidneys, whereas the recipient APOL1 genotype has not yet been shown to affect graft survival [1].

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Underline represents presenting author.

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**PUB223**

**Genetic Analysis and Minigene Splicing Assay of a New Splicing Variant of the COL4A5 Gene Causing Alport Syndrome**

Jinbo Zha, Department of Nephrology, Affiliated Hospital of Inner Mongolia Medical University, Hohhot, China.

**Background:** The aim of this study is to examine the genetic characteristics of a patient with Alport syndrome (AS) and confirm the existence of splice variant.

**Methods:** The study focused on a patient with AS who received a diagnosis at the Department of Nephrology of the affiliated hospital of Inner Mongolia Medical University. Whole exome sequencing and Sanger sequencing were performed to identify gene variation sites. Additionally, mRNA abnormal splicing was conducted to investigate the impact of the variant on transcripts. 3D structure of the variant protein was analyzed. Immunofluorescence and immunochemistry were performed on the renal tissues of the patient to confirm the presence of AS kidney injury.

**Results:** Gene sequencing revealed that the patient had a splice variant c.835-9T>A in the COL4A5 gene, which was not observed in either of the patient’s parents. The experiment conducted in vitro revealed that the mutation c.835-9T>A (p.279_297del) resulted in the deletion of 57bp in exon 15 of the COL4A5 gene mRNA. This deletion caused the loss of amino acid residues from positions 279 to 297, which in turn, impacted the stability of the secondary structure of the α5 chain encoded by the COL4A5 gene. These amino acids are conserved across various species and their damage can be observed through evolution. The results of homology modeling indicated that the trimerization of COL-1V with the mutated α5 chain could be achieved, however, the 3D structure was found to be severely distorted. The diagnosis of AS kidney damage was confirmed through immunofluorescence results. Following the variant rating guidelines of the American Society for Medical Genetics and Genomics, c.835-9T>A was rated as a probable pathogenic variant (PSV1, Moderate-PS3, Moderate-PM2, Supporting-PS2-PP3-PP4).

**Conclusions:** The c.835-9T>A mutation in the COL4A5 gene has been identified as the cause of disease in AS patients. In vitro experiments have confirmed that this mutation leads to splicing variation. Additionally, histopathological examination of the kidneys has provided evidence for the pathogenicity of the mutation and has expanded the spectrum of mutations associated with the COL4A5 gene.

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

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**PUB224**

**Glomerulopathy with Fibronectin Deposits Caused by an FNI Mutation in a Large Family with Variable Clinical Presentation**

Federico Yandian,1 Lucia Spangenberg,1 Victor E. Raggio,2 Maria F. Dominguay,7 Nicolas Delloca,2 Lucia Facal,1 Jessica M. Segarra,1 Oscar A. Noboa,1 Jose Boggia.1 Department of Nephrology, Hospital de Clinicas "Dr. Manuel Quintela", Montevideo, Uruguay; 2Department of Genetics, Facultad de Medicina, Universidad de la Republica, Montevideo, Uruguay; 3Institut Pasteur de Montevideo, Montevideo, Uruguay.

**Background:** Glomerulopathy with fibronectin deposits is a rare hereditary kidney disease with autosomal dominant inheritance. Mutations in the FNI gene encoding fibronectin have been identified as responsible and account for 40% of cases. Light microscopy findings are non-specific. Electron microscopy shows: subendothelial and mesangial electron dense deposits with a granular or fibril-like structure.

**Introduction:** Glomerulopathy with fibronectin deposits is a rare hereditary kidney disease with autosomal dominant inheritance. Mutations in the FNI gene encoding fibronectin have been identified as responsible and account for 40% of cases. Light microscopy findings are non-specific. Electron microscopy shows: subendothelial and mesangial electron dense deposits with a granular or fibril-like structure.

**Case Description:** We describe a family with a diagnosis of focal and segmental glomerulosclerosis (FSGS) in whom the genetic test was crucial for a correct etiological diagnosis. The index case was a 46-year-old female with FSGS. Her mother had chronic kidney disease (CKD) with proteinuria and microhematuria as well as two maternal aunts (one deceased and the other one with FSGS on hemodialysis since 37 years old). Her deceased maternal uncle started hemodialysis at 42 years old, she also had a dead brother with FSGS who was a kidney transplant recipient, two maternal male cousins with CKD (one dead with kidney allograft) and two maternal female cousins with CKD (one of them deceased). The index patient received prednisone for 6 months and developed adverse effects. Interestingly, the patient and relatives had traumatological complaints.

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**PUB22**

**Genetic Testing in Hemodialysis Patients**

Kiran Munir, Steven Fishbane, Kenar D. Juwiler, Daniel W. Ross. Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.

**Background:** There is currently little available knowledge on potentially pathogenic genes present in patients on dialysis. The purpose of this study is to describe the prevalence and relevance in the ESKD population.

**Methods:** At a large suburban academic medical center dialysis unit, patients were consented for genetic testing during dialysis treatment. Massive parallel genetic sequencing was performed using a panel of 385 genes with testing through Renasight experiment conducted in vitro revealed that the mutation c.835-9T>A (p.279_297del) resulted in the deletion of 57bp in exon 15 of the COL4A5 gene mRNA. This deletion caused the loss of amino acid residues from positions 279 to 297, which in turn, impacted the stability of the secondary structure of the α5 chain encoded by the COL4A5 gene. These amino acids are conserved across various species and their damage can be observed through evolution. The results of homology modeling indicated that the trimerization of COL-1V with the mutated α5 chain could be achieved, however, the 3D structure was found to be severely distorted. The diagnosis of AS kidney damage was confirmed through immunofluorescence results. Following the variant rating guidelines of the American Society for Medical Genetics and Genomics, c.835-9T>A was rated as a probable pathogenic variant (PSV1, Moderate-PS3, Moderate-PM2, Supporting-PS2-PP3-PP4).

**Conclusions:** The c.835-9T>A mutation in the COL4A5 gene has been identified as the cause of disease in AS patients. In vitro experiments have confirmed that this mutation leads to splicing variation. Additionally, histopathological examination of the kidneys has provided evidence for the pathogenicity of the mutation and has expanded the spectrum of mutations associated with the COL4A5 gene.

**Funding:** Government Support - Non-U.S.
but with unremarkable neurologic findings. Electron microscopy was not available. We performed a massive parallel sequencing for 70 genes known to be associated with FSGS and detected a heterozygous FNI mutation: NM_212482.exon9:c.A1123G, p(Thr375Ala) which segregated with the disease. This information motivated the performance of a kidney biopsy in one of the female cousins who presented with proteinuria 0.73 g/day and normal creatinine clearance. It showed absence of hypercellularity and discrete mesangial matrix expansion. Immunohistochemistry revealed mesangial and pericapillary fibrinoid staining. Electron microscopy: 70% foot process effacement and mesangial and subendothelial electron dense deposits, some with fibrillar substructure and others finely granular.

Discussion: Here we emphasize the importance of genetic testing when a familial renal disease is suspected, encouraging the use of non-standard histopathologic techniques for a correct diagnosis, like fibrinoid immunohistochemistry stain in this case.

PUB225
Renal ANCA+ Vasculitis Concurrent with Fabry Nephropathy: Coincidence or Complication?
Michael L. West,1 Laurette Geldenhuys,1 Dalhousie University, Halifax, NS, Canada.

Introduction: Fabry disease (FD) in an X-linked disorder of glycosphingolipid metabolism with chronic inflammation triggered by GB3 and lysosomal GB3 metabolites. Various forms of glomerulonephritis (GN) and inflammatory disease have been reported with FD. Immune complex GN has complicated enzyme replacement therapy (ERT), GN including anti-neutrophil cytoplasmic antibody (ANCA) disease has also been reported in association with COVID19 infection and vaccination. We report the case of a 73 year-old woman with type 1 diabetes mellitus, Fabry disease and COVID19 vaccination on ERT who presented with acute ANCA+ GN. Was Einstein right, is there no such thing as coincidence?

Case Description: The patient had stable diabetes since age 27, normal kidney function and low grade proteinuria 1 year prior. ERT (agalsidase alfa 0.2 mg/kg i.v. q2wks) was given for 3 years for Fabry hypertrophic cardiomyopathy with moderate diastolic dysfunction. COVID19 vaccination was given 4 months prior to development of dyspnea, and acute kidney injury with microscopic hematuria. There was no extra-renal disease. Anti-myeloperoxidase (MPO) ANCA was positive. Renal biopsy showed focal proximal tubular and GN with crescents plus background diabetic and Fabry nephropathies. She required hemodialysis. Despite treatment with glucocorticoids and Rituximab, there was no renal recovery. ANCA measurement in 83 FD adults revealed positive results in 24M, 59F; transient false positive anti-PR3 ANCA occurred in 1M in which renal biopsy showed Fabry nephropathy plus an immune complex GN.

Discussion: FD has been previously reported with renal vasculitis ANCA+ (antiPR3) in 1 patient and ANCA- in 2 patients. This is the first such case in which FD was already diagnosed and ERT given. ANCA associated vasculitis and other forms of GN usually occur within 90 days of COVID19 vaccination, mean 19 days, which does not fit with the observed time course in this case. The chronic inflammation of FD plus increased circulating MPO, the association with other GNs and other inflammatory conditions including vasculitis, the presence of kidney and lysosomal ANCA antigens, all suggest that vasculitis with or without ANCA is a rare complication of Fabry disease and Einstein was right. While our case did not improve with immunosuppressive therapy, others have, which suggests that FD patients should be treated for this serious but rare complication.

PUB226
A Decentralized Registry for Adults and Children with Alport Syndrome: Alport Syndrome Foundation (ASF) Alport Patient Registry Design
Lisa Bonebrake,1 B. A. Weinstock,2 Joshua Henderson,2 Fernida Gwadry-Sridhar.2
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Background: The ASF Alport Patient Registry is a retrospective and prospective longitudinal, web-based, decentralized registry of patients of all ages with Alport syndrome (AS) in the USA. Genetic testing has become the primary means by which AS patients are correctly diagnosed in the USA. As such, newly diagnosed and engaged AS patients and their caregivers – as opposed to medical record repositories – are in a unique position to populate an up-to-date registry. The registry’s primary objective is to collect real-time data, including improved awareness of AS, characterisation of different AS subtypes, and non-kidney symptom presentation and diagnosis in patients; understand treatment practices and outcomes; and understand the quality of life and burden of disease. The registry also provides patient education resources and facilitates patient-centered research and therapeutic development.

Methods: Eligible patients of all ages with a verified clinical diagnosis of AS will be invited to participate. Diagnosis will be verified by a certified genetic counsellor or treating physician based on genetic test results -or- familial history, clinical signs, and kidney biopsy pathology if genetic results are inconclusive. Via web-based portals, patients or their caregivers will complete an initial survey and periodic follow-up surveys for as long as the participant chooses to be enrolled. Data collected are based on AS patient and clinical researcher inputs and include disease profile; medical, familial, and treatment histories - in particular RAAAS and/or SGLT2i treatments; and genetic variant(s), audiological, and kidney laboratory results. Demographics and lifestyle characteristics are collected at enrolment and participant surveys are included at follow-up.

Results: Registry enrolment opened in May 2023. Data are anticipated for presentation in 2023.

Conclusions: The registry will be the first longitudinal registry in adult and pediatric AS patients collecting key determinants of patient management and outcomes, including the patient experience from diagnosis and treatment. The registry is positioned to become the primary US platform for real-world AS data that will facilitate education of patients and caregivers, inform clinical decision-making, and contribute to the development of therapeutic strategies with a better understanding of patient impact.

Funding: Private Foundation Support

PUB227
Collapsing Glomerulopathy (CG) in a Patient with High-Risk Apolipoprotein L1 (APOL1) Genotype: 4-Year Clinical Evolution of Use of Standardized Brazilian Green Propolis Extract (EPP-AF)
Marcelo D. Silva Vieira, Sergio P. de Souza, Isadora G. Dufra, Ludmila B. Santos, Marcelo Lopes, Luis M. Conceição, Paulo benigno P. Batista, Rogerio Passos. Hospital Sao Rafael, Salvador, Brazil.

Introduction: Apolipoprotein L1 (APOL1) is expressed in podocytes and gene variants of high renal risk are associated with cell injury and glomerular damage. Collapsing glomerulopathy (CG) is one of the phenotypic expressions of these variants. Immune and inflammatory mechanisms may be related to its genesis, and specific treatments are not yet a reality. We hereby present data concerning the 4-year clinical evolution of a patient with APOL1 mutation of high renal risk in homozygosity and use of standardized Brazilian green propolis extract (EPP-AF).

Case Description: A 41-year-old woman diagnosed with nephrotic syndrome in October, 2018, with proteinuria of 5.3 g/day at the time. Kidney biopsy revealed CG. The patient used prednisone 1 mg/kg for 12 weeks, showing no improvements and was found to have proteinuria of 12.6 g/day at the end of tapering in February, 2019. She did not tolerate ciclosporin. She has initiated the use of EPP-AF in March, 2019. Currently, four years later, the patient has proteinuria of 0.7 g/day. Glomerular filtration rate (GFR) was kept stable between 36-42 ml/min/1.73 m² for more than two years until the moment the patient had severe Covid-19 and GFR dropped and is currently at 32 ml/min/1.73m².

Discussion: APOL1 mutation of high renal risk may be associated with CG with a poor prognosis. Covid-19 may be associated with more severe damages among these patients. Typical immunosuppression is oftentimes ineffective. The use of EPP-AF in this case was able to control nephrotic syndrome for four years.
COLA4A4 and COLA5 may underlie different diseases such as isolated hematuria, Alport syndrome, diabetic kidney disease and focal segmental glomerulosclerosis (FSGS). In Portugal, there are regional diagnostic practices and patterns of genetic diseases. Our aim is to analyze the results of Braga Hospital concerning collagen IV mutations in the last 2 years.

Methods: We reviewed medical records and genetic test results of patients with variants in type IV collagen genes. A targeted panel covering 3 genes (COLA4A3-5) using next generation sequencing (NGS) based on whole exome sequencing was applied. In certain cases, a larger panel covering genes implicated in FSGS was used. Approximately 90% of new patients attending our Nephrology department during 2021 and 2022. During this period, 62 patients underwent genetic testing to search for a hereditary cause of kidney diseases. In particular, 29 were tested for mutations in COLA4A3-5 using the 3-gene (18 cases) or a larger FSGS NGS panel (11 cases). All patients were receiving ACE inhibitors or ARBs at the time of testing. These were women, mean age was 55±1.5 and 20 had a family history of CKD. Most were referred for CKD of unknown cause, microhematuria and proteinuria; 6 had hearing loss and 10 had a biopsy showing FSGS. Pathogenic variants were found in 4 patients and variants of uncertain significance (VUS) in 5. The remainder had negative results. Of the 4 pathogenic mutations, all were heterozygous; 3 affected COLA4A4 and the other COLA5. These were women, with median protein/creatinine urinary ratio of 1.0g/g (range 0.3-3.4g/g). 3 were women and 3 had kidney biopsies with FSGS. Of the 5 VUS, 3 were in COLA4A4, 1 in COLA4A3 and 1 in COLA5, in a female patient.

Conclusions: Despite probable underdiagnosis, genetic tests improved diagnostic accuracy even after renal biopsy. The clinical spectrum of heterozygous variants of COLA4A3, COLA4A5 or COLA5 in female carriers varies: most likely they are disease modifiers for a range of kidney diseases, one of which occurred in our series, is FSGS.

References

1. Cleveland Clinic Akron General, Akron, OH; 2Northeast Ohio Medical University, Rootstown, OH; 3Medanta The Medicity Medanta Institute of Kidney and Urology, Gurugram, India; 4Structure Federative de Recherche Necker, Paris, France; 5Departments of Internal Medicine and Pediatrics, Division of Nephrology, Carver College of Medicine, University of Iowa, Iowa City, IA; 6The Hospital for Sick Children, Toronto, ON, Canada; 7Akron Children’s Hospital, Akron, OH.
Discussion: Our patient’s genetic test returned positive for variant LYZ:c.314A>T. Lysosome is an amyloidogenic precursor protein and in lysosome amyloid, it is a ubiquitous bacteriolytic enzyme synthesized by hepatocytes, polymorphs, and macrophages. Currently, there is no amyloid-specific therapy apart from supportive management. The National Amyloidosis Centre in UK published a case series of three patients who underwent kidney transplantation, and there was no recurrence at the time of publication (0.8, 1.8 and 6.6 years post transplantation). Our patient’s type of amyloid is different to AA, AL amyloid where recurrence might be expected. There may be a role for genomic sequencing for patients with amyloid deposition in biopsy, with no notable family history, which may lead to identification of rare amyloid types.

PUB233
Using Ambulatory Genetic Testing to Improve the Evaluation of Kidney Diseases in Our Veterans
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Background: Chronic kidney disease (CKD) is a major public health issue in the United States, and also for our veterans. Monogenic causes are present in ~10% of cases of adult CKD. Identification of causes of CKD can impact prognosis and patient management. In our Nephrology clinic at the Miami VAMC, we evaluate patients with chronic kidney disease (CKD), and occasionally no clear etiology of CKD is identified. Broad genetic panels can provide an unbiased testing approach, which is advantageous in phenotypically heterogeneous diseases. However, the use and yield of broad genetic panels by VA Nephrologists in clinical practice is not yet well characterized.

Methods: A total of eight patients were selected to have renal genetic testing. Seven patients had unclear causes for kidney disease, and one patient had a questionable genetic condition on imaging studies. Renal genetic testing was performed in 8 patients. Genetic testing was executed using Rensaiht and Fulgent, commercially available sequence-based tests for 385 genes associated with kidney disease. Rensaiht and Fulgent determine if there is a genetic cause for an individual’s kidney disease, or if there is an increased hereditary risk due to family history. Results were available in 4 weeks.

Results: See image.

Conclusions: Use of broad panel genetic testing by our clinical Nephrologists had a high success rate in identifying etiologies of CKD in our veteran population. Establishing a genetic diagnosis is crucial to define the precise etiology of CKD. Accurate genetic testing allows improved genetic counselling and enhanced patient management. Implementation of various genomic strategies has resulted in a direct, demonstrable diagnostic and therapeutic benefit to affected patients.

PUB234
Autosomal Dominant Alport Syndrome in a 62-Year-Old Hispanic Woman: A Clinical Case Report
Jeanine Hernandez,1 Mohamed G. Atta,2 Celia P. Corona Villalobos,1 Chirag R. Parikh,2 Lois J. Arend,1 Steven Menez.3 Johns Hopkins University, Baltimore, MD; 3Johns Hopkins Medicine, Baltimore, MD.

Introduction: Alport syndrome (AS) is a monogenic disease caused by mutations in the COL4A3/4/5 genes encoding collagen IV, often characterized by progressive kidney function decline, hearing loss, and vision loss. It has an autosomal dominant inheritance pattern in approximately 5% of cases. Autosomal dominant Alport syndrome (ADAS) may be underdiagnosed due later onset of disease.

Case Description: We present a case of a 62-year-old Hispanic woman who presented for evaluation in nephrology clinic with bilateral renal cysts, chronic microscopic hematuria, proteinuria (5.13 g/g), and secondary hypertension. She stated that she had been experiencing arthritis, otalgia, and had noted a history of LASIK eye surgery. IgA nephropathy and thin basement membrane disease were highest on the differential diagnosis. A kidney biopsy was performed showing thin glomerular basement membranes with an average width of 130 nm, and focal segmental glomerulosclerosis. However, given her significant proteinuria and subtle GMB changes concerning for a collagen defect, genetic testing using next generation sequencing was performed and revealed a heterozygous pathogenic variant, c.2794A>T (p.Lys932) in the COL4A4 gene that is associated with ADAS. Her baseline creatinine was 0.76 mg/dL, increased at the time of diagnosis to 0.9 mg/dL with a downward trend most recently stabilizing at 0.71 mg/dL. Evaluation by ophthalmology and audiology evaluated ocular findings or hearing impairment. She was subsequently started on Losartan and dapagliflozin, with the goal to slow kidney disease progression and prevent end-stage kidney disease (ESKD).

Discussion: ADAS is characterized by a later age of onset and rare extra-renal manifestations in contrast to autosomal recessive disease. Next generation sequencing has increased the frequency of ADAS diagnosis compared to pedigree analysis and Sanger sequencing and should be considered in suspected patients regardless of age. ADAS carries >20% risk of ESKD highlighting the importance of early recognition and multidisciplinary management for improving outcomes in affected individuals.

PUB235
Mortality Risk Factors in Elderly Patients Undergoing Hemodialysis in a Nursing Home
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1Nagasaki Renal Center, Nagasaki, Japan; 2Nagasaki Harbor Medical Center, Nagasaki, Japan.

Background: As patients undergoing hemodialysis (HD) advance in age, they often exhibit greater mental and physical frailty, resulting in an increased number of patients requiring nursing care. However, few studies have examined the risk factors contributing to mortality in this subpopulation. Our dialysis center is affiliated with a nursing home, and most residents are elderly patients undergoing HD. This setup enabled us to assess the nursing home residents during follow-ups in medical and nursing care aspects. We aimed to clarify the mortality risk factors in this subpopulation.

Methods: We included patients undergoing HD who were admitted to our affiliated nursing home between April 2014 and March 2022. Patients with dialysis duration of <3 months were excluded. All participants were followed up until March 2023 and their medical data were collected upon admission. The association between survival and patient demographics was analyzed.

Results: This study included 106 patients (81.3 ± 7.9 years old; 36.8% men; median dialysis vintage, 32.5 months). The most commonly reported cause of death was pneumonia (19.1%), followed by heart failure (16.0%) and infections (8.5%). The patients were stratified into two groups based on their body mass index (BMI), and Log-rank test analysis revealed a poorer prognosis for those with a lower BMI than those with a higher BMI (p=0.002). Multivariable Cox proportional hazards analysis demonstrated a significant association between BMI (hazard ratio, 0.87; 95% confidence interval [CI]: 0.82−0.94; p<0.001) and survival rate. Additionally, multivariable logistic regression indicated that dementia was significantly associated with a lower BMI (odds ratio: 2.89, 95% CI: 1.07−7.83, p<0.03).

Conclusions: Our findings revealed that low BMI is an important factor contributing to a lower survival rate. Furthermore, low BMI was also associated with dementia. Therefore, energy supplementation and management of dementia could be essential for nursing home residents undergoing HD to improve their survival rate.
AKI in the Elderly: The Tip of an Iceberg
Lakshna Sankar, Pooja Sanghi. Geisinger Health, Danville, PA.

Introduction: Acute kidney injury (AKI) in the elderly is of multiple etiologies. Renal biopsy remains the gold standard for diagnosis.

Case Description: A 68-year-old male with history of rheumatoid arthritis on adalimumab was re-admitted with altered mental status, poor oral intake and AKI after a recent hospitalization for lumbar osteomyelitis requiring long term intravenous (IV) cefepime. Work up including infectious, autoimmune profile and renal imaging were unremarkable. Hemodialysis was contemplated due to worsening renal function with creatinine at 8.4 mg/dl (reference range: 0.5 - 1 mg/dl), hyperkalemia and concern for uremic encephalopathy, but he responded to supportive care with IV fluids and IV piperacillin tazobactam. A thorough history revealed intake of nabumetone for several years at doses as high as 1.5 gm daily. Renal biopsy was obtained due to unclear etiology of AKI in the setting of multiple confounding factors such as medications and recent infection. Biopsy showed features of acute interstitial nephritis (AIN) and few myoglobin positive tubular casts of unclear significance (Figure 1). Antibiotics and nabumetone were discontinued. He was treated with steroids, had marked improvement in creatinine (Figure 2) and was discharged home with steroid taper over 6 weeks.

Discussion: Aging kidneys are more susceptible to AKI due to low renal reserves. AKI developed during hospitalization has high mortality. A thorough understanding of etiology, clinical course and having a low threshold for kidney biopsy aids in diagnosis of AKI with possibilities of better outcomes in the elderly population.

Trajectory of Physical Function and Resilience in Incident Dialysis Patients
Samantha F. Smoger, Derek M. Devine, Katharine L. Cheung. University of Vermont, Burlington, VT.

Background: Initiating dialysis is a stressor and associated with functional decline. Resilience is a protective factor that may help patients starting dialysis. We aimed to describe the correlation between and trajectories of resilience and function in the first year of dialysis.

Methods: Incident dialysis patients ≥50 years were recruited from 2016-19. The short physical performance battery (SPPB) and Resilience Scale were performed at baseline and 1, 2, 4, 6, and 12 months. Age, sex, income, education, eGFR, serum albumin, cognitive status and comorbidities were identified from EMR and surveys. Spearman’s correlation coefficient was used to assess the relationship between resilience and function. Multivariable linear regression was used to identify predictors of resilience and function. Mixed model analyses were used to determine resilience and function trends over 12 months.

Results: 58 incident dialysis patients participated, mean age 68 years, 43% female. At baseline, median (IQR) resilience was 152/175 (135-159) and SPPB was 5.5/12 (1-8). Correlation of resilience and function was \( \rho = -0.23 \). Serum albumin was independently associated with SPPB; no variables were predictive of resilience. Trajectories of function and resilience are shown in the Figure.

Conclusions: Resilience and function are inversely correlated and decrease in both after 4 months then improve to baseline at 1 year. Greater study is needed to understand predictors of resilience and whether it might improve function for this population.

Funding: Other NIH Support - Vermont Center for Cardiovascular and Brain Health P20GM135007-03, The University of Vermont Center on Aging, Private Foundation Support
**PUB238**

**Medication-Induced Acute Encephalopathy in Severely Impaired Renal Function**

Reed Shank, The Christ Hospital, Cincinnati, OH.

**Introduction:** Commonly we as providers understand the importance of renally dosing certain medications or avoiding others altogether when we encounter a patient with impaired renal function. More commonly we will avoid modalities of diagnostic testing fearing we will further damage the already injured kidneys. However almost just as frequently we don’t consider renal impairment when prescribing other common medications due to lack of education, experience or alternatively over confidence in our knowledge of the drug.

**Case Description:** The patient is a 76 year old man with a history significant for end stage renal disease (on peritoneal dialysis), coronary artery disease and diabetes who presented to the ICU with altered mental status. He was recently admitted to a different hospital 3 days ago for right sided facial numbness, pain and dysgeusia for which he was given gabapentin, Percocet and acyclovir as it was suspected trigeminal neuralgia. On day 5 of this previous admission he became acutely encephalopathic while the neurological workup including MRI returned negative. He was transferred to our ICU and was given gabapentin, Percocet and acyclovir as it was suspected trigeminal neuralgia. On day 5 of this previous admission he became acutely encephalopathic while the neurological workup including MRI returned negative. He was transferred to our ICU and was given gabapentin, Percocet and acyclovir as it was suspected trigeminal neuralgia.

**Discussion:** Upon further review, we believed the offending medication to be acyclovir (1) and this was suspicion confirmed by the nephrologist on the case. It is rare but certainly can happen especially in the elderly (2). For many of us this was the first time hearing that acyclovir could be the offending agent. How could a medication so commonly prescribed without consideration of renal function be overlooked as the cause of acute encephalopathy? It is clearly important to have a deep understanding of what medications are renally excreted which is typically information covered in medical school but not necessarily reinforced in the primary care and hospital medicine settings. Additional education and appreciation of this concept would most likely result in safer treatment and shorter hospital stays. Had this been realized in the above patient, he would have not required a transfer nor a 2 day ICU stay costing the medical school both resources and space.

**PUB239**

**Impact of Body Mass Index on Mortality of Elderlies Requiring Acute Hemodialysis**

Alfredo Fonseca Chávez, Liliana Pacchiano, Marcos G. Nava, Ivan A. Osuna Padilla, Jose A. Leon, Maria Carolina R. Bolaños, Jesus Arturo R. Martinez, Instituto Nacional de Enfermedades Respiratorias, Mexico, Mexico.

**Background:** The increasing life expectancy of the world population elicited the increasing numbers of elderly patients starting hemodialysis (HD), however little is known about the impact on those requiring acute hemodialysis. Malnutrition is already related with a higher risk of mortality in non elderly HD patients. The purpose of this study is to evaluate these factors in the elderly population who require acute hemodialysis.

**Methods:** Retrospective cohort of 33 patients ≥70 years requiring Hemodialysis was categorized based on their Body Mass Index as normal (18.5-24.9 kg/m²), overweight (25-29.9 kg/m²) and obesity (>30 kg/m²). Kaplan Meier survival analysis with log-rank test and the Cox proportional hazards model were performed to assess the association between BMI 120-day mortality. Multivariate regression analysis was performed to know the independent association with increased mortality.

**Results:** Differences in BMI were observed between survivors (15 patients) and non-survivors (18 patients) (p=0.02). Cox-Analysis shows a higher risk of mortality in normal BMI (HR 1.98, 95% CI 0.76-5.13, p-value=0.15). A significant association was found between normal BMI and 120-day mortality (HR = 3.28,95% CI = 1.04-10.29;P-value = 0.041).

**Conclusions:** A normal BMI was associated with higher risk of mortality in unplanned hemodialysis elderly patients.

**Clinical and demographics characteristics**

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<th>Non-survivors (n=18)</th>
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<td>(63, 104)</td>
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**PUB240**

**External Validation of a Risk Prediction Tool in Determining Early Death Among Elderly Patients Initiated on Dialysis**

Rachelle Zolla S. Ciudadano-Manalaysay, Trisha Michelle Manalaysay, Southern Philippines Medical Center, Davao City, Philippines.

**Background:** The increase in the senior population is one of the factors that has contributed to the rise in the number of dialysis patients in the Philippines. The elderly generally has an increased risk for poor dialysis-associated outcomes, and studies have been conflicting if they have better survival with dialysis as compared to conservative management. The Thamer Risk Scoring tool uses simple variables to predict early mortality in elderly patients after initiating dialysis, however this has not been validated in the Philippine setting.

**Methods:** A retrospective cohort research design was used. Patients a 60 years old, diagnosed with end-stage renal disease, and initiated on dialysis from 2018 to 2021 in a tertiary institution in the Philippines were subjected to the tool to predict 3-month, 6-month, and over-all mortality after dialysis initiation. Patients with <90 days dialysis duration, recovery of kidney function, and with incomplete data to meet all the variables for the tool were excluded.

**Results:** Majority of the 181 patients included in the study were male (56.35%), and initiated on hemodialysis (97.24%). The mean age of the population was 67.34 years. All-cause mortality was 38.12% at 3 months, and 3.57% at 6 months after dialysis initiation. Patients with heart failure, cancer, asthma, and need for assistance in daily living had significantly higher mortality rates (p-values 0.007, 0.040, 0.040, 0.022 respectively). In comparison to the Thamer study with an AUROC = 0.691 for the tool in their validation cohort, this study showed an AUROC = 0.6245, 0.2847, and 0.5993 in the 3-month, 6-month, and over-all mortality groups respectively. As the score increased for the three groups, the tool became less sensitive and more specific with a concomitant increase in accuracy for predicting mortality.

**Conclusions:** Despite the poor performance of the Thamer risk scoring tool in predicting mortality in terms of AUROC in this study, the sensitivity and specificity had a similar performance in the Thamer study. Furthermore, the consistent trend of accuracy of predicting mortality in these groups reflect that a higher score portends to a higher accuracy in predicting mortality.
PUB241
Kidney Biopsies in Elderly Patients: Analysis of a 7-Year Institutional Experience
Sebastian Consuegra-Flores,1,2 Fernando A. Cuellar-Gonzalez,1,2 Mauricio Arvizu Hernandez,1 Jorge I. Fonseca-Corraa.1,2 Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; 1 Tecnologico de Monterrey Campus Ciudad de Mexico, Mexico City, Mexico.

Background: Kidney biopsies are essential for diagnosing and guiding treatment decisions, but limited data exist on their utility and safety in older adults (> 60 years). This study aims to analyze kidney biopsies performed on patients aged 60 years and above at our institution from 2015 to 2022, considering age-related changes, comorbidities, and survival influences.

Methods: A retrospective analysis of 78 kidney biopsies in elderly pts. was conducted. Demographic data, comorbidities, and pathological findings were collected to evaluate indications, procedural characteristics, and complications associated. All biopsies were performed by Nephrologists and Interventional Nephrology fellows.

Results: Among the 78 biopsies, 53 were performed on pts. aged 60-70 years, and 25 on pts. above 70 years (only 3 pts. aged a 80 years). The mean pts. age was 68±7.1 years, 56% were female. The primary indication for biopsy was Nephrotic Syndrome (58.9%), followed by Acute Kidney Injury (9%). All patients met institutional protocol criteria prior to biopsy. The most common diagnoses were Pauciimmune Glomerulonephritis (19.2%), Diabetic Nephropathy (15.3%), Acute Interstitial Nephritis (12.8%), Focal Segmental Glomerulosclerosis (10.2%), Amyloidosis (10%) and Membranous Nephropathy (8.9%). Frequency needle passes were 1 in 34% and 2 in 55%. Minimal complications were observed, only 3 pts. with small hematomas, were monitored by ultrasound; no blood transfusions or interventions for bleeding were required and no major complications were observed. Conclusions: Kidney biopsies in elderly pts. offer valuable diagnostic information and aid in tailoring management strategies. Nephrotic Syndrome was the leading indication, and Pauciimmune Glomerulonephritis was the most common diagnosis. Understanding the diagnostic yield, prevalent etiologies, and potential complications associated with kidney biopsies in the elderly is crucial for personalized care in this vulnerable population.

PUB242
Diagnostic Impact and Safety of Percutaneous Kidney Biopsy in Adults Older Than 65 Years
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Background: Population older than 65 years has been increasing worldwide and the incidence of kidney disease. Currently, there are no consensus defining an age limit for percutaneous kidney biopsy (PKB). Some centers do not perform routinely this procedure in the population of elderly.

Methods: Retrospective cross sectional study spawning data from 2019-2022 of patients ≥7.1 years, 53 were performed on pts. aged 60-70 years, and 25 on pts. above 70 years (only 3 pts. aged a 80 years). The mean pts. age was 68±7.1 years, 56% were female. The primary indication for biopsy was Nephrotic Syndrome (58.9%), followed by Acute Kidney Injury (9%). All patients met institutional protocol criteria prior to biopsy. The most common diagnoses were Pauciimmune Glomerulonephritis (19.2%), Diabetic Nephropathy (15.3%), Acute Interstitial Nephritis (12.8%), Focal Segmental Glomerulosclerosis (10.2%), Amyloidosis (10%) and Membranous Nephropathy (8.9%). Frequency needle passes were 1 in 34% and 2 in 55%. Minimal complications were observed, only 3 pts. with small hematomas, were monitored by ultrasound; no blood transfusions or interventions for bleeding were required and no major complications were observed. Conclusions: Kidney biopsies in elderly pts. offer valuable diagnostic information and aid in tailoring management strategies. Nephrotic Syndrome was the leading indication, and Pauciimmune Glomerulonephritis was the most common diagnosis. Understanding the diagnostic yield, prevalent etiologies, and potential complications associated with kidney biopsies in the elderly is crucial for personalized care in this vulnerable population.

PUB243
Systemic Lupus Erythematosus and ANCA-Associated Vasculitis Presenting De Novo in the Puerperium

Introduction: Overlap syndrome of systemic lupus erythematosus (SLE) and ANCA associated vasculitis (AAV) is uncommon. Most patients have a worse renal presentation and require more aggressive treatment.

Case Description: A 38-year-old woman with a history of preeclampsia in her first and only pregnancy underwent a cesarean section 5 months ago and presented with chronic arterial hypertension during the gestation period. She is referred to the nephrology clinic for presenting muscle pain, oral ulcers, dyspnea, and foamy urine for 3 months. She presented with blood pressure in 136/89 mmHg, basal crackles in both lung bases, and stage III edema with pitting in lower limbs. The test showed a nephrotic syndrome with ANA and ANCA-P positive (Table 1). A renal biopsy showed pauci-immune crescentic lupus nephritis with AAV (Figure 1). Management began with pulses of intravenous corticosteroids for 3 days followed by prednisone, hydroxychloroquine, cyclophosphamide (6 doses). For 10 months the patient has had a good evolution (Table 1).

Discussion: Overlap of SLE and AAV has been described in less than 3%. The use of steroids at high doses and cyclophosphamide or rituximab is necessary. SLE during pregnancy is difficult to quickly diagnose and when symptoms of preeclampsia persist after delivery, SLE should be ruled out.
Discussion: This patient with untreated HepC, positive MPO-ANCA, ANA and anti-dsDNA, presented with acute nephritic syndrome. Kidney biopsy showed pauci-immune focal segmental necrotizing GN features consistent with MPO-ANCA associated disease. Even though immediate immunosuppressive treatment of necrotizing GN is required for improved renal outcomes, in our case, treatment was withheld in view of 2 active viral infections. HepC therapy was initiated with improvement in renal function, progressive reduction in MPO-ANCA titers and disappearance of ANA and anti-dsDNA positivity.

PUB245
An Atypical Case of Immune Complex-Mediated Glomerulonephritis
Klodia Hernandez, Ryan Sohany, Henry Ford Hospital, Detroit, MI

Introduction: Rapidly progressive crescentic glomerulonephritis is an aggressive clinical syndrome characterized by massive loss in kidney function in a relatively short period of time, days to weeks. The etiology of this disease is varied, with subtypes including anti-glomerular membrane disease, immune complex-mediated injury, or pauci-immune. We report a rare case of acute exudative and crescentic glomerulonephritis leading to end-stage renal disease due to an unknown infection.

Case Description: A 29-year-old African American male with a medical history only remarkable for asthma presents with nausea, vomiting, diarrhea, and severe abdominal pain for 3-4 days. On admission, the patient’s lab data showed a serum creatinine level of 12.28 mg/dL, BUN of 71, and WBC of 23,000. Renal ultrasound showed increased echogenicity of bilateral kidneys suggestive of medical renal disease. Non-emergent HD and kidney biopsy were ordered. COVID-19, flu A/B, hepatitis panel, ANA, p-ANCA, anti-GBM, and anti-CIC were all negative. Serum protein electrophoresis showed mildly elevated IgG lambda. C3 was mildly decreased, and C4 was normal. Blood cultures were negative. The patient was initiated on vancomycin/Ceftriaxone. Kidney biopsy demonstrated 14/16 glomeruli with necrotizing crescents, C3 predominant mesangial and capillary loop staining, and numerous mesangial and segmental endothelial humps.

Discussion: Patients with postinfectious glomerulonephritis and <50% glomerular involvement have a higher chance of mild disease and potential recovery, with >80% glomerular involvement documented as severe disease requiring therapy. This case represents ~87% glomerular exudative crescents due to an unknown cause, likely post-infectious. The patient was treated with pulse steroids x 3 days, but no other immunosuppression was started as data is lacking in severe post-infectious GN as well as idiopathic immune complex RPGN. Initiation of oral or IV cyclophosphamide or rituximab was considered, however, was deferred and the patient was treated with steroid monotherapy. The patient remains on hemodialysis with no evidence of renal recovery. This case highlights the need for further studies in immunosuppression guidelines for patients with this debilitating disease.

PUB246
From Low Hemoglobin to Chronic Renal Failure: An Unusual Presentation of Advanced IgA Nephropathy in a Young Patient with Anemia
Leonardo R. Ramirez Botana, Hospital de la Concepcion, San German, Puerto Rico

Introduction: IgA nephropathy is a leading cause of CKD and renal failure. The most common primary glomerulonephritis in the world among patients undergoing renal biopsy. Its diagnosis is associated with a reduction in life expectancy between 6 and 10 years.

Case Description: We describe a patient case presented to emergency room due to general weakness of 4 weeks evolution. Our patient, with a PNH of asthma, was diagnosis with severe anemia, and admitted due to progressive shortness of breath, moderate chest pain and severe acute renal failure. The patient was worsening clinically over a period of less than 1 hour at the emergency department, blood pressure was uncontrolled and renal failure worsening, for this reason an emergency renal replacement therapy was required. Laboratory tests showed anemia and severe renal failure with high anion gap metabolic acidosis. Urethral analysis showed proteinuria, and moderate blood in urine. Testing for HIV, Hepatitis B, C, ANA, complements C3/C4, Anti Cyclic Citrullinated Peptides and serum free light chains were normal, except Glomerular Basement Membrane Ab that was out of range. A kidney biopsy was recommended and prednisone, plasmapheresis and therapy with Rituxan was started.

Discussion: Cases reviewed have been reported with IgA nephropathy associated with focal segmental glomerulosclerosis. Electron microscopy showed mesangial and subendothelial immune type electron dense deposit. Understanding the pathogenesis of IgA nephropathy reveals therapeutic targets. Mucosal IgA production by plasma cells occurs by T cell dependent and independent processes. B cell and plasma cell inhibitors such as rituximab, may result in decreased IgA production, using as part of the treatment in our patient. Complement inhibitors may prevent formation of immune complexes. This case will further contribute to the diagnosis and management of population of patients with IgA Nephropathy in Puerto Rico. Our patient was discharging home, to continue renal replacement therapy, and using a first line medication for aggressive blood pressure control and high-intensity statin therapy for hyperlipidemia and oral prednisone. She was set up for hemodialysis. There is a strong possibility of this patient is having a progressive course leading to ESRD, so early diagnosis and treatment are of key importance.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
A Case of Hydrostatic, a Common Antihypertensive, Causing ANCA-Associated Vasculitis
Neela Pathways Complement and Coagulation Cascades and Platelet Activation Erythematosus (SLE) Reveals Protein Modification Alteration in PUB248
Neela
A Case of Hydralazine, a Common Antihypertensive, Causing Publication-Only PUB247
J Am Soc Nephrol 34: 2023

Results: Compared with healthy controls, Khib in SLE patients was up-regulated at 865 sites of 416 proteins and down regulated at 630 sites of 349 proteins. The site abundance, distribution and function of Khib protein were investigated further. Bioinformatics analysis showed that 11 Khib differentially modified proteins (DMPs) were significantly enriched in the Complement and coagulation cascades pathway. 23 Khib levels in SLE patients and healthy controls were compared based on liquid chromatography tandem mass spectrometry, then proteomic analysis was conducted. The expressions of JAK2, pSTAT and STAT3 were analyzed, but there was no significant difference. Staining for JAK3 was enhanced in patients with IgA nephropathy compared to controls. The cells were evaluated at 4-time-points (4, 8, 10, 12 days). We examined monocytes (CD14+ and CD14+CD16+ phenotype) and macrophages (pro-inflammatory M1[CD68⁺CD80⁺] and anti-inflammatory M2[CD68⁺CD163⁺]).

Results: Our findings revealed consistent behavior of CD14+ cells in HG, where their percentage decreased over time. In LN patients, the decrease was more expressed in samples exposed to bacteria, particularly E. coli. CD14+CD16+ monocytes were significantly lower at each time-point in samples with bacterial exposure, indicating reduced activity in LN. M1/M22 macrophages increased over time in non-exposed groups, but LN M1 cells decreased from day 8 in samples with bacterial induction. LN M2 decrease was observed even earlier, especially with E. faecalis exposure. These results demonstrate differential behavior of M&M in LN patients compared to healthy individuals when exposed to bacterial antigens. The low percentage of M1 cells in LN samples with bacterial antigens suggests faster activation in LN patients, occurring as early as day 1-3 of incubation.

Conclusions: This study highlights the phenotypic differences in M&M in LN patients, particularly in response to bacterial antigens. Further investigation into the mechanisms underlying these differential responses could provide valuable insights into the pathogenesis of LN and potential therapeutic targets.

Funding: Government Support - Non-U.S.

JAK/STAT Expression in Patients with IgA Nephropathy
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Background: The JAK/STAT signaling pathway is an intracellular signal transduction pathway, that is involved in diverse biological processes, including cell proliferation, differentiation, apoptosis and regulation of the immune system. Recent studies have explored abnormal receptor tyrosine kinase activation in the pathogenesis of IgA nephropathy(IgAN).

Methods: A retrospective analysis was performed on all IgAN patients diagnosed by kidney biopsy. Clinical and laboratory data were collected at baseline and at the end of follow up. Kidney tissue sections were stained with antibodies specific for components of JAK/STAT pathway. We included 63 patients with IgAN and compared with 6 controls.

Results: Staining for JAK3 was observed observed in the renal tubule and glomeruli. Staining for JAK2, pSTAT3 and STAT3 were analyzed, but there was no significant

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marking in the glomerulus. Correlations of JAK3 cell density with markers such as creatinine, proteinuria, as well as the MEST score were performed, but without significant results.

Conclusions: The presence of activation of the JAK/STAT signaling pathway has been demonstrated in patients with IgAN. This pathway may represent a therapeutic target in this pathology.

Clinical and laboratory data at the time of biopsy and at the end of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
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<tbody>
<tr>
<td>Without dialysis</td>
<td>75 (69-86)</td>
</tr>
<tr>
<td>With dialysis</td>
<td>73 (57-86)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>58 (11-95)</td>
</tr>
<tr>
<td>Proteinuria (% p.o.)</td>
<td>31 (14-41)</td>
</tr>
</tbody>
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The primary outcome was defined as end-stage renal disease (ESRD) or doubling of baseline creatinine. Remission has been defined as 50% reduction in baseline proteinuria and <3.5 g/day.

Comparison of JAK3 cell density in patients with IgA and controls

PUB251
Diffuse Alveolar Hemorrhage Presenting in IgA Nephropathy
Yale School of Medicine, New Haven, CT.

Introduction: Immunoglobulin A nephropathy (IgAN) is the most common glomerulopathy worldwide. Clinical presentation of IgAN ranges from isolated hematuria to progressive IgA nephropathy and more rarely as pulmonary-renal syndrome. Here, we describe a case of diffuse alveolar hemorrhage (DAH) accompanying IgAN.

Case Description: A 38-year-old female with a history of end-stage liver disease secondary to alcoholic cirrhosis, presented with oliguria and abdominal distention. Labs showed creatinine of 2.7 mg/dL (baseline 1.2), red blood cells on urine microscopy, and urine protein to creatinine ratio of 7.13 mg/mg and diagnostic paracentesis was negative. ANA was positive with titer of 1-40, low C3/C4, but other serologic markers were negative, including Anti-Smith, MPO, and PR3. During hospitalization, she developed hypoxic respiratory failure with hemoptysis. Chest CT showed diffuse alveolar opacities concerning for DAH. She was electively intubated, and BAL confirmed DAH. She received pulse steroids for four days, followed by two days of 0.5 mg/kg steroids, and underwent an ultrasound-guided kidney biopsy confirming IgAN with acute tubular injury. Due to steroid-associated delirium, immunosuppression was switched to cyclosporine A agents underlying immune pathophysiology could directly involve the kidney as well. We describe a biopsy-proven case of TIN most likely secondary to CD.

Discussion: This case suggests that IgA nephropathy should be included in the differential diagnosis of DAH and emphasizes the importance of a timely renal biopsy with judicious use of therapeutic agents is warranted. Infliximab appears to have low risk of TIN. Even in absence of intestinal flare, kidney injury could have occurred before discharge, she achieved renal recovery sufficient to discontinue dialysis. Creatinine has remained at 0.9-1.0 mg/dL four months after presentation.

PUB252
Active Components of Traditional Chinese Medicine for IgA Nephropathy, Shen Ping, Include Mixed-Linked Glucans That Inhibit Cell Proliferation and Signaling in Human Mesangial Cells Induced by Platelet-Derived Growth Factor (PDGF)
Zhi qiugene Huang, Xianwu Zhang, Stacy D. Hall, Qing Wei, Janet Yother, Lin Wang, Dana V. Rizk, Bruce A. Julian, Yiping Chen, Jan Novak.
1University of Alabama at Birmingham, Department of Microbiology, Birmingham, AL; 2Longhua Hospital affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China; 3University of Alabama at Birmingham, School of Medicine, Birmingham, AL.

Background: Human mesangial cells in 96-well plates were serum-starved for 24 h and SP or SP-derived purified components were tested for capacity to inhibit PDGF-induced proliferation. Signaling tests used confluent serum-starved mesangial cells stimulated with PDGF-BB for 15 min in the presence or absence of SP or SP-derived components. Cell lysates were then analyzed with SDS-PAGE immunoblotting to assess changes in phosphorylation of selected proteins. Active SP compounds were isolated by chromatographic and physical-separation methods and then characterized by physical and enzymatic methods combined with the assessment of biological activity in mesangial cells.

Methods: Human mesangial cells in 96-well plates were serum-starved for 24 h and SP or SP-derived purified components were tested for capacity to inhibit PDGF-induced proliferation. Signaling tests used confluent serum-starved mesangial cells stimulated with PDGF-BB for 15 min in the presence or absence of SP or SP-derived components. Cell lysates were then analyzed with SDS-PAGE immunoblotting to assess changes in phosphorylation of selected proteins. Active SP compounds were isolated by chromatographic and physical-separation methods and then characterized by physical and enzymatic methods combined with the assessment of biological activity in mesangial cells.

Results: The active SP components, precipitated and concentrated using a 10-kDa cut-off ultrafilter, inhibited PDGF-induced cellular proliferation and phosphorylation of ERK, Axl, and Akt. These compounds were heat-resistant and likely consisted of polysaccharides. β1,3-exoglucanase removed β1,3-glycans without impacting the anti-PDG activity. Conversely, an endoglucanase (lichenase) that cleaves mixed-linkage glucans inactivated most of the anti-PDG activity. Thus, the active compounds in SP are mixed-linkage glucans. To further characterize them, we produced a β1,3-exoglucanase-digested SP sample and performed size-exclusion chromatography. Active fractions analyzed by high-performance anion-exchange chromatography coupled with pulsed amperometric detection identified a series of polysaccharides. Lichenase digestion removed most of the polysaccharide material while producing shorter oligosaccharides.

Conclusions: The active compounds in SP are mixed-linkage glucans. Future experiments will determine their detailed structures and mode of action.

Funding: NIDDK Support

PUB253
A Case of Crohn Disease-Related Tubulointerstitial Nephritis
Norely Patel, Oluwadamilola Adisa, Maheen Khan, Yashvi Sethani, Adrian P. Sewpaul.
LSU Health Shreveport, Shreveport, LA.

Introduction: The prevalence of extraintestinal manifestations (EIM) in Crohn’s disease (CD) varies and can involve almost every organ. Renal involvement in patients with IBD is uncommon, with varied manifestations. Nephrolithiasis, tubulointerstitial nephritis (TIN), glomerulonephritis (GN), and amyloidosis are the most common manifestations. Although most cases of TIN have been associated with 5-ASA, and cyclosporin A agents underlying immune pathophysiology could directly involve the kidney as well. We describe a biopsy-proven case of TIN most likely secondary to CD and less likely to drug exposure.

Case Description: A 59-year-old woman with a background of hypertension (HTN) and stable CD on infliximab infusions for about 2 years was referred to Nephrology after a hospital admission for AKI originally thought to be due to uncontrolled HTN. On investigation, renal function drastically decreased over 9 months with a serum Cr increase from 0.8mg/dL to 2.7mg/dL. Urine Analysis was unremarkable without cells or proteinuria. A renal biopsy showed 4/15 glomeruli with global sclerosis. Focal lymphocytic inflammatory in the interstitial compartment associated with rare eosinophils and focal tubular injury confirmed TIN with 30-40% interstitial involvement. It also showed significant thickening of arterioles with ischemic changes in glomeruli, and no immune deposits on immunofluorescence or electron microscopy. TIN was treated with oral steroids for four weeks with tight BP control. No improvement after steroids was seen along with worsening of her CD. A week after resumption of Infliximab therapy her Cr stabilized to 2.4mg/dL followed by 2.1mg/dL a month later.

Discussion: It is difficult to establish whether renal dysfunction is secondary to CD itself or medical treatment. However, recent literature highlighted the link between TIN and IBD. Prompt and thorough evaluation of AKI in patients with IBD via a kidney biopsy with judicious use of therapeutic agents is warranted. Infliximab appears to have low risk of TIN. Even in absence of intestine, kidney injury may be more related as EIM of CD. Excluding other acute and chronic etiologies of TIN, and improvement in renal function after infliximab, Crohn’s disease related TIN was likely the cause of interstitial kidney injury in our patient.

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Underline represents presenting author.
Diagnosed in 80% of all cases and is characterized by the presence of PLA2 R antibodies in nephrotic syndrome in non-diabetic white males older than 40 years. Primary MN is.

Charlottesville, VA

Abdulrahman

Membranous Nephropathy Relapse After 26 Years

Publication-Only

PUB254

Ujjwala

PUB255

J Am Soc Nephrol 34: 2023

bodybuilders with long term AAS abuse. Our case highlights the need for further research.

It is safe and allows us not to miss a major Glomerular disease. We plan to treat her with.

Kidney biopsy with a pathognomonic finding of DNAJB9 staining.

C was sent by his nephrologist to a local Emergency Department (ED) in January 2023 after lab work revealed a significant increase in creatinine from his baseline of 1.7 mg/dL to 3.19 mg/dL. On arrival his vital signs were stable. He denied any acute symptoms or changes in his health. Serological workup was unremarkable. He was taking testosterone proponate 25 mg daily intramuscularly for hypogonadism, somatropin 1.6 mg daily intramuscularly for growth hormone deficiency. Renal biopsy was obtained to determine the cause of the patient’s renal failure. Pathology from renal biopsy showed focal segmental glomerulosclerosis with glomerulomegaly. The patient was instructed to speak with his endocrinologist about lowering the dose and even discontinuing testosterone therapy.

Discussion: The beneficial effects of TRT in the treatment of male hypogonadism are widely known, however the risks and complications of long-term use have not been as widely studied. Both FSGS and glomerulomegaly have been described among bodybuilders with long term AAS abuse. Our case highlights the need for further research on the renal complications of TRT.

Case Description: A 51-year-old man with a history of chronic kidney disease stage 3, hypogonadotropic hypogonadism on chronic TRT, hypertension and chronic hepatitis C was sent by his nephrologist to a local Emergency Department (ED) in January 2023 after lab work revealed a significant increase in creatinine from his baseline of 1.7 mg/dL to 3.19 mg/dL. On arrival his vital signs were stable. He denied any acute symptoms or changes in his health. Serological workup was unremarkable. He was taking testosterone proponate 25 mg daily intramuscularly for hypogonadism, somatropin 1.6 mg daily intramuscularly for growth hormone deficiency. Renal biopsy was obtained to determine the cause of the patient’s renal failure. Pathology from renal biopsy showed focal segmental glomerulosclerosis with glomerulomegaly. The patient was instructed to speak with his endocrinologist about lowering the dose and even discontinuing testosterone therapy.

Discussion: The beneficial effects of TRT in the treatment of male hypogonadism are widely known, however the risks and complications of long-term use have not been as widely studied. Both FSGS and glomerulomegaly have been described among bodybuilders with long term AAS abuse. Our case highlights the need for further research on the renal complications of TRT.

Case Description: A 69-year-old white woman with a past medical history significant for morbid obesity (BMI-55), hypertension, and type 2 diabetes mellitus was referred by her PCP due to a decline in Renal function with a rise of her serum creatinine up to 2.6 mg/dL absolute value. Her rise was noted in August 2019, with a change in a GFR from 55 to 19 with minimal proteinuria and no lower extremity edema. She had no history of NSAID, herbal, or Supplemental usage and had no Family history of Renal disease. Upon evaluation, her serum albumin was 3.6 gram/dL and the protein creatinine ratio was 3.4 mg/mmol on random urine. Serological studies were negative for HIV and Hepatitis C. SPEP, UPEP, and serum-free light chains were nonrevealing. C3 and C4 complements were normal. C3 was 86 mg/dL, C4 was 21 mg/dL, and urine 10s was negative. She had a serum creatinine level of 2.6 mg/dL and a GFR of 19 mL/min/1.73 m². A urinalysis was performed which showed a urine protein creatinine ratio of 1470 mg/g Clinical course: He was started on Losartan with improvement in albuminuria from 1470 to 900mg/g. On September 2021, albuminuria worsened to 4g/g. Serology was remarkable for v+ anti PL2A R. A kidney biopsy showed subepithelial immune complex deposition, mesangial dense deposits and moderately sclerosed arterioles and severely hyalinized arterioles. His Cr was mildly elevated to 1.4 and albuminuria decreased from 4g/g to 2g/g however on December 2021 he started to have worsening edema with rise of Cr to 2.5 and albuminuria worsened to 13g/g. On March 2022 he was started on weekly Rituximab and completed 4 doses. His Cr peaked at 2.6 and then started to trend down after Rituximab to 1.4. He continued to have proteinuria and on 1995 that was treated with Prednisone and Cyclophosomide. He had been on remission within the first 5 years. We present a rare case of MN relapse after 26 years of remission. The biopsy showed features of MN and diabetic kidney disease. Despite maximally tolerated Losartan dose, he continued to have worsening Cr and proteinuria. His Cr improved after Rituximab however he had persistent proteinuria. The decision to use Rituximab rather than CNI was due to poorly controlled diabetes. Diabetic kidney disease is likely a factor in the failure of MN remission in our patient.

Discussion: We present a case of PMS which presented with proteinuria and hyponatremia. To our knowledge this is the first case describing PMS with this constellation of findings. PMS is known to occur in 10% of all MN relapse cases on Renal biopsy. FGN is characterized by the deposition of Microfibrils 10-30nm in diameter in the mesangial and Glomerular capillary walls and is often found in patients with a history of diseases, including Cancer, Autoimmune diseases, and Hepatitis C. The diagnosis of FGN is usually made with a kidney biopsy with a pathognomonic finding of DNAJB9 staining.

Case Description: A 29-3+yos presented at 25+3 weeks gestation had hypertension and clinical vovolume overload. She had a BP of 150/90 with ankle swelling and hemoglobin 8.6 g/dL, platelets 174 k/mm3 & S. creatinine 1.5mg/dL. Urinalysis showed microscopic hematuria and proteinuria. Urine protein:creatinine ratio was 38.2 mg/mmol. NaHCO3 was administered to alkalize the urine, diuretics were started, and blood pressure was controlled with hydralazine. Her serum creatinine improved to 1.4 mg/dL with a GFR of 55 mL/min. She was started on weekly Rituximab and completed 4 doses with a complete recovery of renal function.

Discussion: Complement dysregulation occurs in pre-eclampsia and clinical vovolume overload. She had a BP of 150/90 with ankle swelling and hemoglobin 8.6 g/dL, platelets 174 k/mm3 & S. creatinine 1.5mg/dL. Urinalysis showed microscopic hematuria and proteinuria. Urine protein:creatinine ratio was 38.2 mg/mmol. NaHCO3 was administered to alkalize the urine, diuretics were started, and blood pressure was controlled with hydralazine. Her serum creatinine improved to 1.4 mg/dL with a GFR of 55 mL/min. She was started on weekly Rituximab and completed 4 doses with a complete recovery of renal function.

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but no monoclonal spike. Anti-histone Abs were mildly positive, hyaluronic was discontinued. Renal biopsy revealed total glomeruli 31, global glomerulosclerosis 18, moderate interstitial fibrosis with tubular atrophy, and severe arterial intimal fibrosis. One of four nonsclerotic glomeruli showed fibrin and small crescent formation. The patient was not placed on a pulsed dose steroid due to active infection and was started on prednisone 60 mg daily instead. Outpatient TRUXIMA (rituximab) was started.

Discussion: Pauci-immune GN accounts for up to 80% of RPGN occurrences, affecting 7–10 per million Americans per year. PICG has 80% 1-year mortality without therapy. 5-year survival is 75% with strong immunosuppression. Hyaluronidase-induced pauci-immune GN is rare; we present this case to highlight several critical aspects of drug-induced pauci-immune GN that can aid with early identification and improve patient outcomes. Early detection of MPO Abs helps diagnose the condition and timely biopsy can guide adequate treatment. The offending agent must be discontinued early.

Untreated RPGN evolves to ESRD in days to weeks. Prompt diagnosis and treatment enhance prognosis. We recommend serologies and, if inconclusive, a kidney biopsy. A patient with RPGN-suggestive symptoms needs a clear and urgent diagnosis and treatment.

PUB259

Unanticipated Cause of Minimal Change Disease: A Rare Case due to Hypothyroidism

Yahya Al-Yousif, Amenah Al-Juboori, Charles Nnewhi. AtlanticCare Regional Medical Center, Atlantic City, NJ.

Introduction: Hypothyroidism, also called underactive thyroid, may affect renal physiology and impair kidney function, among other metabolic implications. In certain case studies, hypothyroidism was mentioned as a contributing factor to minimum change disease, which we will be emphasizing here.

Case Description: An 82-year-old female with PMH of Graves’ disease s/p thyroideectomy, non-compliant with Levothyroxine presents to the ED with a complaint of edema, mainly in the lower limbs, slowly worsening over 2 weeks, as well as foamy urine. Laboratory workup showed a high TSH of 65.2 ulU/ml, a normal FT4, and a low FT3 of 0.4 pg/ml, creatinine of 4.35 mg/dl, hypoalbuminemia, and hyperlipidemia, urinalysis showed >500 protein, urine P/C was 3. A Glomerulopathy workup was begun. After ruling out autoimmune kidney disorders, a renal biopsy was done, confirming Minimal Change disease. Prednisone 60 mg daily instead. Outpatient TRUXIMA (rituximab) was started.

Discussion: Inadequate supply of thyroid hormone can impair kidney function by influencing vascular resistance, the re-absorptive process, and renal blood flow. It can also influence the RAAS system, beta-adrenergic receptors, and renal tubular cell’s dopaminergic activity. Gradual deterioration of kidney function causes an increase in the loss of free and bound thyroid hormones, ultimately increasing thyroxine need. GFR is reversibly lowered (by roughly 40%) in more than 55% of hypothyroid people. Thyroxine therapy reduces edema, albumin capillary permeability, and plasma colloid osmotic pressure. Because just a few isolated incidences have been documented in the literature, more study is needed to identify the link between hypothyroidism and nephrotic syndrome.

PUB260

Unilateral Parotid Swelling as the Initial Manifestation for HIV-Associated PLA2R-Negative Membranous Nephropathy

Ramsa Riaz1, Katrina K. Au, Gregory F. Crisafulli, Shreyasvaka Daal1, Craig R. Goldstein.1 Jersey City Medical Center, Jersey City, NJ; 2 Saint George’s University School of Medicine, St George’s, Grenada.

Introduction: There are two major types of HIV-associated renal disease: HIV-associated nephropathy, which is more common, and HIV-associated immune complex disease. Kidney biopsy is necessary to differentiate between these two types as they appear different histologically and may be beneficial to determine overall prognosis. We present the case of a patient with unilateral, painless swelling of the parotid region, who not only had underlying HIV infection but also full-blown renal failure requiring hemodialysis.

Case Description: A 34-year-old African-American male with no medical history presented to the hospital for worsening right-sided parotid swelling at the mandibular angle for 1 week. He also endorsed generalized malaise, intermittent shortness of breath, subjective fevers, and unintentional weight loss. Physical exam showed a soft, non-tender, mobile right-sided parotid mass. Labs were remarkable for renal dysfunction (BUN/Cr 92.9:71 mg/dl) and significant hyperkalemia with non-anion gap metabolic acidosis. Urinalysis revealed a protein-creatinine ratio 931 mg/g and 24-hr urine protein of 862 mg/dl. Imaging of the neck showed a well-margined 3.4x3.0x3.6 cm, hypo-attenuated structure in the right parotid tail. He tested positive for HIV and syphilis. Hemodialysis (HD) was initiated. Drainage of the parotid mass was consistent with a lymphoepithelial cyst with no evidence of malignancy on biopsy. Kidney biopsy revealed an HIV-associated immune complex disease. It is imperative to consider the possibility of undiagnosed HIV infection in a patient presenting with painless cysts of the head and neck region. Furthermore, in cases of suspected HIV-associated nephropathy, obtaining a biopsy is clinically significant to not only provide a histological diagnosis but also aid management and prognosis.

PUB261

Granulomatosis with Polyangiitis in a Diabetic Woman with Nephrotic Proteinurinias: Case Report

Walesa D. Nueve1, Odalina H. Marrero1, Ronald Valdez Imbert, Guillermo Alvarez. Centros de Diagnostico y Medicina Avanzada y de Conferencias Medicas y Telemedicina, Santo Domingo, Dominican Republic.

Introduction: Granulomatosis with polyangiitis (GPA) is an antineutrophil cyttoplasmic autoantibody (ANCA)-associated vasculitides (AAV) is part of a group of disorders. All are associated with ANCA, affect predominantly small-sized arteries, in which it can present with pulmonary hemorrhage, deterioration of renal function, constitutional symptoms that can lead to death if not treated in time.

Case Description: A 71-year-old female with a known morbid history of Diabetes mellitus 2 + systemic arterial hypertension + grade II morbid obesity + hypothyroidism; which she was being investigated by hematology for approximately 3 months for recurrent thrombocytosis + thrombocytosis + lymphadenopathy; began to notice foamy urine and asthma with normal kidney function and that is when she is referred to nephrology. Protein dosage is performed in 24-hour urine (5.2/24hrs) with C-Anca: weakly positive. It was decided to perform a renal biopsy and while waiting for it, the patient developed fever, cough, and respiratory distress that required CPAP 1 week later, and she was admitted to the intensive care unit. A diffuse pattern with opacities is evident on radiography with tomographic data suggestive of pulmonary hemorrhage and rapidly progressive deterioration of renal function. (Family members refused to perform bronchoscoeleval lavage by bronchoscopy). A biopsy was received reporting granulomatosis with polyangiitis. Treatment with cyclophosphamide and rituximab plus steroids was started.

Discussion: After initiating pulses of steroids, cyclophosphamide, and rituximab, the patient remains in the intensive care unit for approximately 3 weeks due to impaired ventilatory mechanics. Subsequently, she is transferred to the clinical ward for 1 week. He also endorsed generalized malaise, intermittent shortness of breath, subjective fevers, and unintentional weight loss. Physical exam showed a soft, non-tender, mobile right-sided parotid mass. Labs were remarkable for renal dysfunction (BUN/Cr 92.9:71 mg/dl) and significant hyperkalemia with non-anion gap metabolic acidosis. Urinalysis revealed a protein-creatinine ratio 931 mg/g and 24-hr urine protein of 862 mg/dl. Imaging of the neck showed a well-margined 3.4x3.0x3.6 cm, hypo-attenuated structure in the right parotid tail. He tested positive for HIV and syphilis. Hemodialysis (HD) was initiated. Drainage of the parotid mass was consistent with a lymphoepithelial cyst with no evidence of malignancy on biopsy. Kidney biopsy revealed an HIV-associated immune complex disease. It is imperative to consider the possibility of undiagnosed HIV infection in a patient presenting with painless cysts of the head and neck region. Furthermore, in cases of suspected HIV-associated nephropathy, obtaining a biopsy is clinically significant to not only provide a histological diagnosis but also aid management and prognosis.

PUB262

Infection-Related Pauci-Immune Golomerulonephritis: To Treat with Immunosuppression or Not, That Is the Question

Katherine E. White, Sanjivani Shrestha, Derek M. Fine, Samir C. Gautam. The Johns Hopkins University School of Medicine, Baltimore, MD.

Introduction: Pauci-immune glomerulonephritis is a common cause of crescentic or rapidly progressive glomerulonephritis. Treatment typically consists of immunosuppression; however, we present a case of pauci-immune glomerulonephritis treated without immunosuppression.
**Case Description:** An 84-year-old female with medical history of breast cancer status post resection and chemoradiation, chronic lymphocytic leukemia with treatment-related myelodysplastic syndrome, and recent SARS-CoV-2 infection with central venous port-related coagulase negative staphylococcus bacteria developed acute kidney injury. Urinalysis revealed proteinuria and hematuria. Urine sediment analysis showed dysmorphic red blood cells and red blood cell casts. Serologic studies were notable for hypocomplementemia, ANA, and e-ANCA; however, myeloperoxidase and proteinase 3 were negative. Kidney biopsy was performed. Light microscopy showed focal segmental glomerular nerosis with small crescent. Immunofluorescence performed on frozen sections showed a full house picture, but immunofluorescence performed on paraffin sections only showed 1-2+ mesangial staining for IgM. However, there were no electron dense deposits on electron microscopy which is most consistent with pauci-immune glomerulonephritis. Despite rising creatinine, immunosuppression was not started in the setting of persistent bacteremia and was planned to be started once blood cultures were negative for more than 48 hours. Once blood cultures became negative, creatinine started to stabilize. Creatinine peaked at 4.9mg/dL. Ultimately, steroids were not started given that creatinine continued to improve with antibiotics once blood cultures remained negative.

**Discussion:** Pauci-immune glomerulonephritis has been reported in cases of infective endocarditis and treated with antibiotics. This case highlights infection as a possible cause of pauci-immune glomerulonephritis with antibiotics being the mainstay of therapy in most cases.

**PUB263**

**Methamphetamine-Associated Thrombotic Microangiopathy**

Nayeli N. López Villa, Giovanna Y. Arteaga Muller, Rita B. Aguilar, Elisa M. Guerrero Gonzalez, Mara C. Olivo Gutierrez, Ricardo A. Garza Treviño.

Hospital Universitario Dr Jose Eleuterio Gonzalez, Monterrey, Mexico.

**Introduction:** Thrombotic microangiopathy (TMA) is characterized by clinical presentation with microangiopathic hemolytic anemia, thrombocytopenia, and target organ damage. It can present acute kidney injury with damage and occlusion of the glomerular circulation. The requirement of renal replacement therapy has a poor prognosis.

**Case Description:** 16-year-old male, with no known pathological history. He has a history of drug use such as crack and methamphetamine. Brought in due to unconsciousness and difficulty of breathing. He was brought to the emergency room, a patient was received with blood pressure 190/80mmHg, HR 112bpm, 35 rpm, temperature 36.9°, saturation 95%, hemoglobin 5.5g, platelets 72,000, BUN 140mg/dL, Cr19.6mg/dL, and potassium 6.1mEq. In its gasometry with pH 7.31 HCO3 12.6. Urinary sediment was obtained with a leukocyte cast, without dysmorphic erythrocytes. In renal ultrasound with adequate renal measurements, it was decided to carry out a renal biopsy. Image 1: expansion of the mesangial matrix with segmental proliferation, folded and healed basement membranes, with duplicated segments, leukostasis, karyorrhexis, and fibrin thrombi, partially increased mesangial matrix, cellularity, and capillary wall thickening. It includes immune-complex MPGN and C3 glomerulopathy. Incidence is rare (1-4 cases per million). Dysregulated complement pathway plays a role. Diagnosis of C3 glomerulopathy is rare. Diagnosis of C3 glomerulopathy relies on kidney biopsy. C3 predominance of at least two orders of magnitude by IF compared with other immunoreactants has been adopted as a diagnostic criterion. Our patient exhibited similar findings and commenced regular hemodialysis with close monitoring. Hence, native kidney biopsy is crucial in most cases.

**Laboratory reports**

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**PUB265**

**Henoch-Schönlein Purpura (HSP) Nephritis in Adults**

Hafiz Sarfraz A. Khan, Irtiza Hasam, Charles W. Heilig. University of Florida College of Medicine - Jacksonville, Jacksonville, FL.

**Introduction:** Henoch-Schönlein purpura (HSP) is a small vessel vasculitis. It affects children more often than adults but renal involvement is more common & severe in adults. Few studies on HSP nephritis (HSPN) in adults have been reported. Prompt evaluation & aggressive treatment in HSP nephritis can prevent progression of kidney damage.

**Case Description:** A 48-year-old non-diabetic, non-hypertensive & non-smoker Caucasian female with PMH of seizure disorder, morbid obesity (BMI 53.8), & asthma, presented with a lower extremity purpuric rash & arthralgia in knees, hip joints. Labs showed normal CBC, normal coagulation profile, normal renal function (creatinine 0.77 mg/dL). UA with microscopic hematuria (5 RBCs/HPF) & proteinuria (100 mg/dL). She was suspected to have Henoch-Schönlein purpura (HSP) based on clinical findings of palpable purpura and arthralgia. Further investigation showed proteinuria of 1904 mg/day & elevated serum IgA level (526 mg/dL). Patient underwent a kidney biopsy that showed mesangial proliferation, mesangial immune complex deposits identified as IgA & C3 on immunofluorescence study and as dense deposits on electron microscopy. These findings were supportive for HSP nephritis. She was started on Lisinopril and prednisone. Repeat urine study showed improvement in proteinuria (119 mg/day) & hematuria (4 RBC/HPF) with 4 months of tapering prednisone therapy.

**Discussion:** HSP is a small vessel vasculitis. Renal involvement in HSP can cause hematuria, mild-to-moderate proteinuria, RBC cast, elevated serum creatinine, hypertension & nephrotic syndrome. Incidence is rare (1-4 cases per million). Dysregulated complement pathway plays a role. Diagnosis of C3 glomerulopathy is rare. Diagnosis of C3 glomerulopathy relies on kidney biopsy. C3 predominance of at least two orders of magnitude by IF compared with other immunoreactants has been adopted as a diagnostic criterion. Our patient exhibited similar findings and commenced regular hemodialysis with close monitoring. Hence, native kidney biopsy is crucial in most cases.

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**PUB266**

**Atypical Hypoprotenemia and Fluid Retention: AKI in an IgAκ Multiple Myeloma with Type 2 Diabetes**

Shinichiro Koga,1,2 Section for Nephrology & Hypertension, Department of Medicine, Tokyo Metropolitan Police Hospital, Tokyo, Japan; 2Department of Diabetes & Endocrinology, Tokyo Hospital, Japan Organization for Occupational Health & Safety, Tokyo, Japan.

**Introduction:** Diagnosis of multiple myeloma (MM) is usually evident when chronic bone pain, pathologic fractures, and hypercalcemia are complicated by proteinuria and kidney failure. Cast nephropathy is considered when proteinuria (often ≥3 g/ day), particularly without concomitant hypoalbuminemia or significant albuminuria, is found in a patient who is ≥40 y/o.1

**Case Description:** An Asian 75 y/o male had dysuria as well as right upper limb weakness for 2 weeks. He was admitted to ED due to difficulty of moving by himself, then admitted to the nephrology with pleural effusion, ascites, and

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1122
Focal segmental glomerulosclerosis (FSGS) is the leading cause of nephrotic syndrome (NS) in adults. The epidemiology of FSGS over a 20-Year Period

Methods: Retrospective longitudinal analysis of primary FSGS at a tertiary renal centre over two decades. Baseline demographics, labs and outcomes: Complete (CR) & partial (PR) remission, relapse, progression RRT and mortality were collected.

Results: 87 patients were identified with primary FSGS after exclusion of secondary causes. Mean age was 49.3 years, 60.9% male, 86.2% white with median eGFR 46ml/min per 1.73m². Rates of PR and CR were 69% vs 39.7% (p=0.01) with no increased rates of relapse. Patients that likely to receive immunosuppression (IS) 86.2% vs 20.7% (P<0.001) and more likely to achieve CR 69% vs 39.7% (p=0.01) with no increased rates of relapse. Patients that presented with nephrotic syndrome were more likely to receive IS and achieve complete remission. Progression to RRT occurred in 27.4%, death in 27.4%. 29 patients presented with NS were more likely to receive IS and achieve complete remission, relapse, progression RRT and mortality were collected.

Conclusions: This Retrospective longitudinal study of primary FSGS over a period of 2 decades provides important prognostic information for this understudied area. Despite the exclusion of important prognostic factors only 1/3 of patients presented with NS. Those who presented with NS were more likely to receive IS and achieve complete remission. Regardless of whether the patient had NS, complete or partial remission was protective of ESKD and CR was associated with reduced risk of death. Given 27.4% die or progress to ESKD, this emphasises the importance of achieving remission, if even partial remission.
**PUB269**

**IgA Nephropathy and Thrombosis Microangiopathy: A Rare Manifestation of Lupus After COVID-19 Infection**

**Kelly V. Liang, Kimberly P. Liang, Timothy A. Fields. University of Kansas School of Medicine, Kansas City, KS.**

**Introduction:** Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease which may present with lupus nephritis (LN), lupus anticoagulant (LAC) and thrombosis microangiopathy (TMA). SLE is rarely described in association with non-lupus glomerulonephritis (GN). We present a case of SLE presenting with renal dysfunction, hypertension (HTN), proteinuria, and microscopic hematuria in a patient with LAC, shortly after COVID-19 infection, in which renal biopsy confirmed IgA nephropathy (IgAN) with TMA.

**Case Description:** A 37-year-old male with history of antiphospholipid syndrome (APS) with LAC, right leg deep vein thrombosis in 2016, osteosarcoma of left distal femur in 2002, melanoma in 2022, HTN, and hyperlipidemia, was referred to Nephrology in December 2022 for elevated creatinine (Cr) and proteinuria. In September 2022, he developed right leg numbness/tingling and facial droop. He caught COVID-19 in late November 2022. In December 2022, he presented with severe HTN (SBP=200), Cr 1.6-1.7 mg/dL, urea 49 mg/dL, creatinine 1.7 mg/dL. On admission, the patient's serum creatinine (Cr) was noted to be 3.49 mg/dL with BP 195/110, requiring 2u pRBCs and complicated by AKI. Patient underwent EGD, which showed normal mucosa. He was started on empiric steroid therapy for concern for SLE associated IgAN. This case supports the utility of HCQ as a therapeutic option in IgAN, particularly in IgAN occurring in SLE.

**PUB270**

**Use of Mycophenolate Mofetil (MMF) in IgA Nephropathy: When Steroids Induce Psychosis**

**Farhana Begum, Daniel W. Ross, Deepa A. Malieckal. Northwell Health, New Hyde Park, NY.**

**Introduction:** IgA nephropathy (IgAN) is one of the common glomerular diseases worldwide and up to 40% can progress to ESKD. Current management of IgAN is focused on supportive care (SC), to slow the rate of progression. This includes BP management, low Na diet, ACE/ARB use if proteinuria >500 mg/d, weight loss, exercise, smoking cessation, and CV optimization. KDIGO currently recommends that patients with nephrotic syndrome at diagnosis - should have a long-term follow-up to identify disease relapse.

**Conclusions:** This is a rare case of SLE presenting with renal dysfunction, HTN, proteinuria, and microscopic hematuria found to be due to IgAN rather than LN, in conjunction with TMA in the setting of LAC. It underscores the importance of performing renal biopsy in patients suspected of having LN, as other GN’s may coexist with SLE. This case is unique in that the onset of IgAN and SLE occurred after COVID-19 infection, which may increase risk of autoimmune disorders. Clinical response was like that of non-SLE associated IgAN. This case supports the utility of HCQ as a therapeutic option in IgAN, particularly in IgAN occurring in SLE.

**PUB271**

**Clinical Characteristics, Histologic Patterns, and Disease Outcomes in C1q Nephropathy (C1qN): A Single-Center Experience**

**Zachary S. Bruss,1 Saeed K. Shaffi,1,2 Brent Wagner,1,2* University of New Mexico Health Sciences Center, Albuquerque, NM; 1Raymond G. Murphy VA Medical Center, Albuquerque, NM.**

**Background:** C1qN is a rare glomerulopathy associated with mesangial dominant C1q deposition on immunofluorescence staining. Clinical presentation and outcomes are heterogeneous, ranging from asymptomatic proteinuria to nephrotic syndrome. We explore the demographic and clinical characteristics of a C1qN cohort stratified on nephrotic syndrome at diagnosis.

**Methods:** We searched the University of New Mexico Kidney Biopsy registry for instances of C1qN. We excluded transplant recipients, obtained the relevant demographic and clinical data from the electronic medical records, and summarized and compared data stratified on nephrotic syndrome at diagnosis.

**Results:** Of the 11 renal biopsies with C1qN, 8 were native and were included in this study. Patients with nephrotic syndrome were younger, had higher proteinuria and serum cholesterol, and lower albumin (table 1). Patients without nephrotic syndrome had greater microscopic hematuria. Apart from a greater degree of foot process effacement in patients with nephrotic syndrome, no other trends were evident on microscopy. Patients with nephrotic syndrome were likely to receive immunosuppressive therapy. Disease relapse was seen often in patients with nephrotic syndrome; however, immunosuppressive therapy led to proteinuria resolution in all patients.

**Conclusions:** C1qN is an immune-complex mediated rare diagnosis affecting children. Nephrotic syndrome is associated with foot process effacement and a trend towards frequent relapses. Patients without nephrotic syndrome have microscopic hematuria and are less likely to relapse. Therefore, patients with C1qN - especially those with nephrotic syndrome at diagnosis - should have a long-term follow-up to identify disease relapse.

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sessions over two weeks, and oral cyclophosphamide, the patient’s serum creatinine returned to relatively stable levels, and her hematuria and proteinuria improved over the subsequent six months.

**Discussion:** Atypical anti-GBM disease manifests milder kidney injury and minimal pulmonary hemorrhaging compared to classical cases. In this case, the patient’s condition improved, and renal function remained relatively stable with corticosteroid, plasma exchange therapy, and oral cyclophosphamide treatment.

**Figure 1a dual pathology of IgA nephropathy and anti-GBM disease.**

**Figure 1**

**PUB273**

Experience with Ravulizumab in Atypical Hemolytic Uremic Syndrome

**Authors:** Víctor Escudero-Saiz, Marta Martínez-Chillarón, Elena Guilleu, Alicia M. Andújar, María Bell Font, Guston J. Poch, Esteban Poch, Luis F. Quintana, Josep Miquel Blasco Pelicano, Hospital Clinic de Barcelona Servei de Nefrologia i Trasplantament Renal, Barcelona, Spain; Hospital Clinic de Barcelona, Barcelona, Spain.

**Background:** The arrival of eculizumab revolutionized the treatment of Atypical Hemolytic Uremic Syndrome (aHUS). Ravulizumab also offers C5 inhibition but with longer half-life. We describe the experience with ravulizumab in two scenarios: switching from another C5 inhibitor in stable patients and direct therapy initiation (naïve).

**Methods:** We present 9 patients with 42±13 years and 81±12.4kg. Switching to ravulizumab began 2 weeks after the last eculizumab dose while in naïve patients it started after excluding other causes of aHUS. Initial dose was 2700mg followed by 3300mg after 2 weeks and subsequently every 2 months. Analytical variables of renal function, hematological and complement parameters were collected.

**Results:** Switch: 6 patients (50% females), 4/6 transplant recipients (3 on prophylactic treatment). Regarding renal function, 5/6 had complete response with eculizumab (creatinine 1.33±0.32mg/dL, eGFR 59.5±3.4mL/min/1.73m², proteinuria 118±91.5mg/g), and all had complete hematological response. After the switch, all maintained complete hematological response, renal function stability and serum complement levels. naïve: 3 cases (2 males); 2/3 required hemodialysis (HD) at presentation. Renal response was complete in two patients and partial in the third (who discontinued HD after 90 days and currently remains with CKD-G3b). All had complete hematological response. Only 3 adverse effects were documented (arthralgia, headache, and rhinitis), no infection cases.

**Conclusions:** Ravulizumab use is effective both maintaining complete response after switching from eculizumab and as first-line therapy. The safety profile is comparable with the main difference being the posology, as ravulizumab requires fewer administrations and may be considered as an option due to the longer half-life. We describe the experience with ravulizumab in two scenarios: switching from another C5 inhibitor in stable patients and direct therapy initiation (naïve).

**PUB274**

Anti-Phospholipase A2 Receptor (Anti-PLA2R) Antibody in Diagnosis and Treatment of Idiopathic Membranous Nephropathy: A Single-Center Experience

**Authors:** Muhammad Sajid R. Abbasi, Rukhsana Manzoor, Khawar Sultan, Pakistan Institute of Medical Sciences, Islamabad, Pakistan; East Kent Hospitals University NHS Foundation Trust, Canterbury, United Kingdom.

**Background:** The aim of this study was to observe the prevalence of serum Anti-PLA2R Antibodies in patients with idiopathic membranous nephropathy (IMN) and to observe its clinical and laboratory parameters in Pakistani population.

**Methods:** We enrolled 84 patients with idiopathic membranous nephropathy who were hospitalized on renal biopsy. A subgroup had nephrotic syndrome at the time of presentation. These patients further had testing for serum anti-PLA2R antibody, serum albumin, 24 hour urinary protein (24 U/P), serum creatinine and GFR estimation. Serum anti-PLA2R antibody was measured by enzyme-linked immunosorbent assay (ELISA). These patients were treated with combination therapy of low dose steroids and CN/tarolimus, CSA) and response was assessed at 6 months.

**Results:** Thirty seven 37 (44%) patients were positive for serum anti-PLA2R antibody while Forty seven 47 (55%) patients were negative among all patients with IMN. Patients who were positive for serum anti-PLA2R antibody had high level of 24 urinary protein, low level of serum albumin at the time of presentation in comparison with those who were negative for serum anti-PLA2R antibody (p = 0.05). In terms of response to treatment, in patients with serum anti-PLA2R antibody positive, at 6 months complete and partial repose was 38% and 45% respectively. In anti-PLA2R antibody negative group at 6 months complete and partial repose was 62% and 20% respectively.

**Conclusions:** Serum anti-PLA2R antibody is non-invasive technique, clinically helpful and specific biomarker for diagnosis of IMN. Our results suggest that serum anti-PLA2R antibody can help to diagnose, predict course of disease and response to therapy in IMN patients.

**Funding:** Private Foundation Support

**PUB275**

A Case of Severe Parvovirus B19 Infection with Glomerulonephritis Requiring Artificial Ventilation

**Authors:** Daisuke Matsui, Daiki Aomura, Takayuki Nimura, Kosuke Yamaka, Koji Hashimoto, Yuji Kamiy, Shizuoka Daigaku Igakubu Fuzoku Byoin, Matsumoto, Japan.

**Introduction:** Initial infection of parvovirus B19 (PVB19) is known to occasionally cause inflammation in systemic organ tissues such as myocarditis and glomerulonephritis (GN), and possibly result in severe outcomes including death. In the present case, we encountered a patient with severe PVB19 infection along with GN, requiring artificial ventilation.

**Case Description:** A 22-year-old female developed a fever along with rashes on her extremities. Antibiotic therapy was initiated at a previous hospital, with less effectiveness. One month later, she also complained about dyspnea and was referred to our hospital. She had no past history and had taken no medicines before the onset of her symptoms. Her blood pressure and heart rate were 127/105 mmHg and 94/ 64 mmHg, respectively. Her respiratory rate was 31 /min and required 4 L/min of oxygen. Chest CT revealed findings of severe pulmonary edema, and ultrasound cardiology found diffuse left ventricular hypokinesis as well. Due to her severe respiratory failure, artificial ventilation was initiated. Blood and urine tests at the admission found as increase in serum level of creatinine (1.1 mg/dL) and C-reactive protein (4.9 mg/dL), and the presence of glomerular hematuria and proteinuria (1.1 g/gCr). These findings indicated the involvement of GN-related diseases; therefore, a kidney biopsy was performed under artificial ventilation to aid in the diagnosis. It revealed the pathological findings of infection-related GN, showing immune-complex glomerulonephritis and the high titer of an IgM antibody for PVB19. Intravenous injection of methyl prednisolone (1000 mg/day for 3 consecutive days) dramatically improved her respiratory failure and urine findings, and she was discharged without any sequelae. With these clinical presentations, we diagnosed her as having severe PVB19 infection accompanied by GN.

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

**Underline represents presenting author.**
Discussion: PV-B19 infection can be fatal due to the inflammation mediated by global antiviral arm mechanism expressed in the heart, lungs, and kidney. However, since the initial symptoms of PV-B19 are complicated and present with various manifestations, it is difficult to detect systemic injury caused by PV-B19 infection at an early stage. For patients who have systemic organ injuries with abnormal urine findings, PV-B19 infection should be suspected, and a kidney biopsy needs to be taken into account.

**PUB276**

**Immunoglobulin A Nephropathy Management Quality Improvement Initiative Project in China**

Gengru Jiang, Fujian F. Lin, Committee of Quality Improvement Initiative Project in China, Renal Division, Department of Internal Medicine, Xin Hua Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

**Background:** In China, Immunoglobulin A nephropathy (IgAN) accounts for 45-53% of biopsy-confirmed primary glomerulonephritis and individuals of Pacific Asian origin are 1.56 times more likely to develop end-stage renal disease compared with other origins. Currently, there is few nationwide data on the diagnosis and treatment patterns of IgAN in China. Immunoglobulin A Nephropathy Management Quality Improvement Initiative Project in China (IGAN-MIC) is established to aim an IGAN cohort collaboration network to learn about the real-world practice of IgAN management in China.

**Methods:** IGAN-MIC project will establish an IGAN Chinese expert committee consisting of 14 experts from 13 regions in China with geographical representativeness to assess differences between regions and ethnicities. These hospitals play leading roles in the nephrology development in their provinces and nearby areas. The first-stage IGAN-MIC project is to establish a nationwide data platform to extract data on clinical characteristics, renal biopsies, diagnosis, comorbidities, laboratory results and medications from electronic medical records and hospital information systems. Biopsy date will be defined as the index date and follow-up data will also be recorded. The second-stage of the project focuses on physician education activities via presentations and handbooks based on the management gap on the data platform.

**Results:** IGAN-MIC is designed to focus on the pathologic classification, prognostic assessment, medication used and improvement of key laboratory results after IgAN management. The project is scheduled to start in July 2023 and end by December 2024. All hospitals with capabilities of performing renal biopsy and IgAN treatment can join the network. Over 100 healthcare institutions in China are expected to participate with a minimum of 5000 IgAN patients enrolled to develop a portrait of IgAN diagnosis and treatment in China, also to fill the gap in this area globally.

**Conclusions:** IgAN is the most common glomerular disease in China. The IGAN-MIC project aims to optimize the management of IgAN in China.

**PUB277**

**Late-Onset Lupus Nephritis Presenting as Acute Decompensated Heart Failure**

Alina Cheema, S, Soo Hyun Kae, S, Matthew Min, S, Sankar N. Niranjani, 2

1 UCHealth, Farmington, CT; *Greater Hartford Nephrology, Bloomfield, CT; +Trinity Health of New England, Hartford, CT.

**Introduction:** Lupus nephritis (LN) occurs in 20-50% of systemic lupus erythematosus (SLE) cases and usually develops within the first 5 years of SLE diagnosis, rarely occurring afterward. We describe a case of late-onset LN in a patient with known SLE who presented with acute systolic heart failure.

**Case Description:** A 64-year-old female with a history of SLE for 31 years without renal involvement, atrial fibrillation, prior right innominate artery occlusion, hypertension and type 2 diabetes presented to the hospital with worsening exertional shortness of breath. Physical exam was notable for stable vitals, bilateral rales on lung auscultation and 3+ bilateral lower extremity pitting edema. Laboratory investigation was significant for serum creatinine (SCr) 2.9 mg/dL, with a baseline of 0.9-1.1 mg/dL, BUN 27 mg/dL, albumin 1.8 g/dL and BNP 110 pg/mL. Echocardiogram revealed a mildly reduced ejection fraction of 40-50% with a small pericardial effusion and a chest x-ray showed vascular congestion and a left pleural effusion. He was admitted for acute systolic heart failure and acute kidney injury. Further workup revealed a urine protein/creatinine ratio of 16.01. C3 and C4 complement levels were within normal range. Given the nephrotic-range proteinuria, the patient underwent a kidney biopsy which showed class V membranous nephropathy with acute tubular necrosis, consistent with LN. Along with diabetes, the patient was initiated on mycophenolate mofetil 1000 mg twice daily and pulse doses of IV methylprednisolone with taper. On discharge, SCr improved to 1.3 mg/dL and the patient had close follow-up for management of the newly diagnosed LN.

**Discussion:** This is a unique case of late-onset LN occurring 31 years after SLE diagnosis. The patient's chronic SLE symptoms of malar rash, fatigue and joint pain were managed with prednisone and hydroxychloroquine up until this presentation of acute systolic heart failure. There are few reported cases in literature of LN occurring 30 years after SLE diagnosis. With the increasing lifespan due to effective treatment options for SLE, late-onset LN may become more prevalent. As such, we recommend that physicians closely monitor signs and symptoms of LN even in patients without initial renal involvement.

**PUB278**

**Hydralazine-Induced Vasculitis: A Case Report**

Jacob Scribner, Kumail Ali, Oladapo A. Oafabi, Ishua Puri, Texas Health Resources Foundation, Fort Worth, TX.

**Introduction:** Hydralazine-induced ANCA-Associated Vasculitis (AAV) is a rare condition in which there is an autoimmune mediated reaction leading to renal and pulmonary involvement and complications.

**Case Description:** A 38-year-old female with a history of hypertension, hyperepidridermia, DVTs, and multiple strokes who presented for anemia and elevated creatinine. Home medications consisted of Lipitor, Coreg, Xarelto, and Hydralazine. After admission, the patient developed fevers and orbital swelling. Hydralazine was stopped due to concerns of association with her periorbital edema. The patient was started on antibiotics for suspected orbital cellulitis. CT imaging showed a large pericardial effusion, as well as multiple pulmonary nodules. ECHO showed cardiac tamponade. The patient had an emergent pericardial window. Autoimmune workup for pericardial effusion was positive for ANCA (p-ANCA positive, MPO and PR3). The patient was worked up for ANCA vasculitis. Further testing revealed high levels of dsDNA and anti-histone antibodies. Renal biopsy was deferred in the setting of anticoagulation use. She was started on high dose steroids and discharged with improved renal indices.

**Discussion:** Hydralazine is a common anti-hypertensive medication. It is known to cause drug induced Lupus (DIL), but it is less commonly associated with ANCA-Associated Vasculitis (AAV). AAV has a predilection for renal and pulmonary vasculature. Infection is caused by autoantibodies against myeloperoxidase (MPO) and Proteinase 3 (PR3). Renal biopsy demonstrates protein casts in both lungs and lenticulitis. Hydralazine-induced AAV is dose and duration dependent. Risk factors include female gender, kidney disease, and old age. Complications of AAV include rapidly progressive glomerulonephritis, as well as a systemic vasculitis and systemic syndrome. The incidence of Hydralazine-induced AAV is about 10-20 cases per million. Treatment consists of drug cessation and immuno modulator therapy. It can be challenging to differentiate between DIL and Hydralazine-induced AAV. Anti-histone antibody positivity and hypocomplementemia are not independent between the two. DIL lacks antibodies to dsDNA, and ANCA levels are usually negative in DIL. ANCA positivity is diagnostic of AAV. Hydralazine-induced AAV can be challenging to recognize and diagnose. Immediate cessation of Hydralazine and prompt initiation of immune modulators mainstay treatment.

**PUB279**

**Kicking a Glomerulus When It’s Already Down**

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**Introduction:** Hydralazine-associated ANCA vasculitis (HA-ANCA) can be a devastating complication, with a pathogenesis that is not well understood. Here, we present a patient with biopsy-proven membranous glomerulopathy and IgA nephropathy who developed HA-ANCA.

**Case Description:** A 74-year-old man with CKD IV from biopsy proven membranous glomerulopathy (negative PL2R and THSD7A) and mild concurrent IgA nephropathy was transferred to our institution with acute kidney injury and acute hypoxemic respiratory failure. The prior biopsy also demonstrated severe interstitial fibrosis and tubular atrophy. CT chest revealed extensive bilateral ground glass opacities with diaphragmatic elevation. Hydralazine-induced AA V caused diffuse pulmonary hemorrhage with bloody aliquots. Hydralazine for hypertension was discontinued. Pulse dose steroid treatment was initiated along with apheresis. Initial work-up returned as follows: ANA titer 1:160, Sjogrens/Sicca titer 990, normal complements, infectious workup negative, Anti-ds-DNA, SSA-, and SS-B antibodies were negative. Patient received IV Cytoscan once and was begun on Rituximab therapy with improvement in respiratory symptoms. Kidney function worsened requiring dialysis briefly with improvement to baseline kidney function.

**Discussion:** HA-ANCA can be a long-term complication of hydralazine treatment and can be quite serious. In this case, the patient was treated by discontinuing the medication. Due to the severity of this patient presentation, apheresis, pulse dose steroids, Cytoscan, and Rituximab therapy were utilized. Of the known risk factors, the patient died has a history of hypothyroidism. Hydralazine also was dosed in a range consistent with most cases on literature review that would put him at risk for developing hydralazine induced MPO ANCA. The patient did not undergo further kidney biopsy due to the degree of advanced kidney disease seen on imaging and previous biopsy. The patient responded well to treatment and was discharged after several weeks to rehab with close follow up.

The patient did quite well for many months. Subsequent medical complications after a cardiovascular procedure have led to progression of his renal disease and transition to ESRD on hemodialysis. We conclude that, given numerous anti-hypertensive alternatives, hydralazine should be avoided if at all possible, and if not, the duration of treatment should not be prolonged.

**PUB280**

**A Rare Case of Anti-PL2R-Negative Membranous Nephropathy and ANCA-Negative Crescentic Glomerulonephritis**

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**Introduction:** It is reported that the sensitivity of PL2R staining is 75% and specificity is 83%, for the detection of primary membranous nephropathy (MN); therefore, negative anti-PL2R does not exclude primary MN. Also, it has been reported
that 10-30% of patients with pauci-immune crescentic glomerulonephritis (GN) are ANCA-negative. Here we have a case of combined PLA2R negative MN and ANCA negative pauci immune crescentic GN.

Case Description: A 59 year old man with a medical history of hypertension, chronic kidney disease stage 3A, and history of treated syphilis presents with shortness of breath, abdomen fullness, and acquired pneumonia. Patient also diagnosed with an acute kidney injury. Labs showed severe creatinine at 3.56, urinalysis with proteinuria (1g) and 2-5 RBC. Immunological studies showed positive SM/RNP antibody (ab) but negative Smith ab, ds-DNA ab, ANCA panel, anti-PLA2R ab, glomerular basement membrane (GBM) and normal c3/c4. Infectious work-up showed positive RPR, negative quantitative, negative hepatitis B surface ab and negative hepatitis C ab. Renal biopsy showed PLA2R antibody negative MN, pauci immune crescentic GN, and acute tubular injury.

Discussion: Our present with findings that suggest an overlap of primary membranous nephropathy and pauci-immune crescentic GN. By renal biopsy, characteristic findings of primary MN such as fine spikes and holes along the GBM are present but PLA2R staining is negative. As well, three glomeruli show cellular crescents and additional fibrocellular and fibrous crescents were identified, and these findings are unusual in primary MN. A secondary MN is also unlikely in view of no endocapillary hypercellularity. Given lack of linear GBM staining and no autoimmune symptoms, the crescentic lesions can be suggestive of a pauci-immune mediated process, however, the patient had negative ANCA serologies checked twice. A recent study showed ANCA-negative pauci-immune crescent glomerulonephritis can be primary or secondary, especially if associated with infection or malignancy that requires prompt identification and specific treatments. It is important to realize that association of vasculitic GN with MN is estimated to be <5% of all membranous GN cases, thus this case can be used as future reference for clinical practice.

PUB281
The utility of Kidney Biopsy in PLA2R-Positive Membranous Nephropathy
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Introduction: Primary membranous nephropathy (MN) is one of the major causes of nephrotic syndrome. In the last decade, studies have shown that anti-phosphoprotein A2 receptor (PLA2R) antibodies are positive in 70% to 80% of patients with a high specificity for MN. Traditionally, the diagnosis was made through kidney biopsy; however, testing for serum PLA2R antibodies has introduced the possibility of diagnosing patients non-invasively. We describe a case of MN that was complicated by a rapid decline in kidney function and discuss the value in obtaining a kidney biopsy even in the setting of a high serum PLA2R titer. 

Case Description: A 67-year-old woman with a history of Type 2 DM and HTN presented due to a 20-pound weight gain and worsening dyspnea; exam was notable for 2+ bilateral lower extremity edema. Objective data showed a serum creatinine of 1.46 mg/dL (~1.0 mg/dL 3 months prior), 24-hour urine protein of 16.7 g/day, and a serum albumin of 2.0 g/dL. Immunologic testing showed an anti-PLA2R titer of 455 RU/mL, positive ANA in > 1:1280 titer, anti-dsDNA < 1 IU/mL, and normal complements levels. She was diuresed for her nephrotic syndrome and continued maximally tolerated Losartan. She was treated using a low dose Prednisone, Cyclophosphamide, and Rituximab regimen. However, her kidney function declined further prompting kidney biopsy 2 weeks after presentation. Serum creatinine at time of biopsy was 2.53 mg/dL. Her biopsy showed MN, diffuse and focal nodular diabetic glomerulosclerosis, moderate (20-30%) interstitial fibrosis and tubular atrophy, and severe arteriosclerosis. Her MN alone did not account for the significant decrease in glomerular filtration rate (GFR) and continued due to increased intraglomerular pressure with hyperperfusion in the setting of renin-angiotensin-aldosterone system blockade with underlying severe arteriosclerosis. Her course was complicated by severe cytopenias resulting in cessation of immunosuppression and she ultimately required dialysis.

Discussion: Although there are many cases of PLA2R positive MN where biopsy can be deferred, it was vital in revealing a secondary diagnosis of severe arteriosclerosis explaining her GFR decline and guiding decision making in our case. Even in the setting of high anti-PLA2R antibody titers, biopsy should be strongly considered for patients with declining kidney function to elucidate whether the decline is secondary to underlying MN or another etiology.

PUB282
Crescentic Glomerulonephritis in Immunoglobulin A-Associated Vasculitis Without Purpura in an Adult Patient
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Introduction: Immunoglobulin A (IgA) vasculitis, formerly called Henoch-Schönlein purpura, is a systemic, immune complex-mediated vasculitis affecting small vessels with dominant IgA deposits. Although rare in adults, it tends to be more severe in children and is defined by a tetrad of features: palpable purpura (leukocytoclastic vasculitis), arthralgia and/or arthritis, abdominal pain and kidney disease. Specific therapies are still controversial and their efficacy poorly known.

Case Description: A 35-year-old healthy male patient with a history of an isolated episode of purpura in childhood pending investigation was admitted at our service a few days after a low-intensity trauma, followed by unilateral visual loss. Brain MRI showed acute ischemia in the right internal carotid artery, not entirely compatible with the mechanism. On admission, acute kidney injury was diagnosed with mesangial hypercellularity, focal crescents and podocyte hyperthrophy/hyalplasia. Abdomen AngioCT showed parietal calcifications at inferenal abdominal aorta and coronary arteries, suggesting the diagnosis of systemic vasculitis. Methylprednisolone and cyclophosphamide were initiated.

Discussion: Purpura has been postulated as a mandatory clinical criterion for IgA vasculitis diagnosis. In this case report, the patient presents with systemic, radiological and anatomopathologic renal signs compatible with IgA vasculitis, lacking the typical purpura.

PUB283
Can Serum and Histologic Biomarkers Predict Kidney and Overall Survival in ANCA-Associated Vasculitides?
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Background: ANCA vasculitides (AVV) still have poor renal and overall survival. The role of histopathologic factors is yet to be defined. Herein, we explored serum and pathological biomarkers as predictors of kidney and patient survival.

Methods: Retrospective analysis of AVV glomerulonephritis diagnosed between 2006-2023 was performed. Most significant markers as ANCA titer, C3 and CRP at admission (d), remission, relapse, and last follow-up (f) were associated to GFR, dialysis need, ESKD and mortality. Brix classes (BC), Brix renal risk score (BRS), IFTA and crescentic glomeruli percentages, C3-IF and interstitial hemorrhage (IH) were also associated with outcomes.

Results: A total of 62 patients 69±10 years old, 56.5% male and 82.3% MPO were included. In 46 biopsies 17.4% were sclerotic, 28.3% mixed, 39.1% crescentic, 15.2% focal; 2.2% with low, 28.3% medium and 58.7% high ESKD risk. dANCA didn’t relate to dialysis requirement and titers didn’t relate to GFR at any time point. IC3 predicted ESKD (p=0.028) and shorter time to dialysis (p=0.006), not confirmed by multivariate analysis (MA). Likewise, dCRP related to dialysis need (p=0.035) only in univariate analysis. Anica titers didn’t predict survival. dANCA did not relate to death. Lower DC3 (p=0.023) and higher IC3 (p=0.012) were markers of mortality. MA with age and gender lost DC3 significance for death. IC3 predicted ESKD. IFTA, BC and ESKD’s didn’t predict mortality.

Conclusions: In our cohort, serum biomarkers value remains uncertain. Higher ANCA at last follow-up related to ESKD and histologic chronocity. Nonetheless, it didn’t predict survival. Less CRP related to death might translate to non-specific bias, although not analyzed. Initial C3 might be prognostic, in line with C3 deposition in other studies, but C3 deposition didn’t predict ESKD. IH might be relevant in future broader studies. Further and larger studies might bring stronger data and we still need better predictive markers.

PUB284
Associations of tSNF1, tTNFR-2, and YK-40 with Histopathologic Lesions in Individuals with Glomerular Disease
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Background: Soluble necrosis factor-1 (tSNF1-1), tTNFR-2, and YK-40 may provide non-invasive assessments of histopathology, but there is limited data on their associations with histopathologic lesions in individuals with glomerulopathies.

Methods: We measured each plasma biomarker in 188 plasma samples from individuals with glomerulopathies, enrolled into the Boston Kidney Biopsy Cohort (BKBC), a cohort of individuals with semi-quantitative assessment of histopathologic lesions from clinically indicated native kidney biopsies. Multivariable linear regression models tested associations between biomarkers and histopathologic lesions in subgroups of individuals with glomerulopathies, including IgA nephropathy, systemic lupus erythematosus with lupus nephritis (SLE), membranous nephropathy (MN), and secondary focal segmental glomerulosclerosis (see FSGS).

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only Underline represents presenting author. 1127
Results: The mean baseline eGFR was 70±35 ml/min/1.73m² and median proteinuria [IQR] was 1.8 [0.7, 3.7] g/g creatinine. Twenty-eight % of individuals with glomerulopathies had IgA nephropathy, 36% had SLE with lupus nephritis, 20% had MN, and 16% had SLE with lupus nephritis, 20% had MN, and 16% had FGSKS. After multivariable adjustment for age, race, sex, and eGFR, higher plasma sTNFR-1 levels were associated with more severe mesangial expansion (beta=1.58, p=0.027) in individuals with IgA nephropathy. In individuals with SLE, higher sTNFR-2 levels were associated with the presence of inflammation in the non-fibrosed interstitium (beta=0.90, p=0.034). Higher levels of plasma YKL-40 associated with more severe arteriolar sclerosis (beta=0.87, p=0.026) in individuals with MN. There were no significant associations between biomarkers and histopathologic lesions in individuals with SFGSKS (Figure 1).

Conclusions: Plasma sTNFR-1, sTNFR-2, and YKL-40 may aid with the non-invasive assessment of histopathologic patterns of injury in individuals with IgA nephropathy, SLE with lupus nephritis, and MN.

Funding: NIDDK Support

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**PUB285**

Prevalence and Trend of Biopsy-Proven IgA Nephropathy in China: A Systematic Review

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**Background:** IgA nephropathy (IgAN) is one of the most common primary glomerulonephritis worldwide, and its distribution varies significantly in different regions. The prevalence and trend in different regions of China remains unclear. Therefore, this study aims to analyze renal biopsy data from different regions in China to figure out the prevalence and trend of IgAN.

**Methods:** Through systematic electronic search of the PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (SinoMed), Cochrane Library and Wanfang databases from inception to March 1, 2023. The search keywords included: “renal biopsy”, “renal pathological diagnosis” and the names of the different provinces, municipalities and autonomous regions. After completed the electronic database search, we performed a manual search of professional medical journals and thesis.

**Results:** After collecting and analyzing literatures, we sorted out renal biopsy data of 143176 patients with primary glomerulonephritis from 34 provinces of China, of which 39.73% were IgAN (in total of 56886 cases). The proportions of male and female patients were 58.67% and 41.33%, respectively. The proportion of IgAN patients was higher in economically developed provinces and municipalities. The weighted average prevalence before 2010 and after 2010 was 40.45% and 37.74%, respectively.

**Conclusions:** IgAN remains the most common biopsy-proven primary glomerulonephritis in China. The prevalence of IgAN was 39.73% in China and was higher in developed provinces and municipalities than in other areas. The weighted average prevalence of IgAN in China decreased slightly after 2010 than before 2010.

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**PUB286**

Low Levels of Hemoglobin Are Associated with Critical Illness and Predict Disease Course in Patients with ANCA-Associated Renal Vasculitis

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**Background:** Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a small vessel vasculitis (SVV) often leading to critical illness by multi organ failure. Data for patients with specifically ANCA associated renal vasculitis requiring intensive care unit (ICU) supportive care are limited and have mainly focused on long term renal and overall outcome. Particularly, data on critical illness during the initial course of disease are scarce and remain poorly determined. Therefore, the purpose of this retrospective study was to identify predictors of critical illness in a cohort of patients with ANCA associated renal vasculitis.

**Methods:** We retrospectively included a total number of 53 cases with biopsy-proven ANCA associated renal vasculitis between 2015 till 2020 in a single center cohort study. Clinical data assessment enclosed age, sex, date of admission, discharge, and ward transfer during hospitalization, parameters relevant for ICU treatment, such as initial heart rate, mean arterial pressure, body temperature, urine output, serum creatinine, eGFR, sodium, potassium, white blood cells, platelets, pH, and hemoglobin levels at admission.

A nonICU (n=29) and an ICU group (n=24) was formed. Between group comparisons, correlative analyses by means of multiple logistic regression and survival curve analyses were conducted.

**Results:** We here identified an association between low hemoglobin levels and requirement of ICU supportive care in patients with ANCA associated renal vasculitis.

**Conclusions:** We here expand our current knowledge that low levels of hemoglobin negatively affect short term outcome in ANCA associated renal vasculitis, further improving our current understanding for the role of anemia in autoimmune kidney diseases.

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**PUB287**

Unexpected Biopsy Finding in a Hispanic Man


**Introduction:** Fibillary glomerulonephritis (FGN) is a rare primary glomerular disease with a very poor prognosis. Defined by the ultrastructural finding of haphazardly arranged, straight fibrils measuring 10 to 30 nm in thickness, deposited in the mesangium, glomerular basement membranes or both. On immunofluorescence, deposits typically stain for polyclonal IgG and complement. These changes are found in 0.5 to 1% of native kidney biopsies. FGN is more often seen in Caucasians compared to Hispanics, with a ratio of 100:1. We present a case of an Hispanic man with chronic proteinuria and progressive kidney disease with unforeseen biopsy findings.

**Case Description:** A 72 y/o Hispanic man was seen for the first time at nephrology clinics due to a progressive decrease in eGFR and nephrotic range proteinuria. Already a CKD IV, normal A1c and work up for causes of proteinuria (including C3, C4, UPEP, SREP, HIV, HEP B-C) was non contributory. Age appropriate cancer screening was negative. ANA was positive at 1:320 with diffuse speckled pattern. Anti-PLA2R was also found normal. The patient eGFR and proteinuria remained stable, without nephrotic syndrome for 3 years. He presented to the ER due to elevated blood pressure and found with increase in creatinine to 3.5mg/dl from 2.7mg/dl. Proteinuria quantified at 5.2g/day and noted with glucosuria without hyperglycemia. ANA positive at 1:80 with speckled pattern, and DS-DNA negative. Biopsy showed changes suggestive of membranous glomerulopathy based on LM and IF as well as tubules with calcium oxalate casts. EM later reported fibrilary deposits consistent with fibrillary glomerulopathy. Kidney function improved and blood pressure controlled, and he was discharged home for continued follow-up at clinics.

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Discussion: FGN typically presents with proteinuria (usually nephrotic), hematuria, kidney insufficiency, and hypertension. It is typically associated to malignancies, autoimmune disorders, and dysproteinemias with only 7% being associated to membranous nephropathy. It is extremely rare in Hispanics. Renal prognosis is dire with average time to dialysis being 87 months. Although there is no available treatment, clinicians should be aware of this possibility of a diagnosis as planning and educating patient about the poor prognosis such diagnosis entails can lead to better outcomes with early preparedness.

PUB288

A Case of Dialysis-Dependent Rapidly Progressing C3 Glomerulonephritis
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Introduction: A 41-year-old woman with history of intravenous drug use presented with acute onset of gross anasarca and frothy urine. She was found to have serum creatinine of 1.6 mg/dL, serum albumin of 2.0 mg/dL, and nephrotic range proteinuria of 25 g/L. Urine sediment was bland without casts or cells. A renal biopsy revealed an immune-complex mediated glomerulopathy with a membranous pattern of injury and “full house” immunoreactivity. Rheumatological workup for lupus was negative, with negative ANA, dsDNA, normal C3, and low C4. Anti-PLA2R was also negative. Of note, she had recently tested positive for chlamydia, gonorrhea, syphilis, and received appropriate antibiotic therapy. She did not follow up in clinic until 6 weeks later to discuss immunosuppression, which was not given as she was noted to have complete resolution of proteinuria, and her creatinine and serum albumin returned to baseline.

Discussion: Etiologies of SNN are diverse and differentials are broad, especially when clinical, morphological and immunostaining do not fit classic presentations. Possible renal manifestations of syphilis include membranous, glomerular, and non-glomerular conditions, with membranous nephropathy being the most common. Although the exact pathophysiology is unknown, renal biopsies have shown presence of immune complexes containing anti- treponemal antibodies. Immunofluorescence stains for IgG, C3, IgA, IgM and C1q, also known as “full-house” pattern. As in our patient, renal response to appropriate treatment of syphilis was dramatic, and possibility of syphilis should be considered in new diagnoses of MN with full-house immunoreactivity to avoid unnecessary immunosuppression.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
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1129
Elevated Inflammatory Biomarkers Are Risk Factors for Composite Outcome in South Asian IgA Nephropathy (IgAN)
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Background: The role of placebo controlled immunosuppression (IS) trial in high-risk South Asian IgAN is still controversial. The effect of IS on longitudinal biomarkers can be surrogate end-points for assessing its impact on CO.

Methods: Serum APRIL levels were measured in baseline and longitudinal sera (1year, 2year) by ELISA. Serum Gd-IgA1 levels were measured in baseline and longitudinal sera (1year, 2year) using KM55 ELISA. Serum levels of TNF-R1, CD27 & BCMA were quantified with a Luminex multiplex assay. CO was defined as ≥50% fall in eGFR (CKD EPI) from baseline and/or eGFR (CKD EPI) <15ml/min/1.73m² or RRT/death. Partial remission (PR) in proteinuria was defined as decrease of 24-hour urine protein by 50% from baseline and <3g/day if nephrotic at baseline or proteinuria <1.5g/day if non-nephrotic at baseline for at least three months.

Results: Out of 201 IgAN patients, 37% of patients reached composite outcome (CO) in 3 years in the GRACE-IgANI cohort. Treatment group II (high-risk group with IS) had 146 patients. The mean time to PR in proteinuria was significantly longer in the CO group (10 vs. 6months, p=0.005). Achieving less than <1g/day at 6month significantly increased renal survival (36 vs. 22months, p<0.001). There was significant longitudinal decrease in serum Gd-IgA1 levels at 6month paralleled the increase in serum APRIL levels from baseline to 2year in patients with favourable renal outcome. The longitudinal decrease in serum Gd-IgA1 levels at 6month paralleled the serum APRIL levels. There was a significant association between baseline inflammatory markers (TNF-R1, CD27 & BCMA) and CO at 3 years whereas baseline elevated hsCRP levels showed a global decrease over time.

Conclusions: Placebo-controlled trial in this high-risk population entails ethical considerations hence assessing the known impact of IS on surrogate end-points can potentially guide rational therapy.

Funding: Government Support - Non-U.S.

Outcomes of Inflammatory Bowel Disease-Related IgA Nephropathy
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Background: Case reports have linked IgA nephropathy (IgAN) and inflammatory bowel disease (IBD) but data remains sparse. We describe a patient cohort with IBD associated IgAN from the nationwide VA database.

Methods: We retrospectively studied patients with IBD who had kidney biopsy confirmed IgAN. We also conducted a systematic search of electronic databases through 2022 using the terms “IBD” and “IgAN” to synthesize the existing literature on this topic.

Results: 25 subjects were included: all men with age 64.2 ± 13 years (mean ± SD), eGFR 41 ± 28 mL/min and UPCR 3.1 ± 3.2 g/ g. 74% received RAAS blockade and 55% required immunosuppression. 28% developed ESKD and 48% died during a follow-up period of 56 ± 49 months (Table 1). The literature search yielded only 3 series of patients with IBD-IgAN (Table 2), prohibiting any pooled analysis.

Conclusions: Our study adds to the limited data regarding IBD-IgAN and highlights the poor outcomes associated with this disease. Large, prospective, multicenter studies are needed to better characterize this association.

Table 1. Patient characteristics. Categorical data presented as % and continuous as mean±SD (range).

Table 2. Comparison of IBD-IgAN patient series. *Reviewed by Joher et al. 2022

Outcomes of IBD-IgAN: a Systematic Review
Lauren Floyd, 1 Joshua Storrar, 2 Sanjeev Pramanik, 1 Adam Morris, 1 Smeeta Sinha, 1 Philip A. Kalra, 2 Ajay P. Dhaygude, 1 Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; 2Northern Care Alliance NHS Foundation Trust Salford Care Organisation, Salford, United Kingdom.

Background: ANCA associated vasculitis (AA V) is a rare autoimmune condition predominantly seen in white Caucasian populations. There are variations in AAV worldwide and little is known about outcomes in ethnic minority patients in particular Indo-Asian populations.

Methods: A multcentre, retrospective cohort study of patients with AAV and who self-identified as belonging to the following ethnic groups; Indian, British Indian, Pakistani, British Pakistani, Asian or Asian British’ was carried out. The study included patients from 2 regional centres in the North West, UK, between 2009 and 2023. A 2:1
ratio of consecutive white patients was included as a control cohort for comparison with Indo-Asian patients. Data collection included demographics, renal histology and clinical outcomes.

Results: The demographics of each cohort are presented in Fig. 1. GPA was observed in 54% and MPA in 40%. There were significantly more diabetics (P=0.002) and history of smoking (P=0.019) in the Indo-Asian group. There was similar distribution of organ involvement and baseline laboratory results including eGFR. Berden’s classification was similar although there were higher rates of crescentic class in the Indo-Asian group (36% v 13%) and a greater number in the medium and high-risk groups of the RRS (71% v 5%). The higher median rate of RRT at presentation, relapse, eGFR and mortality were observed.

Conclusions: Our findings suggest Indo-Asian patients tend to be younger and have a higher prevalence of diabetes, previous TB exposure and abnormal glomeruli on biopsy. Further research is required to comprehend the genetic contribution to AAV’s pathogenesis and clinical phenotype, as well as establishing if disparities among ethnic minorities arise from genetic and / or environmental factors, so as to enhance patient outcomes.

PUB296
Cohort of Mexican Patients Diagnosed with IgA: Mortality and Clinical Outcomes

Background: IgA glomerulonephritis is the most frequent type among primary glomerulonephritis (GN), with highly uneven incidence due to population differences, biopsy indications, and variable outcomes. Mortality and the need for kidney replacement therapy (KRT) were determined in a cohort of renal biopsies conducted on Mexican population.

Methods: Retrospective cohort study on patients with a histological diagnosis of primary IgA nephropathy, from June 2017 to May 2022. The primary objective was mortality and the requirement for renal support therapy.

Results: 692 patients were followed up for 5 years, of which IgA glomerulonephritis accounted for 18% (133 cases), with 33% being female and 66% male. The average age of presentation was 17±1, and the average glomerular filtration rate (GFR) was 77 ml/min/m², 30% progressed to chronic kidney disease, none required renal support therapy, and there was a mortality rate of 6% (2 cases). Conclusions: IgA nephropathy remains one of the primary and most relevant glomerulonephritis in young patients, with a progression to end-stage renal disease within a short period. Therefore, timely diagnosis is of utmost importance for identification and treatment.

Conclusions: IgA nephropathy remains one of the primary and most relevant glomerulonephritis in young patients, with a progression to end-stage renal disease within a short period. Therefore, timely diagnosis is of utmost importance for identification and treatment.

PUB297
Exostosin 1- and 2-Associated Lupus-Like Membranous Nephropathy in Men
Kana R. Amari, Shikha Wadhwani, Yunatan A. Peleg, Northwestern University Feinberg School of Medicine, Chicago, IL.

Introduction: The detection of Exostosin (EXT) 1 and 2 through immunofluorescence (IF) has predominantly been linked to secondary forms of membranous nephropathy, often observed in autoimmune disorders. This report presents two cases of Caucasian males with no known autoimmune conditions who exhibited de novo lupus-like membranous nephropathy with Exostosin positivity.

Case Description: A 61-year-old man presented with subacute onset nephrotic syndrome a few weeks after a COVID-19 infection. His laboratory showed a creatinine (Cr) of 3.3 mg/dL (baseline 1.4 mg/dL), peak proteinuria 34 g/g, albuminuria 2.3 g/dL. Serum workup with strongly positive RF, low C4, ANA >1:1280, negative cryo, cryoglobulins, hepatitis B and C, and phospholipase A2 receptor antibodies (aPLA2R). His kidney biopsy showed subepithelial immune deposits, no tubuloreticular inclusions (TRI), and no cryoglobulinemic deposits on electron microscopy (EM), and full-house pattern by IF with EXT 1 positivity. He was treated with mycophenolate, tacrolimus, and steroid taper. One year later, he achieved remission: Cr 1.6 mg/dL, albumin 4 g/dL, 24h aPCR 0.4 g/gCr. A 57-year-old man with a history of mantle cell NHL in remission and chronic VTE, presented for evaluation of nephrotic syndrome. He had a stable Cr of 1.1 mg/dL, proteinuria 12.5 g/24h, microscopic hematuria, albuminuria 2.4 g/dL. Serologic workup with ANA >1:1280, dsDNA 1:40, +RNP, +Sm Ab; and unremarkable aPLA2R, C3/C4, hepatitis B and C, syphilis, HIV, and parvovirus. Kidney biopsy showed subepithelial and subendothelial deposits and TRI on EM, with full-house pattern and EXT 2 positivity on IF. The patient was treated with tacrolimus and mycophenolate. At 2 months, his Cr is stable, proteinuria is persistent, but albumin improved to 3 mg/dL.

Discussion: Exostosin-associated membranous nephropathy (EMN) is a favorable kidney prognosis subgroup primarily found in young women with autoimmune conditions. Our report observed two males with lupus-like membranous nephropathy (MN) but no systemic lupus symptoms who met the SLICC criteria for standalone renal involvement. Triangulation for EMN are unclear in an atypical age and gender presentation, but a high interferon state from prior chemotherapy or a recent COVID-19 infection may play a role. Further research is needed to understand mechanisms. Initial multimodal therapy shows promise in treatment.

PUB298
Unmasking Lupus: The Great Masquerader
Roopali Dahiya, A.B.V.I.M.S and Dr RML Hospital, Delhi, India.

Introduction: Pyrexia of unknown origin (PUO) has always been a challenging condition that an internist comes across. Infections, inflammatory diseases and neoplasia are among the common etiologies of it. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can virtually affect any organ and is a significant cause of morbidity and mortality. Here we present a case of SLE as the cause of PUO due to its rare occurrence in a young male and presentation as an infective endocarditis mimic.

Case Description: An 18 year old Asian male presented with fever and hematuria for 2 months. Examination revealed bilateral infraorbital pleural rub, a panesystic
murmur in left parasternal area and tender hepato-splenomegaly. Initial lab reports showed anemia (Hb 6.9 g/dL), neutrophilic leukocytosis with schistocytes, urea 127 mg/dL, creatinine 3.1 mg/dL, deranged liver enzymes, hypoalbuminemia with hematuria 3+ and proteinuria 4+. IRCT chest showed multiple cavitary nodules in bilateral peripheral lung fields with mild pleural and pericardial effusion. Blood and urine cultures were sterile, but inflammatory markers were persistently raised. Echocardiography was performed, which revealed vegetations along the tricuspid valve. Transesophageal echocardiography confirmed 1x1cm vegetation above the leaflet of tricuspid valve. A working diagnosis of infective endocarditis was kept, and treatment with ceftriaxone and vancomycin was started. As the patient was not improving, the possibility of autoimmune aetiology (although rare in males), was kept among differentials. An autoimmune workup showed ANA and anti-ds DNA antibodies positivity, low C3 and C4 and negative ANCA and APLA profiles. A renal biopsy confirmed class 3 focal lupus nephritis with acute tubular necrosis. Based on 2019 ACR/EULAR SLICC criteria, a diagnosis of SLE with class 3 lupus nephritis with isolated culture-negative tricuspid valve Libman-Sacks endocarditis was made. There was drastic improvement in patient’s symptoms and kidney and liver functions post-methylprednisone and cyclophosphamide pulse.

Our case is special since it highlights the diagnostic dilemma between infective endocarditis and SLE in a young male. Both diseases have totally different treatment algorithms and prognosis. Hence, SLE should be considered in the differentials of PUO for timely therapeutic intervention to control the progression of the disease.

PUB299
A Brief Clinical Course of Fibrillary Glomerulonephritis
Jason W. Regehr, 1 Alex D. Tarabochia, 1,2 Tracy L. Ingersoll, 1 Thomas M. Kaneko, 1,2 Jason R. Petrus, 1,2 Charles W. Hopley, 1,12 Clay A. Block, 1,2 Dartmouth College Geisel School of Medicine, Hanover, NH; 2 Dartmouth Health, Lebanon, NH.

Introduction: Fibrillary Glomerulonephritis (FGN) can be primary or secondary as in cases, associated with malignancies. The presence of DNA199, a heat shock protein, in the glomeruli is > 98% sensitive and specific for FGN.

Case Description: 62-year-old man with history of long standing hypertension, CKD 3A, with baseline creatinine of 1.6 mg/dL, presented to emergency room with shortness of breath and edema in October 2020. He was on ibuprofen 600 mg three times daily for pain 3 months prior to that, and his creatinine was found to be 4.6 mg/dL. He had normal sodium, potassium, calcium and bicarbonate with low serum albumin of 2.2 mg/dL (3.5- 5). He was diuresed and his creatinine trended down to 2.6 mg/dL. He saw a normal sodium, potassium, calcium and bicarbonate with low serum albumin of 2.2 mg/dL (3.5- 5).

Case Discussion: Fibrillary glomerulonephritis should be considered in the differential diagnoses of proteinuria in the elderly. The presence of DNA 199 and HSP 99 on immunofluorescence highlights the fibrillary nature of the lesion. Biopsy is indicated in patients with refractory proteinuria or hematuria to allow for accurate diagnosis and appropriate management.
France, Germany, Italy, Spain, UK (EUS), China and Japan between August 2022 and April 2023. Nephrologists completed forms for consecutive patients presenting with C3G. The forms included demographic and clinical information including signs, symptoms and lab values.

Results: 111 nephrologists completed records for 385 C3G patients (US 100, EUS 189, China 60, Japan 36). Median patient age at Dx was 38.0 years, and 59% were male. Median eGFR at Dx was 49.0 ml/min/1.73m². Median proteinuria at Dx was 3.4 g/day and was ≥ 1 g/day in 85% of patients. The most common signs and symptoms were hematuria, edema, hypertension and fatigue. Discolored urine, pain and appetite loss were also reported (Table 1). Physicians perceived disease severity at Dx as moderate in 50% and as severe in 34% of patients.

Conclusions: C3G patients experience symptomatic and clinical burden at Dx. This symptom burden, high proteinuria, and relatively low eGFR are consistent with physician assessment of moderate or severe disease at Dx. Effective Dx and treatment is an important goal to improve patient symptoms and disease.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Table 1: Patient signs and symptoms at diagnosis by geographic region

### PUB304

A Unique Presentation of Lupus Podocytopathy with Collapsing FSGS Variant

Klodia Hermecz, Amulya Rajagopal, Sandeep S. Soman, Kausik Umanath.

**Henry Ford Hospital, Detroit, MI.**

**Introduction:** Lupus podocytopathy is a rare subset of lupus nephritis seen with nephrotic range proteinuria that presents with findings on kidney biopsy mimicking that of minimal change disease or focal segmental glomerulosclerosis (FSGS). A rare subset of collapsing glomerulopathy can also be seen. This condition has also been linked to the pathologic APOL-1 gene variant. We report a rare case of lupus podocytopathy with collapsing FSGS.

**Case Description:** A 42-year-old African American male with a history of hypertension and systemic lupus erythematosus/mycophenolate mofetil (MMF) ≥ 5 g twice daily for non-renal manifestations presented after outpatient labs showed dramatically increased serum creatinine and BUN. His only reported symptoms were shortness of breath and fatigue. In the ED, blood pressure was 148/84 mmHg. Labs showed serum creatinine of 10.23 mg/dL (baseline of 2.0 mg/dL), BUN of 111, bicarbonate of 9 mmol/L, and hemoglobin of 7.4 g/dL. The urine albumin to creatinine ratio was 1,463.5 mg/g with a urine protein to creatinine ratio of 2.9 g/l/g. COVID-19, flu A/B, hepatitis panel, EBV, CMV, HIV, blood cultures, and parvovirus were all negative. Kidney biopsy demonstrated acute tubular injury, WHO class II lupus nephritis, and collapsing FSGS in the setting of lupus podocytopathy. APOL-1 gene testing is pending. He was initiated on pulse dose steroids for 3 days, and hemodialysis was initiated due to worsening ascites. He was continued on his home dose of MMF. He currently remains hemodialysis dependent (declared ESRD).

**Discussion:** Patients with SLE podocytopathy represent less than one percent of all SLE flares, with collapsing FSGS variant even more rare and associated with poor prognosis. In recent years the literature started defining non-HIV-related collapsing glomerulopathy, but no unified data regarding treatment guidelines exist. This patient was treated with a combination of steroids and MMF without success, highlighting a unique presentation of a rarely seen syndrome in lupus nephritis.

### PUB305

Delaying Progression of Kidney Diseases in Patient with FSGS with Dietary Interventions

Haley D. Justus,1 Muhammad Sohail,2 Strive Health, 1Strive Health, Hendersonville, NC; 2Strive Health, Princeton Junction, NJ.

**Introduction:** Plant-based diets along with lowering dietary protein intake can lower production of uremic toxins and may provide protection in advancing chronic kidney disease. Nutrition education should be provided via Registered Dietitian to optimize potassium, sodium, and phosphorus intake in patients following plant-based diets in later stages of chronic kidney disease.

**Case Description:** 50-year-old male with history of chronic kidney disease stage V, hypertension, and cardiomyopathy. The etiology of his chronic kidney disease (CKD) is biopsy proven FSGS with IgA glomerulopathy. The patient was diagnosed with CKD in 2019 and had an AV fistula placed in 2022 in preparation for a dialysis start and is actively listed for kidney transplantation. On initial RD visit, patient voiced he follows a whole food and plant-based approach and reads food labels to limit inorganic phosphorus. Interventions to reduce serum phosphorus and potassium included: Continuance of lower protein diet by limiting animal-based protein portions to 3 oz., starting tums as a phosphate binder per nephrologist and double boiling potatoes and sweet potatoes. The patient had maintained GFR <10 without start on dialysis as of April 2023. He reported no uremic symptoms and continued with good appetite. His proteinuria also improved from nephrotic range to non-nephrotic range with dietary interventions.

**Discussion:** High consumption of protein intake is associated with increased incidence and progression of kidney disease. Plant based diets have shown to slow down the progression of kidney disease by lowering intraglomerular pressure in patients with diabetes and hypertension however literature is lacking to support their use to delay progression in patients with glomerulopathies associated with proteinuria. Our patient has biopsy proven FSGS with IgA nephropathy with rapid decline in kidney function which was stabilized after adopting plant-based diet and limiting protein intake. Additionally, proteinuria improved from nephrotic range to non-nephrotic range without the use of any antiproteinuric medication. Typically, normal recommendation for protein intake is 0.8-1.0 kg body weight. CKD recommendations are 0.55-0.6 g/kg body weight non-dialysis, 0.4-0.6 g/kg body weight for diabetic patients. Side effects include elevated potassium and phosphorous levels, and early dietitian intervention can help mitigate these complications.

### PUB306

Intradialytic Amino Acids Improved Malnutrition Markers in ESRD with Complex Congenital Heart Disease on Peritoneal Dialysis

Desiree de Waal, Macaulay A. Omuigbo. University of Vermont Larner College of Medicine, Burlington, VT.

**Discussion:** Peritoneal dialysis (PD) is a cost-effective, home-based therapy for ESRD. The use of amino acid-based solutions resulted in better preservation of the ultra-structure of the peritoneal membrane when compared to glucose containing products. Malnutrition in the PD patient leads to poor outcomes. Intraperitoneal Nutrition (IPN), a nutrition intervention strategy designed specifically for the malnourished PD patient, is non-invasive, well tolerated, yet underutilized. A major obstacle is insurance...
Non-coverage. IPN with amino acid-based PD solutions induce anabolic response in malnourished PD patients and serve as source of proteins and calories. **Case Description:** A 51-year-old male patient with complex congenital heart disease including Tetralogy of Fallot with Eisenmenger physiology, on starting PD for ESRD, had significant malnutrition with a high Malnutrition Inflammation Score (MIS) (Table). He had early satiety. Oral nutrition supplements failed. Albumin was low for many years prior to starting PD. Using one daily exchange (1500 mL), IPN (1% amino acid solution with 1.43% dextrose providing 12 gm amino acids), significant improvements in his MIS and albumin levels followed (Figure). Quality of life including energy level, improved. **Discussion:** The management of any chronic disease must include ongoing nutritional assessment and the implementation of nutrition enhancing intervention therapies. Improving nutritional status improves outcomes. The use of IPN in a PD patient with complex congenital heart disease improved markers of inflammation and nutritional status.

**In conclusion,** IPN contributes to long-term improvement of the nutritional status in malnourished PD patients.

### Malnutrition Inflammation Score (Scores >8 = severe malnutrition)

<table>
<thead>
<tr>
<th>Month</th>
<th>MIS Score</th>
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<tbody>
<tr>
<td>May 2022</td>
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**Alimentation:**

**Serum Albumin Trajectory**

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**Presentation:**

**Serum Albumin Trajectory**

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**Discussion:**

The classical appearance of milky white urine is caused by a fistulous communication between the lymphatic system and the urinary tract resulting in chyle in the urine, known as chyluria. The etiology of chyluria can be divided into parasitic and non-parasitic causes including but not limited to malignancy, lymphatic malformation, and abscess. We present a case of a 67-year-old male who presented with chyluria and nephrotic range proteinuria.

**Case Description:** A 67-year-old male with history of longstanding diabetes mellitus came to the office for milky white urine and known proteinuria for the past one year associated with ~10lbs weight loss in the last six months. Previous workup included a spot urine protein-creatinine ratio (UPCR) of 7.3g and a urinalysis significant for glucosuria, hematuria, proteinuria but negative for leukocyte esterase. His lipid panel was within normal limits. Computerized tomography scan of the abdomen revealed non-obstructing bilateral renal calculi but was negative for mass effect or hydronephrosis. The patient had a thorough infectious disease workup which was unremarkable. Kidney biopsy revealed normal tubules and interstitium with mild arterial sclerosis. The immunofluorescence and electron microscopy were negative for immune complex and deposits. The patient was then evaluated by urology and a diagnostic lymphatic scintigraphy was negative for lymphatic-urinary fistula. Hence, cystoscopy was pursued which revealed chyluria from the left ureteral orifice. Patient had complete resolution of proteinuria and hematuria post-laparoscopic nephrolitotomy.

**Discussion:** Chyluria generally indicates the presence of abnormal communication between intestinal lymphatics and urinary tract. Patients with chyluria typically present with milky white urine and the urine chemistry usually shows heavy protein and moderate blood but remains negative for leukocyte esterase. Further evaluation of such a patient includes a thorough history, physical exam, extensive infectious lab work, and further radiologic testing. Urologic intervention with cystoscopy can be useful to lateralize the chyluria. Nephrolithiasis may be indicated for complete resolution of chyluria.

**Case Description:** A 51-year-old male patient with complex congenital heart disease including Tetralogy of Fallot with Eisenmenger physiology, on starting PD for ESRD, had significant malnutrition with a high Malnutrition Inflammation Score (MIS) (Table). He had early satiety. Oral nutrition supplements failed. Albumin was low for many years prior to starting PD. Using one daily exchange (1500 mL), IPN (1% amino acid solution with 1.43% dextrose providing 12 gm amino acids), significant improvements in his MIS and albumin levels followed (Figure). Quality of life including energy level, improved.

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A Classification of Lipids and Lipoproteins in Cardiovascular Diseases

Shruti Bhargava, 1 Sofia de la Puente Secades, 2 Vera Jankowskii, 1 Joachim Jankowski, 1, 2 *Universitätsklinikum Aachen, Aachen, Germany; 2Experimental Vascular Pathology, Cardiovascular Research Institute Maastricht (CARIM), University of Maastricht, Maastricht, Netherlands.

Background: With imbalances of lipids and lipoproteins being significant contributors to the development and advancement of cardiovascular disease (CVD), there is a growing recognition of the importance of categorizing them according to their mechanistic influence on CVD. This classification is crucial for the identification of novel approaches for predicting and treating CVD. Hence, there is a pressing requirement for a fresh lipid classification system that takes into account their specific impact on cardiovascular health.

Methods: To advance our understanding of the role of lipids and lipoproteins in cardiovascular disease (CVD), it is essential to reclassify them based on their specific mechanistic impact, rather than relying solely on their traditional classification according to biological functions. In light of this, we classified lipids and lipoproteins into three distinct groups: (i) those that enhance CVds, (ii) those with a conditional impact on CVds, and (iii) those with no known effect on CVds due to insufficient evidence.

Results: Low density lipoprotein, very low density lipoprotein, lipoprotein (a), triglycerides, trans-fatty acids, phosphatidylcholine, and lysophosphatidic acid have a strong impact on thrombosis and atherosclerosis. High density lipoprotein, fatty acids, sphingolipids and phospholipids have a conditional impact on CV risk progression based on factors such as oxidation, presence of collocters, and plasma concentration of other lipids. Due to lack of evidence in existing literature proving their impact on CV risk or events, biologically active lipids such as mono- and diglycerides, prenol lipids, steardic acids, galactolipids, sterols, glycolipids, and sphingolipids are placed in this category, implying that these lipids are essential for biological functions but do not have a mechanical impact on the onset or progression of CVD.

Conclusions: By this novel classification of lipids and lipoproteins, we identify the intersecting mechanisms by which lipids that enhance CVs cause genesis and progression of CVs is important to discover new therapeutic avenues.

Funding: Government Support - Non-U.S.

Pathophysiological Insights and Therapeutic Options for Cardiovascular Disease in CKD

Joachim Jankowski, 1, 2 *Universitätsklinikum Aachen, Aachen, Germany; 2Experimental Vascular Pathology, Cardiovascular Research Institute Maastricht (CARIM), University of Maastricht, Maastricht, Netherlands.

Background: Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular complications, including coronary artery disease, heart failure, arrhythmias, and sudden cardiac death. The incidence and prevalence of cardiovascular events are already higher in patients with early CKD stages (CKD stages 1-3) compared to the general population, but the risk significantly escalates in patients with advanced CKD stages (CKD stages 4-5). In fact, cardiovascular disease surpasses end-stage kidney disease (CKD stage 5) as the leading cause of death in this high-risk population. CKD induces a chronic proinflammatory state throughout the body, leading to vascular and myocardial remodeling processes.

Methods: The information presented in this article is based on a comprehensive review of existing literature related to cardiovascular disease in patients with CKD. Relevant studies, research articles, and clinical data were collected from various databases and sources. The selected information focuses on the pathophysiology, clinical consequences, and underlying mechanisms of cardiovascular disease in CKD.

Results: Patients with CKD face an elevated risk of cardiovascular complications, with cardiovascular disease being the leading cause of mortality in this population. CKD contributes to a systemic proinflammatory state that drives vascular and myocardial remodeling processes. These processes give rise to atherosclerotic lesions, vascular calcification, vascular senescence, myocardial fibrosis, and cardiac valve calcification. The cardiovascular manifestations in CKD resemble an accelerated aging process, further exacerbating the cardiovascular risk.

Conclusions: The understanding of cardiovascular disease in CKD is crucial due to its high prevalence and impact on patient outcomes. The systemic proinflammatory state induced by CKD contributes to significant vascular and myocardial alterations, leading to various cardiovascular complications. Recognizing the accelerated aging effect on the cardiovascular system in CKD patients is essential for effective management and the development of preventive strategies. Further research is warranted to explore novel therapeutic approaches and interventions targeting cardiovascular disease in CKD.

Funding: Government Support - Non-U.S.
The patient is a 50yo male with a history of hypertension.

**Introduction:**

Hydralazine is used in the treatment of hypertension and heart failure. It’s side effect profile includes Hydralazine-Induced Lupus (HIL). Typical manifestation of HIL include arthralgias, serositis, myalgias, and a malar rash. It is serologically associated with anti-histone antibodies (Anti-HisAb) and a +antinuclear antibody (ANA).

**Case Description:**

The patient is a 50yo male with a history of hypertension. Management of his hypertension has been complicated by many drug sensitivities. His clinical features and laboratory data were reviewed and compared retrospectively. All the patients lacked medical examination and regular checkups after diagnosis of hypertension. 33% of them were obese with a body mass index > 25. On admission, about 80% had elevated plasma renin activity and serum aldosterone levels, while there were no cases of renal artery stenosis. Between the two groups, there was no significant difference in serum creatinine levels. Serum LDL levels in the non-RRT group were higher than those in the RRT group. Serum potassium levels and platelet counts were lower, respectively. These data at post-antihypertensive treatment was improved significantly in those who were survived.

**Results:**

No significant change was found in the following parameters: blood pressure, renal function, metabolic parameters, and echocardiography. The improved renal function status was sustained. None could tolerate 6 min walking test before operation. The average distance of 6 min walking test in 3 patients was (328.3 ± 138.2) meters one year after operation.

**Conclusions:**

CRT improves left ventricular function and quality of life in uremic patients with chronic heart failure, and none of serious side effects were observed. 27.3% of patients were discharged after 6 months of follow-up. The 6 min walking test distance was significantly increased in the CRT group compared to the non-CRT group.

**Funding:**

Government Support - Non-U.S.
the non-RRT group. Serum values of LDH, potassium, and platelet in the comparison of pre-and post-treatment data of the two groups showed significantly improved by two-way analysis of variance.

Conclusions: In our study, there were young or middle-aged adults and some of them were obese. Therefore, taking health-checkup is helpful for the prevention of the risk of hypertension. Higher HDL levels and decreased platelet counts in the non-RRT group suggested the development of severe endothelial damage with rapid BP elevation in the short term. Severe renal dysfunction in these cases can be improved by appropriate antihypertensive therapy. Furthermore, the lower potassium level suggested the aggravation of the renin-angiotensin-aldosterone system (RAAS) and early induction of RAS inhibitors would be beneficial for the maintenance of BP and renal protection. In conclusion, serum LDH, platelet count, and serum potassium would be useful predictors of renal prognosis.

**PUB318**

**A Case of Primary Hyperaldosteronism with Hypomagnesemia**

**Sriram Sripriemunbuddi, Pradeep Vaitla, Mohammad Attri, Bushra Syed, Sanjana Kapoor. The University of Mississippi Medical Center, Jackson, MS.**

**Introduction:** Primary hyperaldosteronism classically involves a hypertensive patient with spontaneous or diuretic induced hypokalemia and metabolic alkalosis. We describe one such patient with hypomagnesemia and hypocalcemia along with the classic features.

**Case Description:** 51 year-old male, presented for management of 20-year history of hypertension (HTN). He has history of type 2 diabetes mellitus and coronary artery disease. Labs showed serum creatinine of 1.3 mg/dl, low serum potassium at 2.8 mmol/l, metabolic alkalosis with serum bicarbonate at 30 mmol/l, low serum magnesium at 1.2 mg/dl and low serum calcium at 7.9 mg/dl (serum albumin of 4.2 mg/dl). Fractional excretion of potassium (22.4%) and magnesium (4%) were high. Parathyroid hormone was appropriately elevated at 98.6 pg/ml and 25-O vitamin D level was mildly low at 16.2 ng/ml. Laboratory test for primary hyperaldosteronism was suspected due to hypokalemia and metabolic alkalosis. Random plasma renin activity was low at 0.10 ng/ml/hr (normal range: NR, 0.25-5.82 ng/ml/h) and aldosterone was normal at 11 ng/dl (NR: <=21 ng/dl) with elevated aldosterone: renin ratio at 110 (NR: 0.9-28.9). He was started on oral potassium and magnesium supplementation, and spironolactone was prescribed at 25 mg daily. Repeat laboratory values after 2 weeks showed normal serum potassium at 4 mmol/l, 24-hour urine electrolytes at this time showed sodium of 241 mmol, potassium of 78 mmol and a high calcium at 445 mg (NR: <300 mg). Plasma aldosterone: renin ratio remained elevated at 147 even after correcting the serum potassium. Computed tomography scan of the abdomen with intravenous contrast showed a 1.2 cm right adrenal adenoma with normal left adrenal gland. Dose of spironolactone was increased to 50 mg daily. His home blood pressures remained controlled at 135/80 mm Hg. A diagnosis of primary hyperaldosteronism secondary to unilateral adrenal adenoma was made with further plan to do adrenal vein sampling and adrenalectomy as appropriate.

**Discussion:** The case highlights a rare presentation of primary hyperaldosteronism with magnesium and calcium wasting, mimicking Gitelman’s syndrome. Aldosteron escape could potentially decrease sodium reabsorption at the thick ascending limb of Henle, which in turn leads to poor magnesium reabsorption. Consequent hypomagnesemia leads to calcium wasting due to PTH resistance at the level of thick ascending limb. Serum AMH levels were measured using a validated immunoassay. Using standardized serum AMH levels were measured using a validated immunoassay. Using standardized protocols, we assessed pulse wave velocity (PWV) and aortic augmentation index (AIx) with applanation tonometry to determine arterial stiffness. Mean Arterial Pressure (MAP) was calculated using systolic and diastolic blood pressure measurements which were collected using standardized protocols. Multiple linear regression analyses were used to estimate the association between AMH and each measure of arterial stiffness, as well as MAP.

**Methods:** A cross-sectional study was completed in males living with CKD recruited from Calgary, Alberta, Canada. We collected basic demographic and comorbidity data. Serum AMH levels were measured using a validated immunoassay. Calculated using systolic and diastolic blood pressure measurements which were collected using standardized protocols. Multiple linear regression analyses were used to estimate the association between AMH and each measure of arterial stiffness, as well as MAP.

**Discussion:** Serum AMH levels were negatively associated with increased arterial stiffness in males living with CKD, though it is likely that our sample is underpowered to detect a significant association. Given the high CV risk of males with CKD, further investigation into this potential CV risk factor is warranted.

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

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

*Underline represents presenting author.*

**PUB320**

**Impact of Impaired Kidney Function in the Mortality of Patients with Chagas Disease Submitted to Cardioverter-Defibrillator Implant**

**Fernanda M. Tapioca, 1,2 Maria G. Guimaraes, 1,3 Luiz C. Passos. 1,2 Hospital Ana Nery, Salvador, Brazil; 3Universidade Federal da Bahia, Salvador, Brazil; 1Hospital da Bahia, Salvador, Brazil.**

**Background:** on kidney disease impact in HFrEF due to Chagas Disease (CD) is limited in the current literature. Unlike other causes of HFrEF, CD may have such a high prevalence in the area and the use of other comorbidities. We performed a prospective study to access if an impaired glomerular filtration rate (eGFR) had an association with mortality and survival rates in patients with CD submitted to cardioverter-defibrillators (ICD) implant.

**Methods:** We collected data on 141 patients with CD that implanted ICD between 2017 and 2020. An altered kidney function was considered with an eGFR < 60 ml/min. An analysis for the survival rates between the groups was made with the Log Rank test. Multivariable logistic regression was used to identify predictors of death. Statistical analysis was done through SPSS, v.25, and significance level was set in 5% (p<0.05).

**Results:** Baseline characteristics are reported on Table 1. The median follow-up was 563 days. Patients in both groups had similar prescriptions regarding use of triple therapy for HFrEF (p=0.77). During the study, 52 patients died; 47.7% patients had altered kidney function and 32% with normal eGFR. In a univariate analysis for the outcome of death, the presence of a lower eGFR was not statistically significant (p=0.07). In the analysis for the survival rates, there was no difference between them (p=0.06). In a binary logistic regression model, a greater chance of death was not associated with a change in eGFR in these patients [p=0.227 (OR 0.69; CI95% 0.721-3.959)].

**Conclusions:** In our study, a group of patients with HFrEF due to Chagas cardiomopathy using ICD, with similar patterns of disease modifying drugs, there was no significant association between kidney function and mortality.

**Table 1. Baseline characteristics of the patients**

<table>
<thead>
<tr>
<th>Characteristic</th>
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<th>Lower eGFR</th>
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<td>57 (41-62)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>65/76</td>
<td>52/39</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>13 (28)</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Arterial Disease (%)</td>
<td>19 (42)</td>
<td>25 (28)</td>
</tr>
<tr>
<td>Extracellular fraction (E/F)</td>
<td>17.5±2.71</td>
<td>12.3±7.72</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>78 (35-121)</td>
<td>51 (25-75)</td>
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</table>

**PUB321**

**Hyperfiltration, Metabolic Syndrome, and Risk of Adverse Clinical Outcomes**

**Dae Kyung Kim, Yu ho Lee, 2 Jin sug Kim, 1 Yang Gyun Kim, 3 Su Woong Jung, 3 Ju young Moon, 1 Kyungwhan Jeong, 1 Hyeon Seok Hwang. 1,3 Kyung Hee University Hospital, Seoul, Republic of Korea; 2CHA Bundang Medical Center, Seongnam, Republic of Korea; 3Kyung Hee University Hospital at Gangdong, Seoul, Republic of Korea.**

**Background:** Glomerular hyperfiltration and metabolic syndrome increase the risk of cardiovascular disease and all-cause mortality. While hyperfiltration is strongly related to the metabolic risk, it is little known how the combined association of these two factors affects the risk of metabolic syndrome-related complications, CV disease and all-cause mortality.

**Methods:** We reviewed the National Health Insurance Service database of Korea for people who received national health screenings between 2009 and 2011. Hyperfiltration (n = 190,807) was defined as eGFR >95th percentile after stratification for age, sex, height and weight and normal filtration as eGFR 25-75th percentile (n = 2,376,489). Metabolic syndrome was considered as the presence of three or more of the metabolic risks. Individuals were compared based on the presence of hyperfiltration and metabolic syndrome.

**Results:** Compared to normal filtration without metabolic syndrome, coexistence of glomerular hyperfiltration and metabolic syndrome was associated with the greatest risk of hypertension, diabetes and cardiovascular event. Hyperfiltration without metabolic syndrome also increased the risk of diabetes (HR 1.22, 95% CI 1.18-1.27) and hypertension (HR 1.06, 95% CI 1.04-1.07), but it was not associated with higher risk of cardiovascular event (HR 1.04, 95% CI 0.99-1.09). Among four categorized individuals, the risk of all-cause mortality increased highest in those who had hyperfiltration without metabolic syndrome (HR 1.22, 95% CI 1.17-1.28) and there was a significant interaction between hyperfiltration and metabolic syndrome in association with all-cause mortality (P for interaction = 0.003).

**Conclusions:** Our findings indicate that glomerular hyperfiltration was significantly associated with higher risk of hypertension and diabetes in the absence of metabolic syndrome. Notably, hyperfiltration without metabolic syndrome was more detrimental to mortality than that with metabolic syndrome.
**PUB322**

**Dapagliflozin in Patients with Low and High uACR**

Navdeep Tangri,1 Maria K. Svensson,2 Johan Bodgard,1 Samuel Adamsson Eryd,3 Marcus Thuresson,3 Tadashi Hasan, Daniel Rechlin, Jerome Loyola Vellanki.

Text: In non-T2D patients, 332 (54%) new users of dapagliflozin had low uACR and 286 (46%) had high uACR. Corresponding numbers for patients with T2D were 1987 (53%) and 1741 (47%). New users of dapagliflozin with low and high uACR had similar baseline characteristics, both with and without T2D. In non-T2D patients, event rates for cardio renal hospitalizations were similar in the low and high uACR groups (8.3 and 9.2 per 100 patient-years, respectively). There was no significant risk difference between low and high uACR (hazard ratio [HR] 1.16, 95% confidence interval [CI] 0.54–2.49; Figure). Similar results were seen in patients with T2D (HR 0.92, 95% CI 0.68–1.24). In contrast, the risk of ASCVD was significantly higher in patients with high uACR versus low uACR (HR 1.67, 95% CI 1.03–2.72).

**Conclusions:** Dapagliflozin’s beneficial effect on cardio renal risks appeared similar in patients with low and high uACR independent of T2D. ASCVD risk remained higher in high versus low uACR patients. These findings suggest cardio renal effectiveness of dapagliflozin in patients with CKD and low uACR, without T2D.

**Funding:** Commercial Support - AstraZeneca

**PUB323**

**Urinary Features Predict Cast Nephropathy**

Richard E. Wing, Shamsul Hasan, Daniel Rechlin, Jerome L. Jean-Gilles.

*University of Rochester Medical Center, Rochester, NY.*

**Introduction:** Multiple Myeloma may present with a constellation of features including back pain, anemia, hypercalcemia, renal failure, and bland urine sediment. A multitude of findings is possible on biopsy most commonly including cast nephropathy, amyloidosis, monoclonal immunoglobulin deposition disease, and tubular injury. Urinary characteristics may predict biopsy findings.

**Case Description:** A 63 year old woman former smoker presented with two years of progressive back pain treated with NSAIDs. Plain films revealed thoracic compression fractures. Select laboratories are summarized in the table. Urine microscopy revealed a largely intact tubulo-epithelial cast (Image). A percutaneous renal biopsy was obtained. The light microscopy revealed angulated, fractured casts with associated cellular reaction and tubular injury. A Congo red stain was negative. A paraffin based immunofluorescence showed monoclonal Kappa positivity in the casts. Moderate atherosclerosis and severe interstitial fibrosis were noted. Bone marrow biopsy revealed plasma cell myeloma (90% of marrow cellularity).

**Discussion:** Urinary findings include a large intact tubular cast, high sodium:creatinine ratio, and large non-albumin proteinuria. All point to a biopsy finding of a cast nephropathy.

**PUB324**

**When You Hear Hoof Beats, It Can Be a Horse or a Zebra or Both Galloping Simultaneously!**

Danish Wagay, Maria M. Picken, Ewa Borys, Kavitha Vellanki.

*Loyola University Medical Center, Maywood, IL.*

**Introduction:** Multiple primary malignancies are defined as two or more malignancies arising independently of one another. While it is not uncommon to have multiple primary malignancies in a life time, simultaneous diagnosis is rare. Here, we present a case of acute kidney injury (AKI) and hypercalcemia, work up of which lead to simultaneous diagnosis of two different primary malignancies.

**Case Description:** A 74 year old male presented with 2 month duration of abdominal pain, weight loss and poor appetite. He had a large palpable abdominal mass, confirmed on CT imaging as a 13.6 x 13.4 cm mesenteric mass. Laboratory work up revealed AKI (serum creatinine of 5.6 mg/dL) and hypercalcemia (serum calcium of 14.2 mg/dL). Urinalysis was +ve for protein with 24 hour urine protein of 2.5 grams. Mesenteric mass biopsy confirmed our suspicion of lymphoma, final diagnosis being diffuse large B-cell lymphoma (DLBCL). Work of hypercalcemia is shown in Table 1 and kidney biopsy revealed lambda light chain proximal tubulopathy (Figure 1) with subsequent bone marrow biopsy confirming the diagnosis of Multiple Myeloma (MM).

**Discussion:** Simultaneous occurrence of DLBCL and MM is extremely rare. Our case illustrates the importance of a thorough workup of hypercalcemia despite an obvious cause as both malignancies can present with AKI, hypercalcemia and proteinuria. Workup of hypercalcemia (normal 1, 25 (OH)2 D which is usually elevated in lymphoproliferative disorders and markedly elevated serum lambda light chains) prompted us to a kidney biopsy and diagnose MM simultaneously. Conclusion: Even with a concurrent known cause of hypercalcemia, a full workup for hypercalcemia is always warranted. We like to think “When you hear hoof-beats, it can be a horse or a zebra or both”.
Safety of Systemic Anticancer Treatment (ST) in Patients with ESKD and Metastatic Renal Cell Carcinoma (mRCC): A Single Institution Experience

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Background: ST for mRCC is linked to a variety of adverse events (AEs) including bleeding and infections. A significant number of patients with mRCC develop CKD that can progress to ESKD requiring renal replacement therapy. It is not known however whether these patients have an increased risk for bleeding and infections while receiving ST.

Methods: We identified 29 ESKD patients (21 male, 8 female) with mRCC who received ST that included VEGFR/TK inhibitors, immune check point inhibitors (ICI) or mTOR inhibitors alone or in combination at the Institute of Oncology Ljubljana in Slovenia between December 2009 and January 2023. By manual chart review, we determined the frequency and severity of bleeding and infectious AEs in this cohort while on active treatment for mRCC.

Results: The median age for the patients studied was 71 years (range 47-83). At the start of ST, 20 patients were already on chronic hemodialysis (HD). Six patients had eGFR ≤30 ml/min/1.73m² and three had a GFR >30 ml/min/1.73m² at the start of ST but all patients eventually developed ESKD and were started on chronic HD. Before ST, eight patients experienced a bleeding episode including three who had a gastrointestinal bleed (GIb). Grade 4 epistaxis was seen in three patients, including a patient that developed hemorrhagic shock during first-line treatment with sunitinib. Two patients experienced grade 4 anal hemorrhage, one due to hemorrhoids during first-line therapy with sunitinib. One patient underwent an urgent nephrectomy due to bleeding during treatment with sunitinib and a second patient during pazopanib treatment. In four patients, grade 4 GIb was observed during or after the ST. The cumulative incidence of grade 3/4 bleeding was 0.59 (17 events/29 pts), and 1.4 (40 events/29 pts) for all-grade bleeding. During ST, 10 patients experienced grade 4 infectious AEs. Six developed sepsis, and one, who was in the first cycle of first-line treatment with sunitinib and receiving HD, developed septic shock.

Conclusions: Serious AEs during ST, including bleedings and infections, may be more frequent in mRCC patients with ESKD as compared to the general mRCC population. Clinicians should be aware of this increased risk that may have a significant impact on the duration and selection of ST for these patients.

Funding: NIDDK Support, Other NIH Support - NCI

Renal Cell Carcinoma Presenting as Jaw Pain

Matthew T. McAuliffe, Kostas Papamarkakis. Baystate Medical Center; Springfield, MA.

Introduction: Renal Cell Carcinoma (RCC) is the most common renal malignancy. Metastases to bone usually present as osteolytic lesions from T12-L5. This case demonstrates a mandibular mass as the initial presentation of RCC.

Case Description: A 91-year-old female presented with shortness of breath. Medical history was significant for chronic pain for which she took daily oxycodone. She did not smoke. Physical examination revealed a right mandibular jaw mass. No cervical lymphadenopathy, trismus or parotid gland swelling was found. Computed tomography (CT) of the maxillofacial structures demonstrated a 3.5 cm destructive lesion with a displaced pathologic fracture of the right mandibular body. It also showed a large destructive mass at the level of C3 extending into the spinal cord. Biopsy demonstrated renal cell carcinoma. Subsequent CT Abdomen/pelvis revealed a large 8.5 cm multilobulated mass replacing a majority of the right kidney.

Discussion: RCC is the most common solid tumor of the kidney. The classic presenting symptoms are the triad of hematuria, flank pain, and a palpable abdominal mass; however, this presentation only occurs in 10-15% of patients. 25-30% of patients will have metastatic disease at time of presentation. RCC commonly spreads to orofacial soft tissues and sinuses, however, only 1% of patients with RCC demonstrate isolated head and neck metastases. Oral metastases convey a worse clinical prognosis. When multiple osteolytic lesions present in the head and neck, it is strongly recommended that a search for the primary tumor be conducted.

Figure 1

Figure 1

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
Conclusions: The patients receiving checkpoint inhibitors frequently developed AKI due to various etiologies. Genitourinary cancer, previous AKI and anti-PD1/PD-L1 combined with chemotherapy were associated with a higher likelihood of developing AKI.

Funding: Private Foundation Support

PUB328

Wunderlich Syndrome: Spontaneous Perinephric Hematoma in a Patient with Chronic Myelomonocytic Leukemia (CMML)

Nathaniel Klar, Sean Pickthorn, Salman B. Mahmood, Mark E. Rosenberg.
University of Minnesota Twin Cities School of Medicine, Minneapolis, MN.

Introduction: Wunderlich syndrome describes the uncommon presentation of spontaneous perinephric hematoma that are most often caused by renal neoplasms. We present a case of bilateral spontaneous perinephric hematomas in a patient ultimately diagnosed with chronic myelomonocytic leukemia (CMML).

Case Description: A 62-year-old woman presented with acute onset right flank pain, hypotension, and anemia (Hgb 6.8 g/dL) requiring emergent transfusion. Workup showed WBC of 49x10^3/µL, platelets 380x10^3/µL, and Cr 0.9 mg/dL. CT revealed a large right perinephric hematoma, but no active extravasation was seen on angiography. The patient was stabilized with medical management and outpatient bone marrow biopsy was planned. Two days later she presented with acute onset left flank pain. CT showed a stable large right perinephric hematoma and a new left perinephric hematoma (Figure 1). Angiography revealed active extravasation from bilateral segmental renal arterial branches which were successfully embolized. Post embolization, the patient developed oliguric AKI (peak Cr 3.6 mg/dL), likely due to a combination of contrast exposure, ischemia from embolization and acute blood loss, and compression of the kidneys. She briefly required dialysis while her renal function recovered over a period of 2 weeks. During this time, a bone marrow biopsy was performed which revealed CMML. Treatment was initiated with hydroxyurea.

Discussion: The most frequent cause of spontaneous perinephric hematoma is primary renal malignancy or mass. CMML rarely has shown renal infiltration leading to renal failure but has no prior association with Wunderlich syndrome. While no biopsy was performed, we suspect this patient had leukemic infiltration of both kidneys which predisposed her to spontaneous bilateral perinephric hematomas in short succession.

Figure 1: CT with contrast showing bilateral perinephric hematomas.

PUB329

Exploring Uncharted Territories: Unusual Distant Metastases in Renal Cell Carcinoma

Wen Ho Lynn Ng,1 Benjamin Ravichander,1 Lillian Sangha,1 Evelyn J. Calderon Martinez,1 Lay She Ng,2 Chandí Garg,1 UPMB Harriscburg, Harrisburg, PA; 2Mayo Clinic Minnesota, Rochester, MN.

Introduction: Metastatic renal cell carcinoma (RCC) is known for its tendency to disseminate to the skeletal system, particularly as lytic lesions. The predilection of this metastasis primarily involves vascular regions within the axial skeleton (e.g., vertebral bodies and the pelvis). While rare, there have been scant reports documenting the manubrium as the primary site of metastasis. In this context, we present a case of metastatic RCC, wherein the patient’s initial manifestation manifested as chest pain.

Case Description: A 50-year-old male with 50 pack-years of smoking history, presented to the emergency department (ED) with right-sided chest pain aggravated by recent hand trauma. The patient reported progressive difficulty with overhead movements and right-hand lifting. He had no alleviating factors and denied shortness of breath, diaphoresis, or recent weight loss. Further evaluation ruled out acute coronary syndrome (ACS). The chest x-ray was unremarkable. However, a commuted tomography (CT) of the abdomen and pelvis raised concern about a large left-sided renal mass. He was discharged with outpatient follow-up. Within three weeks, the patient returned to ED due to worsening chest pain and now, a growing mass in the sternum. ACS was ruled out again. A chest CT scan revealed a concerning lytic lesion in the manubrium. To establish a diagnosis and stage of a presumed metastatic renal cell carcinoma, the patient underwent a positron emission tomography scan and bone biopsy of the lesion. The subsequent pathology report confirmed metastatic RCC. Treatment was initiated with immunotherapy (nivolumab and ipilimumab) and palliative radiation targeting the sternum. Left radical nephrectomy and adrenalectomy with clear margins were performed. Ongoing treatment involves immunotherapy aimed at reducing the burden of metastatic disease.

Discussion: RCC commonly metastasizes to the lungs and lymph nodes, with axial skeletal involvement being less frequent. Sternal metastases are rare, likely due to the limited vascularity in this region compared to sites like the pelvis or vertebrae. However, RCC is a treatable cancer, and both surgical intervention and immunotherapy have shown efficacy in improving metastatic disease outcomes. Timely treatment can enhance quality of life and potentially even lead to metastatic disease regression.

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

Underline represents presenting author.

1140
flank pain and 15 (31%) presented with hematuria. This is an aggressive tumor so rapid especially in a patient presenting with bone pain and bony metastases. Although a carcinoma may be higher on the differential in a patient presenting with a renal mass, it diagnostic workup included Wilm’s tumor, clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma. Diagnosis of Ewing sarcoma was made by biopsy of a lytic bone lesion and was confirmed on pathology of the left kidney following left nephrectomy. The patient is currently undergoing chemotherapy and responding well to treatment.

Discussion: This is a rare case of a primary renal Ewing’s sarcoma. While more common primary renal tumors such as Wilms’ tumor, clear cell sarcoma, and renal cell carcinoma may be higher on the differential in a patient presenting with a renal mass, it is important to keep less common tumors such as Ewing’s sarcoma on the differential, especially in a patient presenting with bone pain and bony metastases. Although a primary renal Ewing’s sarcoma is very rare, this patient’s presentation was consistent with other cases of primary renal Ewing’s sarcoma. In a metaanalysis of cases of primary renal sarcoma that included 48 patients, Hakky et al found that 36 (73%) presented with flank pain and 15 (31%) presented with hematuria. This is an aggressive tumor so rapid diagnosis and treatment are key to optimizing outcomes.

A Rare Case of a Primary Renal Ewing Sarcoma

Robin Miller,1,2 Elizabeth G. Ingulli,1,2 Rady Children’s Hospital San Diego, San Diego, CA; 3University of California San Diego, La Jolla, CA.

Introduction: Ewing’s sarcoma is a neuro-ectodermal tumor that is typically found in long bones. A primary renal origin of an Ewing’s sarcoma is very rare. It is estimated that there are less than 370 reported cases of a primary renal Ewing’s sarcoma. This case presents Ewing’s sarcoma.

Case Description: A previously healthy 15 year old male presented with two months of hematuria and one day of left flank pain, as well as occasional migratory bone pain. Initial imaging with US kidneys and bladder revealed an area of calcification in the lower pole of the left kidney. Further imaging with CT abdomen and pelvis showed a left renal mass with associated calcification with extension into the renal pelvis. There were also lesions visualized in the liver, spine, and pelvis that were concerning for metastases. The patient was later found to have additional metastases in the skull and sternum. Initial differential diagnosis included Wilm’s tumor, clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma. Diagnosis of Ewing sarcoma was made by biopsy of a lytic bone lesion and was confirmed on pathology of the left kidney following left nephrectomy. The patient is currently undergoing chemotherapy and responding well to treatment.

Discussion: This is a rare case of a primary renal Ewing’s sarcoma. While more common primary renal tumors such as Wilms’s tumor, clear cell sarcoma, and renal cell carcinoma may be higher on the differential in a patient presenting with a renal mass, it is important to keep less common tumors such as Ewing’s sarcoma on the differential, especially in a patient presenting with bone pain and bony metastases. Although a primary renal Ewing’s sarcoma is very rare, this patient’s presentation was consistent with other cases of primary renal Ewing’s sarcoma. In a meta-analysis of cases of primary renal sarcoma that included 48 patients, Hakky et al found that 36 (73%) presented with flank pain and 15 (31%) presented with hematuria. This is an aggressive tumor so rapid diagnosis and treatment are key to optimizing outcomes.

A Case of Thrombotic Microangiopathy (TMA) Secondary to Bevacizumab Followed by Acute Interstitial Nephritis (AIN) Secondary to Nivolumab: A Strong Case for Serial Biopsies

Omar Osmaan, Roman A. Shingarev, Kristen Tomaszewski, Hanny Sawaf. Cleveland Clinic, Cleveland, OH.

Introduction: In recent years, onconephrology has gained prominence as a crucial field at the intersection of oncology and nephrology. With the rapid growth of cancer treatments that are often used concurrently, it has become important for oncologists and nephrologists alike to recognize and manage kidney injury and develop a consistent and efficient approach to establishing etiology of acute kidney injury (AKI). Here we present a patient who experienced biopsy proven thrombotic microangiopathy (TMA) caused by bevacizumab, was switched to nivolumab which resulted in biopsy proven acute interstitial nephritis (AIN).

Case Description: Patient is a 69-year-old female with a medical history of stage IV malignant mesothelioma of the lung. This was treated with platinum-based therapy, pemetrexed and bevacizumab followed by maintenance therapy with bevacizumab. Patient was diagnosed with normal kidney function with a baseline creatinine of 0.9 mg/dL; however, 2 years after initiation of therapy her kidney function worsened, with a creatinine rising to 2.4mg/dL and a uric acid to creatinine of 2.7g/g. Patient underwent a kidney biopsy revealing focal segmental and global glomerulosclerosis with microangiopathic features as well as moderate arteriolar sclerosis. A diagnosis of bevacizumab induced TMA was made and this medication was stopped. Patient then began treatment with the immune checkpoint inhibitor (CPI) nivolumab. Five months after her first kidney biopsy and 3 months after beginning treatment with nivolumab, patient’s creatinine rose again to then new peak of 7 mg/dL. Repeat kidney biopsy was obtained revealing acute tubulointerstitial nephritis which was suspected to be secondary to nivolumab. This medication was held, patient was started on a short prednisone course with recovery to baseline kidney function followed by a taper and plan to possibly rechallenge with an CPI.

Discussion: As demonstrated by this case, serial kidney biopsies may be required to ascertain etiologies of recurrent AKI in patients exposed to different cancer treatments. These biopsies can effectively guide oncological treatment and help avoid progression to end-stage kidney disease that would otherwise severely limit further treatment options and preclude patients’ participation in new drug trials.

Kidney Palliative Care: Key Tool to Facilitate Shared Decision Making

Kaitlyn Lorsch, Pooja D. Amarpurkar, Jane O. Schell. UPMC, Pittsburgh, PA.

Introduction: Patients with cancer and kidney disease have complex symptoms and needs. This is especially true for those with advanced chronic kidney disease (CKD) who are at risk for worsening progression due to cancer-directed therapies or their side effects. Palliative care is team-based care that focuses on managing symptoms and addressing goals of care including kidney treatment decisions. Our institution developed a specialty kidney palliative care (KPC) team to manage these complex patients through collaboration with referring clinicians. The following case describes how KPC can promote patient-centered care in a patient with advanced CKD and cancer.

Case Description: An 80-year-old man with CKD stage 3bA2 established care with our KPC team. His kidney function remained stable until about a year before his cancer diagnosis, with estimated GFR dropping to the mid-20s. These notable changes prompted a goals of care discussion that led to a decision for medical management without dialysis. He was later diagnosed with metastatic lung cancer. After receiving this diagnosis, the KPC team worked with both the patient and his wife to outline goals of palliative chemotherapy, which included a quality of life with the ability to garden, enjoy reading and be at home with family. Shortly after starting treatment, he required hospitalization for dehydration and AKI in the setting of diarrhea related to the chemotherapy. Due to the strong relationship established with the patient and his family, the KPC team collaborated with his oncology team to help determine that starting dialysis and continuing chemotherapy were not consistent with his goals. These relationships and prior discussions helped the patient choose hospice care, passing away peacefully at home.

Discussion: This case exemplifies how patients with advanced kidney disease and cancer benefit from specialty palliative care. It demonstrates how the KPC team has a role in having early conversations regarding goals, revisiting these goals, and then collaborating with oncology. It allows patients and their families to build trust in their medical team, which is especially needed during challenging decisions. It gives patients and families the opportunity to express their values and receive patient-centered care especially at end of life.
A Rare Manifestation of Multiple Myeloma in a Patient with Kidney Injury

Nader Ismail, Goutham Kondapi, Anthony Chang, Marco A. Bonilla Arevalo. University of Chicago Division of the Biological Sciences, Chicago, IL.

Introduction: Acute kidney injury (AKI) is a common complication of multiple myeloma (MM), most frequently attributed to underlying myeloma cast nephropathy. By contrast, infiltration of kidney tissue by neoplastic plasma cells is a rare occurrence and a rare mechanism of acute kidney injury in these patients.

Case Description: A 75-year-old male with a past medical history of long-standing hypertension and diabetes was admitted for evaluation of AKI. He reported unexplained weight loss but was otherwise asymptomatic. Upon laboratory evaluation, he was found to have increased serum creatinine from his baseline of 1.0 mg/dL to 3.8 mg/dL. A urinalysis revealed proteinuria, and a urine protein and creatinine ratio of 8.3 g/g. Further evaluation revealed free kappa and lambda light chains of 1.0/432 mg/dL with a ratio of 0.0025. Serum protein electrophoresis showed a monoclonal free lambda. Serological workup was negative. Renal ultrasound was unremarkable. A kidney biopsy demonstrated a Lambda light chain-restricted plasma cell myeloma and a Light chain proximal tubulopathy, non-crystalline type (lambda light chain-restricted). Subsequently, he underwent a bone marrow biopsy showing a lambda-restricted plasma cell myeloma with lambda light chain-restricted plasma cells and started on daratumumab-based therapy.

Discussion: The etiology of kidney disease in patients with multiple myeloma can be multifactorial. On kidney biopsy, a broad spectrum of kidney lesions has been described. This case demonstrated a rare mechanism of acute kidney injury in a patient with MM and highlights the importance of kidney biopsy in the diagnosis and prognosis of these patients.

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

Underline represents presenting author.
Case Description: This is a 63-year-old male with PMH significant for stroke who presented to the ED at an outside facility due to a fall in his garage. He experienced agitation, multiple skin lesions on the arms consistent with bruising, and reports of suicidal ideation. For severe anemia, patient was transfused. Hematology/oncology suggested catheter placement for plasmapheresis. The patient was transferred to our facility where nephrology was consulted to evaluate thrombocytopenia with possible TTP and begin plasmapheresis. Given suicidal ideations, psychiatry involuntarily committed the patient upon arrival. Nephrology believed this to be B12 deficiency with pancytopenia, not TTP due to elevated MCV. B12 was 276. Nephrology was concerned for pernicious anemia and recommended against plasma exchange. The patient regardless refused plasmapheresis. He did agree to 1000 mcg IM of cyanocobalamin, administered every 24 hours over 3 days. MRI confirmed absence of subacute combined degeneration. Labs improved substantially after treatment. Full workup was performed for B12 deficiency. He continued to have agitation but was deemed competent and the involuntary commitment was lifted with the patient discharged.

Discussion: Vitamin B12 is considered deficient with levels measuring less than 200 ng/L, with borderline deficiency of 200-400 ng/L considered equivocal, with any discrepancy. For AA amyloidosis treatment focuses on controlling the underlying inflammatory process with the goal of reducing the amount of circulating SSA protein 

Abundance of proteosome related proteins in the different EV fractions. Asterix marks a statistically significant difference (<0.05)

Conclusions: Implementing low centrifugation along with a high ionic strength buffer effectively prevents co-sedimentation and increases detection yield. The uEV's P20 pellet contains proteosome components, specifically the 19S subunit indicating a shared pathway potentially associated with apoptosis.

Funding: Private Foundation Support

Conclusions: High-speed ultracentrifugation is a commonly employed technique for isolating small extracellular vesicles (EVs). In contrast, the low-speed centrifugation pellet can be an advantageous source for large EVs. In this study we sought to describe and compare the characteristics of EV pellets obtained through different centrifugation velocities, with a specific focus on their protein content and cellular localization.

Methods: A healthy volunteer provided a morning urine sample that was divided into three aliquots. Each urine aliquot underwent centrifugation to eliminate cell debris, and the resulting supernatant was then subjected to a centrifugation at 21,200g to generate a pellet known as P20. The supernatant from P20 was subsequently centrifuged at 164,000g, resulting in a pellet referred to as P100. The P20 pellets were subjected to uromodulin depletion using a low ionic strength buffer, while the P100 pellets were purified using size exclusion chromatography. The individual pellets were analyzed using mass spectrometry separately and combined.

Results: in all three replicates 929 proteins were identified the P20 pellets, 1103 proteins in the P100 pellets, and 1676 proteins in the combined P20 and P100 pellets. 398 proteins were uniquely identified in P100 and 224 were uniquely identified in P20. 473 proteins were uniquely expressed in the combined P20+ P100 that were not identified in either fraction alone. The abundance of S19 proteosome subunit components were increased in P20 compared to P100.

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

Underline represents presenting author.

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Indigenous Variables | Correlation Coefficient | p Value
--- | --- | ---
Age | 0.16 | 0.005
Gender | 0.31 | 0.002
BMI | 0.2 | NS
HTN | 0.14 | 0.002
DM | 0.18 | 0.002
3 x creatinine | 0.49 | 0.002
BMI x creatinine | 0.47 | 0.002
Systolic BP | 0.18 | NS
Parsnip Severity | 0.25 | NS

PUB343
Statin Therapy Activates a Programme of Skeletal Muscle Wasting In Vitro
Emma L. Watson, James Burton. University of Leicester, Leicester, United Kingdom.

**Background:** Skeletal muscle wasting is a serious and common complication of chronic kidney disease (CKD), which starts very early in the disease process. This is an important clinical problem as it is strongly associated with increased risk of mortality and decreased quality of life. Despite its prevalence and impact, mechanisms of skeletal muscle (SM) wasting are unclear. One possible contributor is statin medication that CKD patients are frequently prescribed, which are documented to have negative effects upon muscle health. The aim of this study was to assess the effect of simvastatin therapy on protein degradation in human derived primary skeletal muscle cells (HDMCs).

**Methods:** Isolated HDMCs were cultured for 4 days in medium supplemented with fetal bovine serum (FBS, 20%) followed by 7 days in either 2% horse serum (HS) to establish mature myotubes. HDMCs (n = 5 CKD patients) were incubated with either 10µM and 30µM simvastatin for 24h and effects upon atrophy were assessed by myotube diameter by immunofluorescence, and activation of protein degradation and inflammation pathways by qPCR.

**Results:** Cells exposed to 10µM and 30µM simvastatin displayed significant reductions in myotube diameter (Control = 9.904 ± 2.56, 10µM = 8.424 ± 1.68 and 30µM = 7.998 ± 2.05, p<0.0036). 10µm statin therapy significantly increased the mRNA expression of RRM63 (a muscle specific E3 ligase; 3.7-fold increase, p<0.005) and resulted in significant intramuscular inflammation (IL-6 ~ 1.6-fold increase, p=0.008 and TNFα ~ 2.7-fold increase) and TNFα (~0.001). Significant effects were seen with 30µm statin therapy which resulted in significant inflammation (IL-6 ~ 1.7-fold increase, p<0.001, TNFα ~ 2.2-fold higher, p=0.025 and CCL2 ~ 2.2-fold increase, p=0.027).

**Conclusions:** Short term exposure of HDMCs to 10µM and 30µM simvastatin resulted in myotube atrophy, likely to be regulated by an increase in intramuscular inflammation. Whilst statin therapy has strongly beneficial effects for these patients in terms of reducing cardiovascular risk, an unwanted side effect is muscle wasting. It is unknown if this is an effect that is restricted to simvastatin alone, or also occurs with other statin use. This early pilot data suggests that we might need to think about strategies to preserve muscle mass in patients that are prescribed this class of drugs.

PUB344
Comparison of Two Scores for Renal ANCA-Associated Vasculitis (AAV) in Predicting Renal Outcomes
Nathan Lordes,1,2 Myros K. Phanish,1 Fiona E. Harris,1 David Makanjuola,1 Rukrma Doshi,1 Nicholas Cole,1 Bhrigu Raj Sood.1 1Epsom and Saint Helier University Hospitals NHS Trust, Carshalton, United Kingdom; 2The Dudley Group NHS Foundation Trust, Dudley, United Kingdom.

**Background:** ANCA associated vasculitis (AAV) is a rare but important cause of renal impairment and ESRD. Two classifications used for prognostication of renal AAV at presentation are Breden et al (Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol.2010.21(10)) and the renal risk score -Brix et al (Remote Education Program Improving Transition of Care in Pediatric Patients with CKD via a Publication-Only).

**Results:** 83 patients were included. 14 developed ESRD. 8 required early RRT but recovered and are not counted as ESRD. Berden Class We found no statistically significant relation between Berden class and ESRD and it did not predict recovery from early need for RRT. As KM curves vary at 52 months- fig 1-we calculated Cox proportional hazard up to 48 months. There was no statistically significant hazard There was significant association with creatinine at 1 year but not 4 Renal Risk Score Again the KM plot-fig 2-overlap. Cox hazard analysis up to 48 months found a hazard ratio of 4.178 for risk score class (p< 0.0017). The classification of our cohort using the renal risk score statistically significantly associated with ESRD but did not predict recovery from RRT. Also the renal risk class significantly associated with creatinine at 1 and 4 years.

**Conclusions:** In our cohort renal risk score by Brix et al performed better as predictor of ESRD and future creatinine than Berden class.

PUB345
The Role of Mitochondrial Metabolism in Inflammation Process of Brain-Dead (BD) Patients
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**Background:** As previously established, the renal prognosis of the recipient depends on the donor type. The decline in renal function has been observed to be greater in deceased donors (DD). We analyzed a cohort of brain-dead patients (DD). This could be related to the pre-implantation inflammation state and the development of fibrotic processes. Succinate, an intermediate in mitochondrial metabolism, plays a key role in the inflammatory processes of different pathologies. On the other hand, we observed previously, the involvement of adenosine pathway (linked to mitochondrial ATP production) in the same process. The aim of this study was to determine whether DD samples, succinate and purinergic pathways are involved in the infiltration of inflammatory cells.

**Methods:** Serum and whole cell extracts from circulating monocytes of 27 Brain Dead (BD) and 10 healthy volunteers (HV) were incubated in a Custom-Quantibody array to determine the levels of 18 monocyte/macrophage markers (CCL2/MCP-1, CCL3/MIP-1α, CD163, B7-1/CD80, B7-2/CD86, ICAM-1, IFN-γ, IL-10, IL-13, IL-1β, IL-4, IL-4Rα, IL-6, RANTES, TACE, TGF-β1, TNFα and VEGF). Succinate levels were measured in serum from the same samples with the EnzyChromTM Succinate Assay Kit. All statistical data was analyzed using GraphPad Prism 5.

**Results:** The results showed that in BD serum compared to HV ones, there was a significant increase in the expression of cytokines involved in monocyte recruitment and adhesion. Serum levels of IL-6, implicated in polarization of macrophages towards the proinflammatory subtype, were higher in BD. Concerning monocyte protein extracts, a significant increase in anti-inflammatory M2 proteins, such as CD163, IL-4Ra and IL-13 was observed. BD succinate levels in sera were increased in the same way. The results showed that in BD samples, there would be recruitment and differentiation of monocytes to macrophages towards the M1 or M2 subtype. Most of the molecules found to be upregulated belong to proteins related to the M2 phenotype, leading us to suggest that in BD, the process is mainly reparative/pro-fibrotic.

PUB346
Improving Transition of Care in Pediatric Patients with CKD via a Remote Education Program
Melvin Chan, Sarah E. Young, Melisha G. Hanna. University of Colorado, Denver, CO.

**Background:** Healthcare transition is the process of preparing a pediatric patient for the adult care model. There are no studies evaluating methods for improving transition readiness in patients with chronic kidney disease (CKD). Our project evaluates the effectiveness of an education program.
Methods: Eligible patients between 14-22 years of age with CKD stage 2 or higher were approached about this quality improvement project at a single pediatric center covering a 7 state referral region. Transition readiness was assessed by electronically administering the Transition Readiness Assessment Questionnaire (TRAQ), a validated tool evaluating 4 key domains of readiness. All patients received written and verbal education to address deficit domains. Coaching sessions were also offered, reinforcing written information and occurring every 3 months via telephone. After 6 months, a follow-up TRAQ was administered. Paired t-test was employed to compare pre- to post-education scores, and repeated measures ANOVA was used to evaluate the effects of coaching sessions.

Results: Thirty-four patients enrolled in the program, with 15 patients being eligible for the 6-month follow-up TRAQ survey. Ten patients (67%) completed the follow-up survey, and 5 of them requested for coaching sessions. Both cohorts showed significant improvements in multiple domains (Figure 1). Coaching and education sessions did not show more significant improvement than education alone in transition readiness.

Conclusions: Our preliminary data suggest that education and coaching sessions may be an effective, feasible method for improving transition readiness from pediatric to adult CKD care. Additional research is needed to assess this intervention in a larger cohort and to see if this intervention will translate to improved clinical outcomes.

PUB347

Efficacy and Safety of Eculizumab in Enterohaemorrhagic E. coli-Associated Partial Hemolytic Uremic Syndrome


Introduction: Partial hemolytic uremic syndrome (HUS) presents atypically without the full triad of classical HUS. We report the utility of eculizumab in enterohaemorrhagic E.coli (EAEC) associated partial HUS.

Case Description: A 2-year-old previously healthy female presented with vomiting. Evaluation showed an afebrile normotensive child with non-immune hemolytic anemia, oliguric acute kidney injury (AKI) but without thrombocytopenia and peripheral schistocytes. Bloody stools appeared later; stool examination for Shiga toxin (ST) was negative but positive for EAEC. Bone marrow examination showed no malignancy. Serum complements were normal but soluble complement 5b-9 was elevated. She required several sessions of hemodialysis (HD) and received one dosage of eculizumab with rapid reversal of AKI and hemolytic markers (Fig 1). Kidney biopsy revealed acute tubular injury (ATI) and segmental glomerular basement membrane splitting, with no glomerular or vascular thrombosis (Fig 2). No further dosages of eculizumab were required. Genetic testing was negative for complement mutations or deficiencies. A follow-up 4 weeks later showed persistent normalization of renal function and hematological markers, without any adverse effects.

Discussion: Efficacy of eculizumab in atypical HUS and in severe ST associated HUS has been described. We report its efficacy in EAEC associated partial HUS as well. Typical histologic manifestations of HUS may not be present in partial HUS as shown here. In one study of HUS patients, ATI was present in 70% and GBM duplication was present in 70% of those without peripheral schistocytes. This is an interesting novel finding which will need to be studied further.

PUB348

Assessment of Tryptophan Metabolism in Pediatric ESKD

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Background: End-stage kidney disease (ESKD) is associated with dysregulated tryptophan metabolism leading to systemic accumulation of toxic tryptophan metabolites derived from the indole and kynurenine pathways, which have been linked to systemic inflammation and an increased risk of thrombictic events and cardiovascular disease. Our study aimed to identify clinical variables that impact the plasma concentration of toxic tryptophan metabolites in children with ESKD on chronic hemodialysis (HD) and peritoneal dialysis (PD).

Methods: We designed a single-center cross-sectional study of children on chronic dialysis. Patients who received a kidney transplant between enrollment and sample collection were excluded. A total of 18 subjects had samples collected (HD n = 10; PD n = 8). Clinical characteristics are shown in Table 1. Serum specimens were collected at the time of routine monthly labs and were analyzed by liquid chromatography tandem mass spectrometry to measure tryptophan metabolites of the serotonin, indole, and kynurenine pathways. The association of target metabolites with demographic and clinical variables was determined t-test and Pearson correlation coefficients.

Results: Patients with residual renal function had a lower kynurenine:tryptophan (kyn:tryp) ratio (0.213 +/- 0.0553 vs 0.291 +/- 0.0564: t = -2.885: p = 0.011). Serum serotonin level was positively correlated with the normalized protein catabolic rate (nPmCR) (r = 0.568, p = 0.0175). However, there were no differences based on demographic variables, dialysis modality, or dialysis vintage.

Conclusions: Dialysis modality does not appear to influence tryptophan metabolism in children with ESKD. However, residual renal function is associated with a lower kyn:tryp ratio, which could reflect a reduction in systemic inflammation and immune dysregulation. The correlation between serum serotonin levels and nPCR suggests that nutrition status could influence serotonin-mediated pathways involved in neurocognitive outcomes. Larger prospective studies are needed to further evaluate the association of dysregulated tryptophan metabolism and clinical outcomes associated with pediatric kidney disease.

Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HD (n = 10)</th>
<th>PD (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>11.4 +/- .5</td>
<td>81 +/- 25</td>
</tr>
<tr>
<td>Gender (m/f)</td>
<td>18/0</td>
<td>2/6</td>
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</tbody>
</table>

PUB349

Audio/Podcasts and Art: A Collaboration Between the Renal Patient Support Group (RPSG) and the Kidney Disease and Renal Support Group (KDARs) for Kids and ZtormLabostix Productions

Shahid N. Muhammad, The Renal Patient Support Group (RPSG); The Kidney Disease and Renal Support Group (KDARs) for Kids; ZtormLabostix Productions. Coventry University, Coventry, United Kingdom.

Background: Chronic Kidney Disease (CKD) is ‘recognized’ as a silent, irreversible long-term condition (LTC), and tends to establish itself as a health complication and/or co-morbidity. Service user access to educational support surrounding kidney care can be challenging between health sectors owing to clinical environments. Aims: To understand how Audio/Podcasts and Art offer a collaborative basis for Service Users and Service Providers to align healthcare practices. Objectives: The Audio/Podcasts and Art have
been focused between two leading educational social media platforms to help highlight pertinent aspects surrounding healthcare and disease.

Methods: The Audio/ Podcasts and Art here focus on how healthcare professionals and service users could be working together through social media to improve experiences.

Results: Collaboratively, between the RPSG, KDARs and ZornLabostix Productions, there is the useage of several social media platforms, including four (4) YouTube Channels and two (2) Sound Cloud Channels with over 600 audio/ podcasts, and educational webinars highlighting context supporting service users and service providers surrounding nephrology/ paediatric nephrology, clinical medicine, and biomedical science. Audio/ Podcasts and Art can prompt service user and service providers to join up healthcare.

Conclusions: The RPSG is supports over 10,000 service users amongst adult population and KDARs is supporting near 2,000 service users amongst a paediatric/ young people population. Audio/ Podcasts and Art can help incorporate practice excellence.

### PUB350

**The Impact of Pathological Findings of Mitochondrial Disorders in Low-Birth-Weight Infants**


**Introduction:** Preterm infants with a low birth weight (LBW) show reduced numbers of nephrons at birth and a higher risk of developing kidney dysfunction during their lifetime. They demonstrate oligonephropenia and focal segmental glomerulosclerosis (FSGS) lesions in their glomeruli. We examined the association between mitochondrial disorders and the pathological characteristics of LBW-related nephropathy.

**Case Description:** Methods: We retrospectively evaluated the renal pathology in 6 infants including pairs of twins and 2 LBW infants demonstrating renal dysfunction. In addition to routine staining, the kidney biopsy specimens were analyzed using cytochrome c oxidase subunit IV (COX IV) and transcription factor A (TFAM) staining. Results: FSGS was diagnosed in 2 and oligonephropenia in 4 infants. The mean density of glomeruli was 3.8/mm² (0.3–7.2) Granular swollen epithelial cells (GSECs), which have previously been reported exclusively in patients with mitochondrial cytopathy, were observed in the distal tubules and/or collecting ducts in all 6 infants. Electron microscopic examination revealed that these GSECs included an increased number of enlarged mitochondria. Furthermore, we observed unbalanced expression patterns of COX IV and low expression of TFAM in the glomeruli and a part of the tubular cells.

**Discussion:** FSGS, a characteristic feature of glomerular involvement in patients with mitochondrial cytopathy is very commonly observed in LBW infants. In our study, all infants did not show FSGS lesions because a renal biopsy was performed in the early stages of the disease in contrast to previous reports. However, most patients revealed similar pathological changes of mitochondrial cytopathy such as unbalanced expression of TFAM, which plays a role in maintaining the mitochondrial DNA. This finding suggests that these lesions could appear during early childhood, resulting in the development of FSGS in the future. Conclusions: These findings could suggest the application of a new approach targeting mitochondrial DNA to prevent the development of LBW-related nephropathy.

**PUB351**

**Correlation of Serum Creatinine in Pregnant Mothers and Preterm Neonates**

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**Background:** Neonatal serum creatinine (n-sCr) in the first few days of life have been reported to correlate with maternal serum Cr (m-sCr). To our knowledge, no regression equation was reported on the correlation between n-sCr after birth and m-sCr before delivery. The purpose of this study is to perform a simple linear regression analysis and to obtain a regression equation indicating the association between n-sCr within 24 hours after birth in preterm neonates and m-sCr within 7 days prior to delivery.

**Methods:** From March 2017 to October 2022, among 659 preterm neonates treated in the University of the Ryukyus Hospital, cases who died before discharge, cases with multiple births, chromosomal/ genetic abnormalities, congenital anomalies of the kidney and urinary tract, severe heart disease, congenital diaphragmatic hernia, intrathoracic lymphangioma, cases whose mother were on dialysis, and cases in which n-sCr and m-sCr were not measured in pairs were excluded. A simple linear regression analysis of all 366 cases and three subgroups (gestational age [GA] ≤27 weeks [n=27], 28-31 weeks [n=60], ≥32 weeks [n=279]) was performed.

**Results:** In all cases, median (IQR) weeks of GA, birth weight, n-sCr, and m-sCr were 33.9 weeks (32.0–35.1 weeks), 1,901 g (1,757–2,260 g), 0.55 mg/dL (0.47-0.63 mg/dL) and 0.47 mg/dL (0.41-0.56 mg/dL), respectively. The regression equation for all cases and subgroups (GA ≤27, 28-31, ≥32 weeks) was n-sCr=0.097+0.962×m-sCr (R²=0.726, p<0.0001), n-sCr=0.104–0.949×m-sCr (R²=0.934, p<0.0001), n-sCr=0.098+0.930×m-sCr (R²=0.835, p<0.0001), and n-sCr=0.094+0.975×m-sCr (R²=0.647, p<0.0001), respectively.

**Conclusions:** This study showed that n-sCr=0.1+m-sCr approximately, regardless of the gestational age. n-sCr at birth in preterm infants reflect m-sCr and should not be used to determine the presence of kidney dysfunction in preterm neonates.

### PUB352

**Food Insecurity and Trends in Risk Factors for CKD in Adolescents**

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**Background:** The high prevalence of obesity and prediabetes in adolescents in the United States is a public health concern. We hypothesize that food insecurity may promote the burden of these conditions, which can increase chronic kidney disease (CKD) risk. We explored trends in obesity and prediabetes and how they may differ by food insecurity.

**Methods:** We included 10,013 adolescents (12–17 years) from the National Health and Nutrition Examination Survey (2001–March 2020). HBO1c of 5.7%–6.4% and/or a random glucose of 140–199 mg/dL defined prediabetes. Body mass index (BMI, kg/m²) percentiles were calculated from BMI Z-scores corresponding to the participants’ sex and age (in months) from the 2000 Centers for Disease Control and Prevention growth charts. A BMI percentile >95% defined obesity. Household food security classified as marginal, low, or very low were deemed food insecure. Analyses applied sample weights.

**Results:** The mean age was 14.5 (SEM=0.02) years, 51% were male, and 90% had health insurance. The sample included 58% Whites, 14% Blacks, 14% Mexican Americans, 8% non-Hispanic Others, and 7% Other Hispanics. Nearly 20% had obesity and 5% had prediabetes. During 2001–March 2020, the prevalence significantly rose for obesity (17%–22%) and prediabetes (2%–7%). Obesity and prediabetes prevalence were higher in food insecure adolescents (Figure). Among those, over 30% were obese and 9% were prediabetic in 2017–March 2020 (Figure).

**Conclusions:** Food insecurity may exaggerate rising trends of CKD risk factors like obesity and prediabetes in adolescents. Identifying food insecure adolescents may improve healthy food access and lower risk for CKD in adulthood.

**Funding:** Other U.S. Government Support
**PUB353**

**Mexican Wolf Hunting! Epidemiological Report on Mexican Lupus Nephropathy in Pediatric Age**

**Edgar Eduardo Morales-Montes,**1,2 Linda F. Perez,1,2 Luis A. Aparicio Vera,1,2

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**Background:** Childhood-onset systemic lupus erythematosus (cSLE) exhibits worse survival rates than its adult counterpart, primarily due to renal involvement. The epidemiology of renal involvement in cSLE is poorly understood in Latin America. Existing research primarily relies on studies involving both adults and children. In contrast, our study provides the unique epidemiological panorama of an exclusively pediatric center.

**Methods:** Retrospective, analytical, cross-sectional study. Patients diagnosed with cSLE in our center in the period 2000-2020 for men and 2010-2020 for women were included. No patient was excluded. The data on renal involvement correspond to the time of diagnosis.

**Results:** Renal involvement occurred in 100% of men against 82.1% of the women (p=0.032). Only 60.9% of the men and 28.4% of the women underwent biopsy (p=0.005). Urinalysis reported a higher frequency of granular casts (p=0.019) and proteinuria (p=0.006) in men than in women. Furthermore, estimated glomerular filtration rate was significantly lower in men (p=0.002). Finally, when comparing the frequency of renal involvement, no difference was found between our sample and countries with the highest renal involvement reported in pediatric literature.

**Conclusions:** cSLE in the Mexican population is, at the renal level, among the most aggressive reported in literature, with males being the most affected group. Despite the high frequency of renal involvement, biopsy was underutilized.

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

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**PUB354**

**Poor Sleep Efficiency and Shorter Sleep Duration Associated with Increased Blood Pressure in Pediatric Hemodialysis Patients**

Jonathan S. Chawla,1 Molly R. Vega,2 Shweta S. Shah,1 Kevin Kaplan,1 Jessica Geer,2 Cortney T. Zimmerman,2 Ayse Akan Arikan,1 Sarah J. Swartz,1 Leyat Tal,1 Poyyapakkam Srivaths,1 2 Baylor College of Medicine Department of Pediatrics, Houston, TX; 1Texas Children’s Hospital, Houston, TX.

**Background:** Cardiovascular disease (CVD) is the leading cause of death in pediatric (ped) patients (pts) with end-stage kidney disease (ESKD). Hypertension (HTN) is an important modifiable risk factor for CVD in this population. Poor sleep is associated with HTN in adults and ped pts without other comorbidities. We previously used actigraphy (ATG) to demonstrate high prevalence of poor sleep efficiency (SE) and inadequate total sleep time (TST) in a cohort of ped hemodialysis (HD) pts. We hypothesize poor sleep per ATG will be associated with elevated BP in ped pts on HD.

**Methods:** In this prospective cohort study, pts 8-18 years on HD for >3 months were asked to wear an Actigraph® accelerometer on non-dominant wrist for one week, logging sleep/wake times daily. Oscillometric BP obtained pre-, mid-, & post-HD and indexed to 95th percentile. Pts considered hypertensive if pre-HD BP was >95th for age, sex, and height per published AAP standards. Central BP taken with SphygmoCor® EM3 and compared to published standards and cutoffs for age, sex, and height.

**Results:** 21 pts completed ATG-62% male, mean age 15±2.9yr, mean HD vintage 1±1yr, mean BMI Z-score -0.63±1.4. All pts had three 240min HD sessions per week. 43% (n=9) met AAP definition of HTN per pre-HD oscillometric BP. Central BP was elevated in 48% (n=10). Pre-HD BP persistedly correlated with shorter TST and lower SE by Pearson’s R (see Table). Paired T-tests comparing pts with and without HTN by office BP showed that pts with HTN slept 1.65hr less than pts without HTN on nights following HD (p=0.035).

**Conclusions:** This is the first study assessing sleep quality and its association with HTN in ped HD pts, using actigraphy to provide objective measures of sleep quality and duration. The significant association of shorter TST and lower SE with higher BP represents actionable changes that can reduce CV mortality by improving sleep hygiene and identifying patients that warrant polysomnography to assess for obstructive sleep apnea.

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**PUB355**

**Etiologic Associations, Clinical Characteristics, and Histologic Findings of Children with Acute Interstitial Nephritis**

Ke Xu, Fang Wang. Peking University First Hospital Department of Pediatrics, Beijing, China.

**Background:** To explore the etiologic factors of acute interstitial nephritis (AIN) in Chinese children confirmed by kidney biopsy, and its correlation with clinical and pathological manifestations.

**Methods:** The clinical and pathological manifestations of 21 children diagnosed with AIN in Peking University First Hospital from January 2012 to December 2022 were retrospectively analyzed. According to final diagnosis, the patients were divided into Tubulointerstitial nephritis and uveitis (TINU) group and non-TINU group. T-test, Mann-Whitney U test and Fisher’s exact probability test were used for comparison between the groups.

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Results: Twenty-one patients were included in this study, accounting for 1.6% of kidney biopsy patients during the same period. Ten cases (48%) were characterized as TINU, 2 cases (10%) were associated with Sjögren syndrome, 1 case (5%) was likely drug induced, and 1 case (5%) was sarcoidosis. The etiology for 7 cases (33%) remained unclear. Compared with the non-TINU group, the TINU group had a higher proportion of uveitis ($P=0.024$) at the same time with AIN, a higher proportion of late-onset uveitis ($P=0.05$) diagnosed after the onset of the AIN, and a lower proportion of metabolic acidosis ($P=0.024$). There was no significant difference between the TINU group and the non-TINU group in other clinical manifestations, laboratory tests, and pathological findings. In the TINU group, three cases had preceding infection within 20 days before onset; four patients had received at least one antibiotic due to fever or respiratory tract infection symptoms before renal biopsy: one case received NSAIDs and one case received traditional Chinese medicines in concert with antibiotics.

Conclusions: The proportion of TINU in children with AIN in China is likely to be severely underestimated, given that the clinical manifestations, laboratory tests, and pathological findings of TINU in children are similar to those caused by other causes of AIN. Therefore, it is recommended that all pediatric AIN patients suspected to be related to medication, infections, or unclear etiology undergo a systematic eye examination and receive regular follow-up visits from ophthalmologists for at least one year.

Funding: Private Foundation Support

PUB356
Clinical Characteristics of Pediatric ANCA Vasculitis
Binil Mathew Jacob,1 Jacqueline Kruglyakova,2 Lois J. Arend,2 Olga Chernyaya,1 2Ben-Gurion University of the Negev Faculty of Health Sciences, Beer-Sheva, Israel; 2The Johns Hopkins University School of Medicine, Baltimore, MD.

Background: Pediatric ANCA-associated glomerulonephritis (AAGN) is a rare diagnosis with limited data describing the natural history of characteristics that can be used for clinical prediction at the time of diagnosis.

Methods: Single-center retrospective cohort of pediatric patients diagnosed with ANCA vasculitis by kidney biopsy between 2002 – 2022. Patient characteristics were compared by Wilcoxon-rank sum and chi-squared for continuous and categorial variables, respectively. Survival analysis was done with Kaplan-Meier and Cox proportional hazards for a composite outcome of end-stage kidney disease or death.

Results: Seventeen patients (<20yr) were diagnosed with AAGN, accounting for 1.4% of all pediatric kidney biopsies performed during the study period. Median (IQR) age at diagnosis was 15 (12-17) years old with most patients diagnosed with pANCA disease, and a slight female preponderance. There was no statistically significant difference in the extra-renal symptoms at presentation between the CANCA and pANCA groups, however a trend towards more patients with pANCA presenting with fever. Seven of 17 patients (41%) reached the composite end-point at a median time of 7 yrs. Increased age at diagnosis was associated with increased hazard of ESKD/Death. Role of C4 in this disease is unclear and warrants further exploration in a larger cohort.

Conclusions: Pediatric AAGN is a rare diagnosis in pediatric patients presenting during adolescence and associated with significant morbidity. Proteinuria and higher C4 at diagnosis were associated with increased hazard of ESKD/Death HR 2.29 (1.00 – 5.28) and HR 1.28 (1.06 – 1.53), respectively. Survival analysis was done with Kaplan-Meier and Cox proportional hazards for a composite outcome of end-stage kidney disease or death.

PUB357
Obinutuzumab in Recurrent Focal Segmental Glomerulosclerosis After Pediatric Kidney Transplantation: A Case Report
Marina Vivarelli, Luca Antonucci, Francesca Semeraro, Manuela Colucci, Martina Riganati, Raffaella Labbadia, Andrea Cappoli, Francesca Emma, Isabella Guzzo. Ospedale Pediatrico Bambino Gesu, Roma, Italy.

Introduction: Recurrence of immuno-mediated forms of FSGS after kidney transplant occurs in about 30% of cases and is often associated with poor outcome. Currently, standardized therapeutic protocols are not available. Possible options are plasmapheresis, rituximab, cyclosporine, and immunoadsorption. We describe a pediatric FSGS recurrence treated with the 2nd generation humanized anti-CD20 antibody obinutuzumab.

Case Description: A 3 years-old child with multidrug-resistant FSGS underwent a related-donor kidney transplant. Twelve hours after anastomosis, he developed a severe anuric FSGS recurrence (Fig.1a), treated with high doses of steroids, cyclosporine, rituximab, and plasmapheresis, with poor response. About 3 weeks later, obinutuzumab was given as rescue therapy. One week after drug infusion, proteinuria became sub-nephritic (48 mg/dL), and kidney function normalized (Fig.1a). After about 7 months on plasmapheresis and standard immunosuppression, proteinuria was absent with a subsequent reduction in plasmapheresis' frequency. A complete and lasting depletion of total CD19+ and memory CD19+CD27+ B cells was maintained for more than 12 months after obinutuzumab infusion (Fig.1b). About one year after transplant, plasmapheresis was discontinued. One month later, in parallel with B-cell reappearance, low-grade proteinuria reappeared (Fig.1a). Therefore, a second rituximab infusion associated with plasmapheresis was planned.

Discussion: To our knowledge, this is the first case of pediatric post-transplant FSGS recurrence treated with obinutuzumab, which determined remission and long-lasting B-cell depletion. Further clinical trials are needed to establish the real efficacy of this approach.
Ravulizumab De Novo in Pediatric Patients with Atypical Hemolytic Uremic Syndrome (aHUS): First Worldwide Cases

Alvaro Madrid Aris,1 Pedro Arango Sancho,1,2 Hospitale Sant Joan de Deu, Barcelona, Spain; 2Pediatric Cancer Center Barcelona, Barcelona, Spain.

Introduction: Ravulizumab is a long-acting C5 inhibitor that has recently demonstrated its effectiveness for the control of hemolytic uremic syndrome compared to eculizumab, allowing average annual infusion times (up to 70 percent less). There is still no evidence in the literature of naive treatment with this drug in pediatrics. Our objective is to present the first two cases worldwide using de novo Ravulizumab (in the onset of the disease and post-kidney transplant).

Case Description: 13-year-old girl with history of bloody stools, vomiting and compromise of consciousness with TMA, AKI III evolves to anuria and convulsive shock in the immediate post-transplantation. In the first case we observed a functional recovery to normal renal function with normal creatinine value at discharge. Protein/Creatinine urine ratio was 0.2 at discharge.

Due to persistent TMA and requirement of renal replacement therapy (RRT), ravulizumab was started with a loading dose (2400mg) and a second one after 2 weeks. The need for RRT ceased with improvement of hemolysis and renal function. Genetic:CFHR1/CFHR1 deletion. Case 2: 7-year-old girl in chronic hemodialysis secondary to aHUS (CD46 mutation) was admitted for kidney transplant from a living donor. Low-intermediate deletion. Case 2: 7-year-old girl in chronic hemodialysis secondary to aHUS (CD46 mutation) was admitted for kidney transplant from a living donor.

The patients with mutations in CD46 and CD55 are critical for maintaining tolerance in immunoglobulin A nephropathy (IgAN). They achieved partial clinical remission after this treatment. Serum CD4-positive and CD8-positive cells were elevated in one case, but Foxp3 levels showed no apparent change in the two cases. T-cell markers in HLA class II cells were increased to a maximum of 8mg/mg (negative DSA levels). The option of renal biopsy showed normal ADAMTS-13, negative direct Coombs and decreased complement. Histopathological findings of tonsils showed infiltration with both CD4-positive and CD8-positive cells was prominent in interfollicular areas. Cytokinin staining showed that the layer of crypt epithelium was replaced by squamous epithelium.

Discussion: Take-away lesson The efficacy of tonsillectomy for IgAN is thought to be due to the regulation of tolerance abnormalities. Replacement from the layer of crypt epithelium implies the involution of lymphoepithelial spongiosus. The distribution of CD4 and CD8 is characteristic in the tonsils of those with IgAN. Our objective is to present the first two pediatric cases worldwide using de novo Ravulizumab (in the onset of the disease and post-kidney transplant).

PUB359
Tolerance and Pathologic Tonsillar Findings Change in Intractable Immunoglobulin A Vasculitis (IgAV) with Nephritis in Two Child Cases


Introduction: Background Several studies have reported that regulatory T (Treg) cells are critical for maintaining tolerance in immunoglobulin A nephropathy (IgAN). We list the tolerance changes and the pathologic tonsillar features in 2 cases (a 12-year-old girl; ISKD grade IVA and a 14-year-old girl; grade IIIB) with intractable IgAV nephritis who underwent tonsillectomy for disease control. Serum CD4-positive and CD25-positive cells, and Foxp3 levels were detected. In addition, immunohistochemical staining for tonsillar CD4, CD8, HLA-DR, and CD151, and cytokeratin was performed.

Case Description: Outcomes Additional tonsillectomy decreased proteinuria and they achieved partial clinical remission after this treatment. Serum CD4-positive and CD25-positive cells were elevated in one case, but Foxp3 levels showed no apparent change in the two cases. T-cell markers in HLA class II cells were increased to a maximum of 8mg/mg (negative DSA levels). The option of renal biopsy showed normal ADAMTS-13, negative direct Coombs and decreased complement. Histopathological findings of tonsils showed infiltration with both CD4-positive and CD8-positive cells was prominent in interfollicular areas. Cytokinin staining showed that the layer of crypt epithelium was replaced by squamous epithelium.

Discussion: Take-away lesson The efficacy of tonsillectomy for IgAN is thought to be due to the regulation of tolerance abnormalities. Replacement from the layer of crypt epithelium implies the involution of lymphoepithelial spongiosus. The distribution of CD4 and CD8 is characteristic in the tonsils of those with IgAN. Our objective is to present the first two pediatric cases worldwide using de novo Ravulizumab (in the onset of the disease and post-kidney transplant).

PUB360
A Boy with Henoch-Schönlein Purpura Nephritis and Mutations in CD151

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Introduction: Glucocorticoid (GC) and immunosuppressants (IS) have been found to be effective on treating Henoch-Schönlein purpura nephritis (HSPN). The children with HSPN may be with genetic defect when they don’t respond to GC and IS. Here we report a boy with HSPN, who didn’t respond to GC and IS, carried mutations in the CD151 gene.

Case Description: A 15-year-old boy with no family history of kidney disease was admitted for evaluation of recurrent proteinuria in 2022. He initially presented with abdominal pain and purpuric rash on his bilateral lower legs in 2014, and developed recurrent proteinuria. His first renal biopsy tissues in 2018 revealed HSPN with mesangial deposits of IgA together with IgM by immunofluorescence technique. However, his proteinuria was negative to 3+ for many years although he used mycophenolate mofetil and prednisone. The second renal biopsy was performed in 2022, and the renal tissues revealed focal segmental glomerulosclerosis (FSGS) with no evidence of immunocomplex deposition. A homozygous mutation in the CD151 gene, c.606C>A, p.Y202*, 52, was identified using whole-exome sequencing in the boy, and the same heterozygous mutation was in his parents. Then, the boy was treated with a combination of benazepril and losartan, and his proteinuria reduced to 1+ - 2+. They achieved partial clinical remission after this treatment. Serum CD4-positive and Foxp3 levels showed no apparent change in the two cases. T-cell markers in HLA class II cells were increased to a maximum of 8mg/mg (negative DSA levels). The option of renal biopsy showed normal ADAMTS-13, negative direct Coombs and decreased complement. Histopathological findings of tonsils showed infiltration with both CD4-positive and CD8-positive cells was prominent in interfollicular areas. Cytokinin staining showed that the layer of crypt epithelium was replaced by squamous epithelium.

Discussion: The boy with HSPN, based on his abdominal pain, purpuric rash on his bilateral lower legs, proteinuria and first renal pathology, didn’t respond to mycophenolate mofetil and prednisone, so we performed the second renal biopsy. The second renal pathology revealed FSGS with no evidence of immunocomplex deposition, which is inconsistent with HSPN, therefore we suspected the boy may be with genetic defect. A homozygous missense mutation in the CD151 gene identified in the boy confirmed our hypothesis. CD151 encoded by the CD151 gene is implicated in the integrity of basement membranes in kidney, skin and inner ear. Mutations in the CD151 gene can cause isolated proteinuria and FSGS as well. The patients with mutations in CD151 and nephrotic syndrome have no response to GC and IS, which could explain that the boy had persistent proteinuria for many years with treatment with both mycophenolate mofetil and prednisone. In conclusion, the children with HSPN is necessary to detect genetic defect when they don’t respond to GC and IS.

PUB361
Implementing a Structured Transition from Pediatric to Adult Care Can Impact Clinical Outcomes in Young Adult Kidney Transplant Recipients

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Background: The transition period between pediatric and adult care is a challenging time marked with high risk and vulnerability, and is described as the period with the highest rate of graft loss in young adult kidney transplant recipients. Data are limited regarding HCT outcomes, but some studies suggest improvements in patient outcomes with a structured transition protocol.

Methods: A retrospective chart review of patients who transitioned from Rady Children’s Hospital San Diego to adult care at UCSD Health transplant clinic from the years 2020-2023 is being performed to examine metrics such as change in creatinine
and blood pressure during this period of transition. We will look at outcomes following the implementation of our transitions program which includes structured transition-specific visits to assess and address individual areas of need before they transition.

**Results:** Our initial study population consists of 24 patients, 50% female. The data show a weak positive correlation between days from last RCHSD clinic visit and first UCSD visit and blood pressure elevation that is not statistically significant (rho=0.393, p=0.071). The data show a weak positive correlation with an increase in the number of days between last RCHSD clinic visit and first UCSD visit and increasing creatinine which is not statistically significant (rho=0.399, p=0.073).

**Conclusions:** Further research will be conducted to determine if an established kidney transplant transitions program can decrease gaps in care and improve outcomes in young adult patients with a kidney transplant.

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**PUB362**

**Horseshoe Kidney with Childhood Recurrent Urinary Tract Infection: A Harbinger of CKD Progression and Opportunity for Interventions**

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**Introduction:** Congenital anomalies of the kidney and urinary tract (CAKUT) constitute the most common malformations diagnosed prenatally and account for most chronic kidney disease (CKD) in children. We report a case of a woman with childhood recurrent urinary tract infections (UTIs) who was incidentally diagnosed with a horseshoe kidney in adulthood complicated by advanced CKD.

**Case Description:** A 62-year-old woman with non-nephrotic range proteinuric stage 4 CKD secondary to CAKUT was referred for kidney transplant evaluation. From age 6 months to 12 years old, she experienced recurrent UTIs and persistent borderline elevated blood pressure yet was never seen by a pediatric nephrologist. At age 52, she was found to have abnormal kidney function during a pre-operative laboratory procedure, and an abdominal and pelvic MRI showed an atrophic right kidney, bilateral nephrolithiasis, bilateral renal cysts, and a horseshoe kidney (Figure 1). While the frequency of UTIs decreased, with the most recent episode of UTI 5 years prior, her eGFR had progressively declined from 24 to 16 ml/min/1.73 m² over a 5-year period.

**Discussion:** Although one-third of patients with horseshoe kidneys are asymptomatic and are incidentally diagnosed in adulthood, our patient presented with a horseshoe kidney in adulthood complicated by advanced CKD.

**Conclusions:** Further research will be conducted to determine if an established kidney transplant transitions program can decrease gaps in care and improve outcomes in young adult patients with a kidney transplant.

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**PUB363**

**AKI with COVID-19 Infection due to Drug Interaction of Tacrolimus and Nirmatrelvir/Ritonavir**


**Background:** The mortality of SARS-CoV-2 infection of kidney transplant recipients(KTR) is higher than that of general population. Nirmatrelvir(RN) is a good option for outpatient-based antiviral treatment by reducing mortality.

**Methods:** However, RN is metabolized mainly by cytochrome 3A4(CYP3A4), which also metabolize calcineurin inhibitor(CNI). Hence, co-administration of these two drug could results in drug interaction increasing serum tacrolimus(TAC) level almost 50 times. We report serial three cases of KTR prescribed NR with/without AKI.

**Results:** In case 1, the patient took these two drug together, inducing acute kidney injury(AKI) due to CNI toxicity. After discontinuation of TAC, renal function was recovered. Contrastively, in case 2, three days of simultaneous administration of NR and TAC led to AK, progressed even though discontinuation of TAC. Intravenous hydration with cessation of TAC improved renal function. In case 3, patient was informed to stop TAC for 5-days with NR initiation, resulting harmless to renal function with stables serum TAC concentration after NR taking.

**Conclusions:** Instruction for patient for drug interaction of TAC with NR is important for KTR.

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**Baseline Characteristics**

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</table>

**Conclusions:** Instruction for patient for drug interaction of TAC with NR is important for KTR.
PUB364

**Title:** SGLT2 Inhibitors in Membranous Nephropathy: Worthy of Consideration?

**Authors:** Sehaipreet Kaur, Sulekho Egal, Ikete S. Jabbal, Fernando M. Abanilla.

**AdventHealth Sebring, Sebring, FL**

**Introduction:** SGLT2 inhibitors have encouraging evidence supporting their benefits beyond diabetic kidney disease, as seen in DAPA-CKD and EMPA-KIDNEY trials as well as case reports on IgA nephropathy and Alport syndrome. We describe the early results of SGLT2i therapy in 2 patients with membranous nephropathy (MN), which, we believe, has not yet been reported in the literature.

**Case Description:** A 67-year-old female with CKD stage 3b, PL2AR negative MN, sepsis, and AKI, developed increasing proteinuria (baseline 1.6 to 3.2 g/g UACR) despite irbesartan therapy. The addition of 10 mg empagliflozin daily improved UACR to 3.1 from 3.2 g/g over 5 days of hospitalization. A 68-year-old non-diabetic male who presented with scrotal edema, chronic bilateral leg swelling, and massive proteinuria of 8.8 g/g UP CR was diagnosed with nephrotic syndrome with PL2AR negative MN on renal biopsy. Increasing UPCR to 12.5 g/g prompted the addition of 10 mg empagliflozin daily after optimisation of lisinopril to 40 mg daily. However, 2 months of follow-up resulted in worsening of proteinuria to 15.8 g/g. For both patients, proteinuria serological workup was negative with workup for malignancy pending.

**Discussion:** As illustrated in Image 1, SGLT2i can synergize with RASi to improve proteinuria, which warrants their exploration in MN. While patient 1 had significant improvement in renal function over 5 days of treatment but empagliflozin could not be continued due to clinical inertia, patient 2 improved clinically but had an early negative response to proteinuria despite 2 months of dual therapy with empagliflozin and lisinopril. An underlying secondary malignancy or other causes of secondary MN could be attributable. Our case series was limited by small sample size, medication non-adherence, and absence of long-term follow-up. Nonetheless, this calls for the medical community’s attention to explore the use of SGLT2i in MN and other proteinuric non-DKD using prospective, randomized controlled trials.

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

Underline represents presenting author.

PUB365

**Title:** Baclofen Toxicity in Patients with ESRD on Hemodialysis (HD)

**Authors:** Ashraf A. Suliman, Irtiza Hasan, Ronald L. Mars, Charles W. Heilig.

**University of Florida College of Medicine - Jacksonville, Jacksonville, FL.**

**Introduction:** Baclofen, a commonly prescribed muscle relaxant is a GABA agonist with potential toxicity in patients with CKD.

**Case Description:** We report three cases of potential Baclofen toxicity in patients with ESRD on HD. The 1st case was a 68-year-old female with PMH of DM, HTN & ESRD on HD, presented with a fall associated with altered mental status (AMS) & inability to move both right extremities, a GCS of 6 & intubated. Home medications included Carvedilol, Doxazosin, Gabapentin (300 mg BID), Hydralazine, Baclofen (5 mg TDS) & Nifedipine. Brain CT without acute abnormality but MRI revealed a small 3 mm left parieto-occipital lobe subdural hematoma with no mass effect or intercurrent hemorrhage with no plan for intervention. The 2nd case was a 50-year-old male with PMH of HTN, CVA, Paroxysmal A Fib & ESRD on HD, presented with AMS, GCS of 15 & no intracranial abnormality. Home medications included Amiodipine, Baclofen (10 mg BID), Carvedilol, Losartan & Sevelamer. Another case of a 66-year-old male with PMH of HIV, HTN, ESRD on HD, transverse myelitis with lower extremity weakness, presented with AMS. Initial workup was negative. Clinical status later improved. However, a week later he became disoriented & unable to follow commands after he was started on baclofen 10 mg bid for muscle spasms. Workup was inconclusive. All of the above cases had no other potential causes for AMS including infection or any signs of uremic encephalopathy other than use of Gabapentin by one of the patients. In the first two cases, patients had missed a couple of dialysis (HD) sessions. Baclofen toxicity was suspected in all cases, exacerbated by missed HD treatments in two cases. There was marked improvement of mentation soon after resumption of HD.

**Discussion:** Baclofen is a lipophilic compound which is primarily absorbed in the GI & largely excreted by the kidneys. Baclofen toxicity is rare in the general population. It manifest rapidly in patients with impaired renal function who receive this medication. AMS is one of the major manifestations of toxicity, developing with as little as a single dose. However, due to small molecular weight, low volume of distribution & relatively low protein binding, Baclofen is easily dialyzable. Although no medical inhibitor of Baclofen toxicity is available, hemodialysis was effective in treating this condition here, and is the preferred therapeutic modality.
days due to the lab’s lack of liquid/gas chromatography. Nephrology was consulted and recommended early component initiation of hemodialysis in the setting of severe acidemia, hyperkalemia, and AKI. Fomepizole was never given.

Discussion: A high anion gap metabolic acidosis of unknown cause, acute kidney injury, and an increased serum osmolal gap established a high suspicion for toxic alcohol ingestion in this patient. Nephrology appropriately initiated emergent hemodialysis urgently, however, the administration of fomepizole was deferred pending a definitive diagnosis via serum concentration of toxic alcohols using high pressure liquid chromatography. This result was not available to providers for several days as it is often the case in small community hospitals. Delays in treating toxic alcohol poisonings lead to worse outcomes, therefore therapy with the antidote should be initiated rapidly when unexplained high anion gap metabolic acidosis with high osmolal gap is present, as was the case with this patient. To improve treatment outcomes there should be a standard treatment algorithm agreed upon by each hospital as to when and how fomepizole should be administered without a definitive diagnosis.

 PUB367
Prevalence, Clinical Profile and Risk Factors of Cefepime Induced Neurotoxicity among Chronic Kidney Disease Patients in a Tertiary Hospital in Southern Philippines
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Background: Cefepime induced neurotoxicity is a clinically diagnosed adverse event that presents in vast array of neurologic symptoms, from mild cognitive and behavioural changes to seizure and coma. Although a highly recognized clinical adverse event the diagnosis and standard clinical criteria is still lacking. We aimed to characterize the clinical profile and possible associated risk factors of cefepime induced neurotoxicity among Filipino chronic kidney disease patients.

Methods: This is a retrospective, case control study of adult chronic kidney disease patients treated with Cefepime in a tertiary hospital in Southern Philippines from January 2019 to March 2022. Patients were treated with Cefepime with new onset neurologic deterioration were included while those with baseline neurologic abnormality or alternative cause for neurologic symptoms as ruled out by additional diagnostic tests were excluded. The Naranjo scale was utilized to establish the likelihood of causality.

Results: A total of 263 medical charts were reviewed but only 132 cases were included. Majority of patients were on hemodialysis (126), six of whom developed neurotoxicity. The overall prevalence of cefepime induced neurotoxicity is 4.5%, with higher prevalence rate at 10% among patients given non renally adjusted dose. The mean age of patients CIN was 54 ± 14, predominantly females (5 vs 1). Half of the cohort presented with agitation while the other 50% had decreased level of consciousness. The appearance of symptoms has a latency period of 5 days following initiation of therapy. Five (5) patients responded to hemodialysis and discontinuation of cefepime, while one (1) patient responded to appropriate dose adjustment. Resolution of symptoms was observed 2 days after providing therapy. All patients (6) recovered without neurologic deficit. Binary regression analysis identified female gender (OR 9.65) and congestive heart failure (OR 12.1) increased the likelihood of cefepime neurotoxicity.

Conclusions: Overall prevalence of cefepime induced neurotoxicity is comparable to preceding studies, with higher prevalence rate among patients who were given non-really adjusted dose. Possible additional risk factors for CIN were female gender and heart failure.

 PUB368
Higher Intragraft Granzyme-B+ and PhosphoSMD3+ Cell Staining Are Associated with Inflammatory Intestinal Fibrosis and Tubular Atrophy in Renal Allograft Recipients
Narayan Prasad, Brijesh Yadav, Vinita Agrawal. Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.
Background: Inflammatory intestinal fibrosis and tubular atrophy (IIF/TA), a histological lesion reported in late biopsy, is associated with graft survival. Cytotoxic T cell secrets Granzyme-B, cleaves cytoketone protein, and activates pro-IL-1β, and TGF-β into their active form, leading to inflammation, fibrosis, and apoptosis of cells. Association of Granzyme-B+ cytotoxic T cell and phosphoSMD-3 expression has not been studied in IIF/TA in depth. We studied the circulating and intragraft Granzyme-B+ cytotoxic-T cells and phosphoSMD3+ cell in renal transplant patients with biopsy proven I-IFTA.

Methods: The circulating frequency of CD3+CD8+Granzyme-B+ cytotoxic T (CTC) was measured by flow cytometry; serum and PBMCs culture supernatants Granzyme-B and cytokines TGF-β, IL-1β level by the ELISA, Intragraft Granzyme-B mRNA transcript expression by the RT-PCR and Cefepime-B, pSMD3- cell were analyzed by immunohistochemistry. Independent T-test for continuous variables and Pearson correlation were applied for different variables.

Results: The circulating frequency of cytotoxic T cell (CD7 CD8 Granzyme-B+ in SFG vs IIFTA was (27.9±6.85 vs 23.1±3.85%, p=0.011), CD3 T cell was (66.08±6.85 vs 65.18±3.95%, p=0.68), CD3 CD8 T cell was (37.29±11 vs 34.68±4.53%, p=0.28). Serum Granzyme-B level was in SFG vs IIFTA was (100.82±22.81 vs 130.32±46.96, p=0.01), phosphoSMD3 level was (37.81±9.2 vs 6.73±4.21, p=0.005). The intragraft Granzyme-B+ cell was positively correlated with pSMD3+ cell (r=0.31, p=0.047).

Conclusions: Our technique allows clinicians and researchers in the field to be able to identify Apol1 genotyping with QPCR in 3-4 hours. Retrospective studies might allow to compare these findings with long term allograft rejection and can create an estimation for patients for early-stage stage transplant outcomes with haplotype evaluation.

 PUB370
Unveiling a Protective Role of Endomucin in Endothelial Cells During Cefepime Induced Allograft Rejection
Ahdum Halawi,1,2 Connor J. O’Brien,1 Tamara Merbej,1 Sour K. Younis,1 Rania El Fekih,1 Sacha A. De Serres,1 Jamil R. Azzi.1 Brigham and Women’s Hospital, Boston, MA; 3Mount Auburn Hospital, Cambridge, MA; 4Universite Laval, Quebec, QC, Canada.
Background: Understanding the role of endothelial cells in autoimmune and alloimmune mediated kidney diseases promises to develop more targeted therapies. Our single nuclei RNA sequencing (snRNAseq) identified an unexpected role for endothelial cells in cellular rejection. Notably, we reported a novel role of endomucin (EMCN), a molecule known for its anti-adhesive and anti-inflammatory properties, in kidney allograft rejection.

Methods: We performed snRNAseq of human kidney allografts with non-rejection, borderline rejection, and T-cell mediated rejection (TCMR) based on Banff criteria. We performed pathway analysis focusing on immune and endothelial cells. As validation for our endothelial cells findings, we isolated and cultured blood outgrowth endothelial cells (BOECs) from different patients using our optimized protocol (S Beland et al., JASN 2023). We stimulated BOECs with IFNγ, TNFa, and allologeneic PBMCs. We studied the expression of EMCN and ICAM1 over time under different stimulation using Flow cytometry.

Results: Our snRNAseq showed that TCMR samples had enrichment for allograft rejection pathway, suggesting that our borderline sample reflects an early rejection. Hence, this allows for studying the early stages of rejection. Pathway analysis of endothelial cells (ECs) of borderline and non-rejecting samples showed that focal adhesion and IFN-gamma pathways were significantly enriched compared to TCMR. Major genes related

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
to focal adhesion were upregulated in borderline, suggesting a role of focal adhesion as a physical obstacle to immune invasion. ECs upregulated EMCN in early rejection, suggesting a critical role in protecting against T cell adhesion and infiltration in the allograft. EMCN was then downregulated when rejection advanced. Similarly, in our in vitro model, activated human ECs downregulated the constitutive expression of EMCN when stimulated with allogeneic PBMCs, contrary to ICAM1, which was significantly upregulated. This observation was not seen when ECs were stimulated by IFNg and TNFa, suggesting that the effect of immune cells on ECs is not mediated by these cytokines.

Conclusions: Our data showed that late during rejection, focal adhesion and EMCN are downregulated in endothelial cells suggesting a possible role in protecting the graft from immune invasion and rejection.

PUB371

Variability in Commensal Gut Microbiota Associated with Tacrolimus Metabolism in a Longitudinal Kidney Transplant Cohort Study
Guillaume C. Onyeahula,1,2 Duy Vo,1 Henry Madden,1 Julia J. Munoz,2 Bryan P. Brito Sanchez,1 Moataz Mohamed,1 Abdelrahman Saq,2 Sarah Elmer,2 Christopher Staley,2 Casey R. Dorr,1,2 Levi Teigen,2 BaoLin Wu,1 Weilhua Guan,1 Rasha El-Rifai,1 William S. Oetting,2 Arthur J. Matas,2 Pamala A. Jacobson,2 Ayaj K. Israni,1,2 Hennepin Healthcare Research Institute, Minneapolis, MN; 1University of Minnesota Twin Cities, Minneapolis, MN; 2University of California Irvine, Irvine, CA.

Background: Tacrolimus (TAC), an immunosuppressant used with mycophenolate mofetil (MMF), has a narrow therapeutic range which is associated with outcomes in kidney transplant recipients (KTRs). Evidence of an association with the gut microbiome and TAC metabolism is emerging. Multiple commensal gut bacteria, including Faecalibacterium prausnitzii, have been shown to metabolize TAC to a less potent metabolite which is less able to induce apoptosis. We hypothesized that the gut microbiome of TAC metabolizers would exhibit high variability in TAC metabolizers.

Methods: We evaluated the relative abundance of 22 known gut microbial TAC metabolizers in a cohort of 40 KTRs who had stool samples collected at 60 and 120 days post-transplant (tx). All KTRs received oral MMF and TAC twice daily. Microbiota were characterized by sequencing the V4 variable region of the 16S rRNA gene.

Results: We detected 15 out of 22 previously reported tacrolimus metabolizers among the gut microbiota, with the most abundant being Faecalibacterium prausnitzii at 7.50% average relative abundance at 60 days post-tx (range 0.06% – 22.15%) (Fig 1A) and 7.95% (range 0.02 – 20.45%) at 120 days post-tx (Fig 1B). We did not find a statistically significant change in relative abundance of these organisms between 60 and 120 days post-transplant (Fig 1C, P< 0.005 for all microbiota). Overall, these 15 TAC metabolizing microbiota accounted for 15.6% (range 0.1 – 41.1%) of the total gut microbiome composition at 60 days, and 14.1% (range 0.2 – 37.6%) at 120 days.

Conclusions: The gut microbial composition of TAC metabolizers exhibits high variability post-tx, with Faecalibacterium prausnitzii as a predominant member. The association between the abundance of these organisms and TAC interpatient variability should be studied to understand the unexplained variation in TAC concentrations among KTRs.

Funding: NIDDK Support

PUB372

Donor LIMS1/GCC2 Region Is An Important Determinant of Allograft Kidney Response to Ischemia and Reperfusion

Background: LIMS1 rs983403-G influences LIMS1 and GCC2 expression and associated with kidney allograft rejection. Using non-utilized human kidneys, we investigated the effects of ischemia reperfusion injury (IRI) on LIMS1, GCC2, and associated gene expressions by normothermic machine perfusion (NMP) model and compared with cold storage (CS).

Methods: Non-utilized deceased donor kidney pairs underwent 6-hr NMP (n=6) and CS (n=6). Perfusion, biochemical, and histologic parameters were recorded. NMP was compared with CS in paired donor kidneys using simulated transplantation with allogeneic red blood cells, followed by assessment of the gene expression. Genotyping for rs983403 variant performed by Sanger sequencing.

Results: Kidneys were successfully perfused with evidence of urine output (Table 1). Transcriptional analyses showed induction of GCC2, HIF-1α and KIM-1 expression in kidneys with rs983403-GG genotype compared to kidneys with rs983403 AG/AA (rejection risk donor genotype) under NMP (p<0.017, p<0.001 and p<0.17, respectively) (Fig 1a-b). Change in GCC2 expression after 6 hrs of NMP was significantly correlated with HIF-1α in LIMS1 (r=0.94, p=0.005), KIM1 (r=0.83, p<0.04), TGF-beta1 (r=0.89, p=0.019) and HIF-1α (r=0.945, p=0.005) expressions. Change in GCC2 expression during NMP was not correlated with donor characteristics including age, KDPI, Remuzzi score, cold ischemia time and urine output.

Conclusions: NMP significantly increased the GCC2 expression in kidneys with LIMS1 rs983403-GG variant. Donor rs983403 genotype is important in the transcriptomic response to IRI and understanding the interaction between LIMS1, GCC2 and HIF-1α will help to develop genotype and pathway specific therapies for rejection.

Funding: Private Foundation Support

PUB373

Cognitive Improvement in ESRD Patients After Renal Transplantation: A Prospective Observational Study
Srimay Sashidhren1, Vijay K. Khurana2, Medanta The Medicity, Gurgaon, India; 2Epitome Kidney and Urology Institute, New Delhi, India.

Background: Although there is a well-established survival benefit of renal transplant, the evidence of its effect on cognitive function is limited and not entirely consistent. Up to 30 - 70 % of end stage renal disease patients are reported to have cognitive deficits. The etiology of cognitive impairment in chronic kidney disease patients is multifactorial. Kidney transplantation can correct the metabolic derangements and eliminate the fluid and oncotic shifts that patients can experience on dialysis; however, cognitive impairments still persist post-transplant. Further research is warranted to better understand the impact of kidney transplant on a wide array of cognitive domains.

Methods: 100 patients, age between 18 to 60 years who underwent renal transplantation in Medanta Hospital, India were prospectively studied from September, 2021 to December 2022. The aim was to determine the proportion of patients showing cognitive improvement 3 months and 6 months post renal transplant using Montreal Cognitive Assessment (MoCA) and to find the cognitive domains which show significant improvement 3 months and 6 months post-transplant.

Results: Proportion of patients showing cognitive improvement 3 months and 6 months post transplant was 26% and 56%, respectively. The mean MoCA score (out of total of 30) at pre transplant, at 3 months and 6 months post-transplant was 24.08 ± 3.08, 24.32 ± 2.90 and 25.14 ± 3.05, respectively. Mean MoCA score after 6 months of transplant, when compared to the mean score at pre transplant level was found to be statistically significant (p value <0.001). Delayed recall showed significant improvement 3 months and 6 months post-transplant (p value <0.001 and < 0.001 respectively).

Conclusions: Significant cognitive improvement was seen 6 months post renal transplant. Delayed recall showed significant improvement 3 months and 6 months post transplant.
LECT2 Amyloidosis in Allografts

Introduction: LECT2 deposits are subclinical. The risk of transplanting an allograft with this condition is not zero.

Case Description: In 2011, a 26-year-old male was found with a serum (Cr) of 1.6 and a protein in the urine of 2.37 g/day. The histopathology reported glomerulonephritis IgA. Years later, patients brother was ruled out as a donor due to proteinuria, and the cross-match test was performed with the patients father. In 2022, he underwent kidney transplant but two months later due to proteinuria, a renal graft biopsy was performed that showed mild LECT2 FIAT amyloidosis.

Discussion: LECT-2 is a chemotactic factor for neutrophils. It is involved in cell proliferation, inflammation, immunomodulation, and carcinogenesis. Its gene is located in a chromosome that harbors a cluster of genes involved in immune regulation. LECT-2 is produced in the liver and increases in response to proinflammatory stimuli such as hepatic steatosis. ALECT2 can be found in association with other types of amyloidosis, plasma cell dyscrasia, membranous nephropathy, carcinomas, or autoimmune disease. Amyloidosis restricted to the kidney is uncommon. The 88%-92% of cases reported are in Hispanics. The median age is 69 years old, and men and women are equally affected. The proteinuria could be not present in 21%, nephrotic range proteinuria was noted in only 33%, and when it is present, you need to consider concomitant nephropathy (as IgA nephropathy), and end-stage renal disease ranges from approximately 30% to 40%. In our patient, the time for a novo or recurrent amyloidosis is too short. The Hispanic background in the father and the proteinuria in his brother, lean us towards a case of familiar donor-derived ALECT2. It has been reported that ALECT2 does not interfere with the allograft function.

Risks and Harms of Minimizing Total Immunosuppression in Stable Kidney Transplant Recipients
Bruno Watschinger, Bernhard Gromann, Peter Hlavac, Robin Ristl, Bettina Kroyer, Katharina Hohenstein-Scheibenecker. Medizinische Universitat Wien, Wien, Austria.

Background: While minimizing steroids or calcineurin inhibitors was advocated to be advantageous for kidney transplant outcomes, the effect of total cumulative immunosuppression on patient/allograft survival has not yet been evaluated. In our retrospective single center study, we investigated the long-term impact of cumulative immunosuppression exposure in a large cohort of patients with stable graft function.

Methods: 887 stable patients (s-creatinine <2 mg/dl @ 1 yr and stable GFR slope in the preceding 3 months, transplanted from 1/2000 to 12/2012 and followed exclusively at our institution; median follow-up 6, 3 (1-15,3) yrs were studied. Graft function and immunosuppressive (IS) therapy were recorded at 84.140 patient visits. Individual drug exposure was calculated by grading each drug (no=0, low=1, medium=2, high dose=3) and then adding single drug grades (in mono, dual, triple therapies) to a cumulative score that represents a low (0-3), intermediate (4-6) or high (7-9) total IS exposure load. This load, calculated over time, was used in adjusted Cox-regression models with time-dependent covariates, together with Kaplan-Meier survival analysis. Patient/allograft survival was compared between the 3 exposure groups.

Results: 84 of these stable patients (9.5%) lost their graft during the observation period, 89 patients (10%) died with a functioning graft. In single drug analysis, variant exposure levels of steroids or calcineurin inhibitors did not show differences in graft and patient survival. Conversely, cumulative exposure was associated with differentiated outcomes. An intermediate total IS load yielded the best graft survival, while patients with low (HR = 4.68; CI 1.6-13.9, p<0.005) or high (HR = 2.08; CI 1.2-3.6, p=0.008) cumulative IS exposure had a significantly elevated risk for graft failure. Patient survival did not differ between the groups.

Conclusions: Analyzing the effects of single drugs does not capture the risk for graft loss in patients with stable allograft function @ 1 yr. High and low cumulative total immunosuppression exposures are independent risk factors for graft failure but do not impact patient survival. Thus, the degree of total, cumulative immunosuppression should be carefully considered, whenever individual immunosuppressants are minimized.
PUB376

Successful Treatment of Kidney Transplant Rejection in the Setting of COVID-19 Infection
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Introduction: Kidney transplant recipients are at increased risk for complications from COVID-19 infection. There are no guidelines for rejection treatment in the setting of COVID-19 infection.

Case Description: A 44-year-old male with a history of living donor kidney transplant underwent a kidney biopsy due to rising creatinine that showed features suspicious for chronic active antibody-mediated rejection and acute vascular rejection 2A, with De novo class II DSAs emergence. The patient tested positive for COVID-19 and was asymptomatic with normal CXR. Cycle threshold was 21 indicating high viral replication, nucleocapsid antibodies were negative, but he had a suitable spike antibodies titer. Rejection was treated with pulse steroids, IVIg, and immunosuppression optimization. COVID-19 was treated with three doses of remdesivir. Two weeks later, the patient was treated with thymoglobulin, PLEX, and rituximab. Follow-up biopsy showed no rejection, and creatinine improved.

Discussion: Kidney transplant rejection with active COVID-19 infection is challenging and requires an individualized approach. Rejection treatment may lead to clinical deterioration, but untreated rejection may lead to graft failure. COVID-19 infection severity can be assessed by symptoms, chest images, cycle threshold to assess viral replication, anti-nucleocapsid antibodies as a marker for natural immunity against COVID-19, and spike antibodies as a measure of vaccine. Dexamethasone is used in viral replication, anti-nucleocapsid antibodies were negative, but he had a suitable spike antibodies titer. Rejection was treated with pulse steroids, IVIg, and immunosuppression optimization. COVID-19 was treated with three doses of remdesivir. Two weeks later, the patient was treated with thymoglobulin, PLEX, and rituximab. Follow-up biopsy showed no rejection, and creatinine improved.

PUB378

Should We Treat Asymptomatic Bacteriuria (ASB) in Post-Transplant Patients: A Systematic Review and Meta-Analysis
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Background: Urinary tract infections (UTIs) are the most common infectious complication in kidney transplant recipients (KTRs). Therefore, routine screening for and treatment of asymptomatic bacteriuria (ASB) is a common practice in post-kidney-transplant surveillance. However, little is known about the impact of antimicrobial therapy on ASB in KTRs. Some data reports overtreatment of ASB increases the risk of Clostridiodes difficile infection in this population. This study aimed to investigate whether antibiotics reduce the risk of UTI in KTR with ASB.

Methods: We searched MEDLINE, EMBASE and Cochrane Library from inception to March 2023. Included studies were RCTs or cohort studies that compared the incidence of UTI among treated ASB group versus untreated ASB group, using the random-effects calculation to compare the outcomes of UTI between the ASB group. Secondary outcomes included rate of graft rejection, hospitalization and mortality.

Results: Five RCTs and 6 cohort studies were included in the analysis with a total of 1750 subjects (699 treated ASB group and 1051 untreated ASB group). Our study showed that there was no statistically significant difference in incidence of UTI between the ASB group with treatment and ASB group without treatment (pooled RR 1.07, 95% CI 0.77-1.48, p=0.682, I2=16.9%), and all-cause mortality (pooled RR 1.20, 95% CI 0.96-1.51, p=0.110, I2=0%). Secondary outcome analysis revealed none of the outcomes were significantly different between these two groups including acute graft rejection rate (pooled RR 1.34, 95% CI 0.99-1.81, p=0.061, I2=23.8%), and all-cause mortality (pooled RR 1.20, 95% CI 0.96-1.51, p=0.110, I2=0%).

Conclusions: There is no difference of incidence of UTI, acute graft rejection rate, hospitalization rate, and all-cause mortality rate among treated ASB group versus untreated ASB group in kidney transplant recipient patients.
Successful Treatment of Ganciclovir-Resistant Cytomegalovirus (CMV) in Kidney Transplant Patients by Reduction of Immunosuppression and Withdrawal of Valganciclovir

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Introduction: Cytomegalovirus (CMV) is a common opportunistic infection after kidney transplant, causing increased morbidity, mortality, and graft loss. Resolution of infection requires both antiviral drugs and the host immune response. Ganciclovir (GCV) and Valganciclovir (VGCV) are currently 1st-line treatment, though GCV-resistant (GCV-R) CMV is increasingly reported. Treatment of GCV-R CMV infection involves use of 2nd-line agents Cidofovir, Foscarnet, or Maribavir. We propose a therapeutic strategy combining withdrawal of GCV with reduction in immunosuppression in refractory CMV replication.

Case Description: We describe 3 patients who underwent kidney transplantation from CMV-positive deceased donors. One seronegative recipient received VGCV prophylaxis. All developed CMV syndrome at a mean 40 days post-transplant. One patient developed chronic inflammatory demyelinating polyneuropathy, requiring intravenous immunoglobulin. In all cases mycophenolate mofetil was withdrawn and eGFR-adjusted doses of GCV or VGCV commenced. A persistent/increasing viral load following > 4 weeks led to resistance testing. A UL97 mutation was identified in all cases, one patient also demonstrating a UL54 mutation. GCV-R was diagnosed at a mean 160 days post-transplant. Given persistent viremia despite prolonged, adequate dose treatment, we decided to withdraw VGCV and monitor CMV viral load. By a mean of 60 days following VGCV withdrawal we could show a 50% reduction in viral load with no detectable GCV-R virus and ultimately a complete and sustained virological clearance in all patients.

Discussion: We demonstrate that in patients treated for CMV but with persistent GCV-R viremia without evidence of invasive CMV disease, VGCV withdrawal may be a therapeutic strategy, rather than commencement of problematic second-line drugs. GCV resistance is an adaptive process, we propose that discontinuing GCV significantly reduces selection pressure for UL97 mutants. As resistance mutations are often not maintained in the population after drug cessation, we believe this allows immune clearance of the CMV, perhaps aided by the improved white cell count on withdrawal of VGCV, as seen with our 3 cases. This approach potentially promotes re-population with a ‘wild type’ GCV-sensitive strain which may respond to subsequent challenge with GCV.

Tacrolimus-Induced Post-Transplant (pT) Thrombotic Microangiopathy (TMA)

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Introduction: TMA is a well-recognized complication that may occur at any time pT. It has a significant impact on graft and patient survival. TMA may result from the recurrence of the original disease. or denovo. Patient presentation with pT-TMA varies from localized form affect the graft and diagnosed only by biopsy, to systemic form, consist of hemolysis, thrombocytopenia and kidney injury. Here we present a case of TAC induce pT-TMA which was treated by changing tacrolimus(TAC) to cyclosporin(CsA) with plasma exchange(PLEX).

Case Description: A 33 year-old male known to have HTN, ESKD on regular hemodialysis for 9-months, before receiving living-related kidney transplant from his mother. Pre-transplant preparation yielded HLA matching of 50%. Negative lymphocytotoxicity by CDC. Induction with basiliximab (2 doses), pulse steroid, extended-release TAC0.2mg/kg/day) and mycophenolate mofetil (MMF)720mg*2. The early pT period went smoothly without delay in graft function. On the 4th pT day platelet count (PLT) dropped to 135000 with stable hemoglobin(hb), creatinine(Cr), and blood film(BF) showed NO schistocytes. The MMF dose decreased to 360mg*2, after which the PLT normalized and the patient was discharged with a Cr of 1.2mg/dl on:TAC-trough.

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

Evaluation of Indications for Genetic Assessment in Living Kidney Transplant Donors and Relevant Canadian Practices in Light of the Current International Guidelines

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Background: End stage renal disease (ESRD) is a prevalent condition with tendency for familial clustering. Living donor kidney transplantation is a superior treatment option, however, up to 40% of living kidney transplant donors (LKTDs) are biologically related to their recipients which subjects recipients to worse graft survival and donors to higher future risk of ESRD. Genetic testing of potential LKTDs could improve risk assessment and inform safety of donation, however, the strategies to evaluate these donors are still evolving. In this context, the standard use of genetic testing for LKTDs in Canada is unknown.

Methods: International guidelines were reviewed to compare the indications for genetic assessment of LKTDs. Surveys were sent to 25 Canadian adult transplant centers to examine their protocols and relevant practices for LKTDs genetic assessment.

Results: Response rate was 70%. Generally, donor’s family history of chronic kidney disease does not provide indication after informed discussion regarding risks and benefits. Autosomal Dominant Polycystic Kidney Disease, Alport syndrome and atypical Hemolytic Uremic Syndrome are the most frequently encountered conditions. Based on our case scenario questions, most centers assess LKTDs on a case-by-case basis and a minority have specific policies for donor genetic evaluation. The current Canadian transplant centers practices generally align with available international guidelines’ recommendations. The most cited guidelines are KDIGO, CSN/CST, and Kidney Paired Donation Protocol.

Conclusion: Canadian transplant centers have diverse strategies for genetic evaluation of LKTDs, mostly based on case-by-case assessment. Current recommendations are largely based on expert opinion due to lack of a reliable body of evidence and inefficiency of the current testing modalities. More studies are needed to provide stronger, evidence-based recommendations to ensure safety of donation. Prognostic risk assessment scores could be helpful for better quantification of long term effects of abnormal genetic testing.
Correlation of Te99m-Diethylene-Triamine-Pentaacetate (DTPA) Clearance to Long-Term Outcomes of Kidney Donors

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Background: Live kidney donors allow for gold-standard transplantation. Evaluating candidates entails assessment of kidney function. An eGFR <60 ml/min is a contraindication to donation. A method for assessing donors is measuring GFR (mGFR) based on radioisotope (Te99m-DTPA) clearance from the plasma. However, there is little evidence that pre-donation mGFR values to long term donor function.

Methods: This study included all donors (N=107) at one institution (1/17-12/20) with preoperative DTPA-Te99m and 2 year follow up eGFR. Serum creatinine eGFR calculations were performed. Pre-donation mGFR for donors with 2 year eGFR above and below 60 ml/min were compared using Wilcoxon rank sum test. A logistic regression model was fitted for the binary indicator of 2-year eGFR < 60 including a nonlinear effect for preoperative mGFR. To visualize the effect of preoperative mGFR on 2-year eGFR, the model-estimated probability (2-year eGFR > 60) was plotted against pre-donation mGFR.

Results: Wilcoxon test showed significant differences in pre-donation mGFR values between 2-year eGFR >60 ml/min group compared to the <60 ml/min group (p=0.001). In the logistic regression model, the effect of mGFR was nonlinearity (p=0.001) with evidence for nonlinearity. Pre-donation mGFR increases beyond 95 ml/min, the probability of the patient having a 2 year eGFR <60 decreases (Figure 1). In the linear regression model, pre-mGFR was significantly positively related to the 2-year eGFR (p=0.001).

Conclusions: Our results suggest that in kidney transplantation donor factors have a relevant impact on early transplantation outcomes. The use of donor-based clinical scores could potentially improve acceptance decisions and post-transplant outcomes.

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Underline represents presenting author.

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Vitamin C Deficiency After Kidney Transplantation: Results of the TransplantLines Biobank and Cohort Study

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TransplantLines Biobank and Cohort Study
Vitamin C Deficiency After Kidney Transplantation: Results of the Publication-Only PUB387

Jun-Y
in Peritoneal Dialysis Patients

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J Am Soc Nephrol 34: 2023

non-supplemented KTR (p<0.001).
day) and, on average, supplemented KTR had 19
months post-transplantation. An additional cohort of 374 KTR (median 8 years post-
deficiency post-kidney transplantation.

Deficiency was defined as plasma vitamin C
months post-transplantation. An additional cohort of 374 KTR (median 8 years post-

Results:
The mean age was 54±10.1 in group A and 45.8±12.0 in group B. Among the factors that may affect the prognosis after KT, the donor’s serum creatinine level and patients’ base serum creatinine level and ischemic time showed significant differences between the two groups. There was no difference in serum albumin and blood urea nitrogen levels between the two groups. Serum creatinine improvement after KT was significantly slower in group A than in group B. There was no difference in blood urea nitrogen and urine volume between the two groups.

Conclusions: It was found that the improvement of serum creatinine level after kidney transplantation was rather slow in the group with high kt/v. In the group with high kt/v, donor serum creatinine level was high and the ischemic time was long. These factors seem to have more influence on the prognosis than kt/v itself. Due to the small number of subjects, additional studies on kt/v and the prognosis after KT are needed.

Plasma vitamin C was measured in 579 KTR at 3, 6, 12, 24, and 60 months post-transplantation. An additional cohort of 374 KTR (median 8 years post-transplantation) was added to study the long-term determinants of vitamin C deficiency. Deficiency was defined as plasma vitamin C ≤28 µmol/L. Diet was assessed by a 177-item food frequency questionnaire, including data on supplementation.

Results: At inclusion, the 953 KTR were 62% male, mean age 55 years and mean eGFR 55 ml/min/1.73m². The intradividual coefficient of variation of plasma vitamin C during follow-up was 17%, while vitamin C deficiency ranged from 52% (6 months post-transplantation) to 29% (prevalent KTR, Fig 1). At ≥12 months post-transplantation, diabetes mellitus was the main clinical characteristic associated with higher risk of vitamin C deficiency (OR 2.30, 95% CI 1.46-3.61). Higher dietary vitamin C was associated with a lower risk of deficiency (OR 0.38, 95% CI 0.24-0.61/100 mg/day) and, on average, supplemented KTR had 19 µmol/L higher plasma vitamin C than non-supplemented KTR (p<0.001).

Conclusions: Plasma vitamin C is stable after kidney transplantation with a high prevalence of deficiency among KTR, particularly among KTR with diabetes mellitus. Higher intake of vitamin c, both dietary and supplemented, decreased the risk of deficiency among KTR. Further research is warranted to assess if correcting vitamin C deficiency improves patient and graft survival in KTR.
Discussion: Plasmacytoma like PTLD is a rare presentation and have poor prognosis. Prevalence was less than 0.1%. It is reasonable to have systematic screening of light chains in KDIGO recommendations before and after kidney transplantation to prevent the death of patient and graft.

Mohammad Correlation of Urine Analysis Findings with Biopsy-Proven Acute Kidney Rejection Congophilic casts


Introduction: ABMR of kidney allografts has been difficult to treat with TPE, IVIG, rituximab and tocilizumab. We present a patient with ABMR that was reversed with the use of SC daratumumab (Dara).

Case Description: A 69-year old man had his first kidney transplant on 2008. He developed chronic ABMR that was unresponsive to rituximab and tocilizumab. He had a second transplant on October 2021. He had no DSA, CDC and flow crossmatches were negative. His discharge serum creatinine was 0.95 mg/dL and biopsy was normal. 16 days post-transplant, he had proteinuria of 4.4 gms/24 hrs, creatinine rose to 1.56 mg/dL, dd-cfDNA (Prospera) was raised at 3.78%. A repeat biopsy showed MVI, g/pct=4 with +ve C4d staining. MMDx confirmed severe early ABMR. His DSA, anti-ATI-1, MICA antibodies, endothelial cell crossmatch were negative. As he had previously failed rituximab and tocilizumab, he gave informed consent to be treated with SC daratumumab (Dara). 1800 mg weekly for 4 weeks then 3 monthly for 3 doses for a total of 10 months, ending on September 2022. After 4 doses of Dara, his proteinuria decreased to 1.5 gms/24 hrs, creatinine; 1.42 mg/dL, dd-cfDNA decreased to 1.41%. In March 2023, his proteinuria; 1.0 gm/24 hrs, creatinine; 1.36 mg/dL, dd-cfDNA had normalized to 0.14%. His biopsy showed MVI, g/pct=3, mild C4d staining, MMDx improved to mild-early-stage ABMR. In June 2022, his proteinuria; 0.20 gm/24 hrs, creatinine; 1.41 mg/dL, dd-cfDNA was 0.57%. In September 2022, he had no proteinuria, creatinine; 1.45 mg/dL and dd-cfDNA was 0.28%. In January 2023, he had no proteinuria, creatinine; 1.32 mg/dL, dd-cfDNA had normalized to 0.14%. His biopsy had no ABMR, g/pct=0, negative C4d staining and MMDx had no ABMR.

Discussion: We report a man with rapid onset ABMR that was successfully reversed with SC Dara over a 10-month period with complete remission in proteinuria, slight decrease in creatinine, progressive improvements in serial dd-cfDNA and resolution of rejection findings on serial biopsies and MMDx. SC Dara was tolerated with minimal side effects. It was conveniently administered as an out-patient over 15 minutes. Dara had been reported to reverse ABMR in a patient who had an ABO-1 kidney transplant. Dara had been used to desensitise patients prior to kidney transplant. However, this is the first patient who had an ABMR successfully reversed with SC Dara. We are continuing to enrol more patients with proven ABMR to be treated with SC Dara.

PUB391 Correlation of Urine Analysis Findings with Biopsy-Proven Acute Kidney Transplant Rejection Mohammad Attar,1 Bushra Syed,2 Prathap Simhadri,2 Pradeep Vaitla,1 Sanjana Kapoor.2 1The University of Mississippi Medical Center, Jackson, MS; 2AdventHealth East Florida, Daytona Beach, FL.

Background: Although the incidence of acute kidney transplant rejection within the first year has decreased, it remains a major cause of allograft dysfunction. Kidney biopsy remains the gold standard to diagnose rejection. Urine analysis is used in evaluating kidney dysfunction, but no previous studies correlated urine analysis findings with acute rejection.

Methods: We performed a descriptive study evaluating urine analysis findings (proteinuria, hematuria, and pyuria) at the time of biopsy-proven acute rejection in adult kidney transplant recipients. We examined the most recent urine samples before kidney biopsy. We excluded patients with acute rejection who have other histopathological findings that may impact urine analysis findings (advanced diabetic glomerulosclerosis, collapsing glomerulopathy, FSGS, active glomerulonephritis, BK nephropathy, anatomical abnormalities, or concomitant chronic rejection).

Results: Between 2020 and 2023, 44 biopsy-proven acute rejection episodes were diagnosed in 38 patients. Eighteen biopsies showed acute TCMR, ten showed AMR, sixteen showed mixed rejection, and of all the biopsies ten had evidence of vascular rejection. Thirty-six episodes (81.1%) were preceded by abnormal urine analysis. Thirty urine samples (66.6%) tested positive for protein (≥10 mg/dL), thirteen samples (29.5%) tested positive for hematuria (≥3 RBCs/HPF), and eighteen samples (40.9%) tested positive for pyuria (≥3 WBCs/HPF). Of the eight normal samples, 3 were in the setting of AMR, 4 in the setting of TCMR, and 1 in the setting of mixed rejection. Interestingly, mixed rejection was associated with the highest likelihood of having abnormal urine analysis (93.7%, 7/12 cases).

Conclusions: There is no single urine analysis abnormality that correlates well acute rejection. Although various degree of proteinuria is not uncommon, it is non-specific. Even in the setting of glomerular injury as seen in glomerulitis, hematuria and/or pyuria are inconsistently seen at low rates.

Urine analysis abnormalities in various types of rejection

PUB392 Skin Lesion Unmasking Disseminated Nocardia in Renal Transplant Recipient Sarah Abu Kar, Amber Anwar, Laura Binari, Saed Shawar. Vanderbilt University Medical Center, Nashville, TN.

Introduction: Nocardiosis is a rare opportunistic infection that can cause localized or systemic diseases. Therefore, a high index of suspicion is required for the diagnosis as it carries high morbidity if not treated early. We present a disseminated Nocardia infection presenting with an isolated skin lesion.

Case Description: A 47-year-old male suffering from end-stage renal disease due to hypertension underwent a deceased donor kidney transplant in 2/ 2022. He was induced with Almurtazumab and maintained on tacrolimus, mycophenolate mofetil, and prednisone. He also received daratumumab. He developed disseminated nocardiosis with non-resolving fever for 6 months due to a reported sulfonamide allergy and Valcyte for 4 months post-transplantation. His course was complicated by AMR in 12/ 2022, treated with PLEX, IVIG, and Rituximab. Three months later, he presented with an ulcerated skin nodule on the medial aspect of his right knee. It started after a few days of soil-related teaching activities involving planting and terrarium work. No other symptoms were reported, treated with antibiotics for one week without improvement, so a biopsy and wound culture from the lesion revealed Nocardia pseudobrasiliensis. Subsequent diagnostic workup, including a chest CT scan and an MRI of the brain, discovered a spiculated lung lesion, a consolidation in the left lower lobe, and two cerebral abscesses. Bronchoscopy with BAL and LP results were negative for malignancy and infection. Additionally, all non-invasive fungal markers were negative. In collaboration with the infectious diseases and pulmonology teams, a diagnosis of disseminated nocardiosis was excluded, aligning with the patient’s symptomology. Treatment commenced with linezolid, Bactrim (after consulting with Allergy and tolerating the medication well), and imipenem-cilastatin, which was later adjusted to Bactrim and Linezolid based on sensitivity. Follow-up imaging showed a reduction in the sizes of both the lung nodule and brain abscess, indicating successful treatment progress.

Discussion: Skin lesions can pose diagnostic challenges in transplant patients, necessitating vigilance for atypical presentations of opportunistic infections and proactive biopsy for unresponsive lesions. However, Nocardia, when identified early and treated with targeted antibiotics, can result in successful outcomes for renal transplant recipients.

PUB393 Ultra-Long Survivors of Kidney Transplantation: 40 Years and More of Graft Function Matthew Madden,1,2 Gavin Comerford,1,2 Patrick O’Kelly,1 Anne M. Cooney,1 Peter J. Conlon,1,2 Beaumont Hospital, Dublin, Ireland; 3Royal College of Surgeons in Ireland, Dublin, Ireland.

Background: It is nearly sixty years since the first kidney transplant in Ireland in 1964. We examined our cohort of patients with allografts functioning for over forty years. We sought to identify factors associated with this ultra-long-term allograft survival and to describe clinical features of these patients.

Methods: A retrospective analysis of the Irish National Kidney Transplant Registry included all kidney transplants performed in Ireland between 1st January 1970 and 31st March 1983. Follow-up was until 31st March 2023. Results: 428 transplants occurred in 394 patients. There were 33 (8.4%) patients with graft function for ≥40 years, of whom 25 are functioning at date of analysis. 4 patients were lost to follow-up. Kaplan–Meier estimated survival at 20, 30 & 40 years was 25%, 15% & 8% respectively for all grafts; figure 1 illustrates survival differences between
living and deceased donor grafts. Multivariate analysis identified age at transplant (HR 1.02, CI 1.00–1.04), male recipient (HR 1.39, CI 1.04–1.45) and living vs. deceased donor (HR 0.42, CI 0.27–0.67) as significantly associated with long-term graft loss. The median age at death was 49 years (IQR 40–59). The most common causes of death were cardiovascular disease and malignancy. The major causes of graft loss were death with a functioning graft and interstitial fibrosis/tubular atrophy. The median creatinine of 25 surviving grafts was 1.21 mg/dl (range 0.75-3.64 mg/dl). Most (61%) patients were prescribed a combination of azathioprine/glucocorticoid. Comorbidities included non-melanoma skin cancer (67%), coronary artery disease (24%) and invasive malignancy (30%). Skin cancer was by far the commonest malignancy, with 93 incidences in 22 patients.

Conclusions: Of those who survive to forty years, graft function is excellent maintained on low-level immunosuppression. Recipient female sex and living donor kidney transplantation are associated with improved graft survival.

PUB394
Impact of Donation After Circulatory Death on Outcomes of Expanded Criteria Donor Kidney Transplants
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Background: Expanded criteria donor (ECD) kidneys experience suboptimal outcomes compared to standard criteria donor (SCD) kidneys.

Methods: To examine the additional impact of deceased organ category, donation after circulatory death (DCD) and neurological determination of death (NDD), on ECD outcomes, we examined 1- & 3-year patient and graft survival in all ECD kidney recipients in our institution between January 2008 and December 2017.

Results: Of 166 ECD recipients, 49 (29.5%) were DCD and 117 (70.5%) were NDD. Delayed graft function was higher in the DCD/ECD group 61.2% vs 32.9% among NDD/ECD recipients. Graft loss was significantly increased among DCD/ECD (HR for graft loss 4.81 (95% CI, 1.78, 13.01), p value 0.002 at 1 year and 2.03 (95% CI, 1.03, 4.0), p value 0.042 at 3 year). Death-censored graft loss was higher among DCD/ECD (HR was 10.12 (95% CI, 2.14, 47.92), p value 0.004 at 1 year and 2.83 (95% CI, 1.24, 6.46) p value 0.014 at 3 years). There was no statistically significant difference in all-cause mortality.

Conclusions: Our study demonstrated that DCD/ECD kidneys have lower graft survival compared to NDD/ECD kidneys. Time on dialysis, waiting time and panel reactive antibody should be taken into account when offering these organs to patients.

PUB395
Safety and Efficacy of Mycophenolate Reduction After Kidney Transplantation
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Background: Adjusting the dose of maintenance immunosuppression (IS) after kidney transplantation is essential to balance the risk of allograft rejection with that of infections and malignancy. Contrary to tacrolimus, there are no high-quality data to guide mycophenolate (MMF) dose changes in kidney transplant recipients (KTRs). The aim of this study is to determine the allograft and patient outcomes in KTRs who underwent MMF dose reductions compared to those who did not at our institution.

Methods: We conducted a retrospective cohort study of all kidney transplants from 1/1/2015 to 12/31/2020 who received MMF-based IS. The “intervention” group included KTRs who underwent MMF dose reduction after the first year, while the control group was KTRs whose MMF dose was maintained. The primary safety outcomes were graft failure or death, de novo DSA development, allograft rejection, and eGFR change during follow-up. The primary efficacy outcome was a composite of new viral infections (CMV, EBV and BKV), infections requiring hospitalization and malignancy. We excluded patients who developed infections or malignancy prior to MMF reduction from our analysis. Follow-up was censored at occurrence of the outcome, last follow-up or five years.

Results: 69 KTRs met the inclusion criteria. Mean age was 49.5±15.3 years, 61% were male (n=42), 59% received a deceased donor allograft (n=41), and 86% (n=59) received Thymoglobulin. 42 KTRs (61%) had a reduction in the MMF dose after 1 year of transplantation to ≤500 mg BID. No deaths occurred during follow-up. 3 (4%) KTRs developed rejection during follow-up: 1 mixed acute rejection in the MMF dose maintenance group, and 2 cellular rejections in MMF dose reduction group. There was no change in eGFR between groups (Figure 1A). DSA occurred in 3 KTRs (4%), all in the MMF dose maintenance group (Figure 1B). There was no difference in the incidence of composite outcome of infections and malignancy (Figure 1C).

Conclusions: MMF dose reduction after the first year may be a safe strategy in low-risk KTRs. Larger prospective studies are needed to confirm these findings and establish the long-term benefits of this intervention regarding infection and malignancy.
Publication-Only

PUB396

Tacrulimus Intrapatient Variability as a Tool to Gauge Nonadherence in Adolescent Kidney Transplant Recipients
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Background: Long-term survival of kidney allografts is limited by rejection, a common cause of graft loss in adolescent transplant recipients. High tacrolimus intrapatient variability (IPV) has been associated with DSA formation and increased risk of rejection. Non-adherence is considered a cause of high tacrolimus IPV, but has not been demonstrated conclusively.

Methods: This cross-sectional retrospective study included kidney-only transplant recipients a11 to ≥23 years old, ≥10 months post-transplant at the Miami Transplant Institute, and maintained on tacrolimus. A composite adherence score ranging from 0-4 points was developed using four tools, each awarded 1 point if positive: (1) patient reported non-adherence on Baseline Assessment of Adherence to Immunosuppressive Medical Scale (BAASSIS®); (2) provider report; (3) inability to recall medications; and (4) intentional missed visits. A composite score a1 was considered non-adherent. Tacrolimus levels were monitored at least monthly. IPV is the coefficient of variation: SD/mean tacrolimus concentration x 100%, using tacrolimus samples in the 6 months prior to adherence assessment. Levels drawn while hospitalized/sickness or mis-timed levels were excluded.

Results: 33 patients were enrolled, 60.6% male, median age 16 years (IQR 13-19). Non-adherence was noted in 18 (54.5%) patients. The median tacrolimus IPV was significantly higher in non-adherent (32%, IQR 14-37.5) compared to adherent patients (18%, IQR 13-22), p=0.02 (Figure 1a).

Conclusions: Tacrolimus IPV was significantly higher in non-adherent patients. Recognizing high IPV may be a useful tool to detect non-adherence in adolescent kidney transplant recipients at high risk of rejection, allowing for early interventions to prevent adverse graft outcomes.

PUB397

Disseminated Intravascular Coagulation in the Immediate Postoperative Period After a Simultaneous Kidney Pancreas Transplant (SKP)
Mohammed A. Sayeed Khan, Tanu Duggal, Aadal Kaisani. Baylor Scott and White Central Texas, Temple, TX.

Introduction: Disseminated intravascular coagulation (DIC) is a clinicopathological syndrome associated with consumptive coagulopathy and fibrinolysis with a potential of causing microvascular thromboses and hemorrhage. DIC is commonly caused by inflammation, drugs, sepsis, severe trauma or major surgery, cancer, obstetric complications, immune reactions. While there are multiple cases of DIC in deceased donors, there is no data or case reports on recipients developing DIC immediately post-op after SKP.

Case Description: 59-year-old female underwent a SKP for a history of ESRD secondary to IDDM2. Measured PRA was 61%/43%. DBD Donor -18 year old female in inflammation, drugs, sepsis, severe trauma or major surgery, cancer, obstetric complications, recipients demonstrated conclusively.

Discussion: SPK has evolved as the gold standard treatment for patients with ESRD with diabetes as a surgically acceptable candidates. It is a more complex procedure with a higher complication rate. Reexploration is seen in ≥20% with the most common etiology being anastomotic leaks, intraabdominal fluid collections, Intradobtal infections, graft pancreatitis and graft thrombosis. Cases of DIC have been reported after surgical intervention but to our knowledge there is no documented case of rapid onset DIC in a patient post SKP. This case highlights the need to consider DIC in a postoperative setting after DIC in patients with hemorrhagic shock which has previously not been reported.

PUB398

To Bleed or to Thrombose: The Potential Risks and Complications of Blood Thinners in Kidney Transplant Recipients
Anam Rehan,1 Grace Qiu,1 Prashamsha Shonoy,1 Rachel Greene,1 Goni Katz-Greenberg,2 Maria P. Martinez Cantarin,1 Thomas Jefferson University, Philadelphia, PA; 2Duke University, Durham, NC.

Background: Many patients on the kidney transplant waitlist are on anticoagulation (AC) or antplatelet therapy for various indications and co-morbidities. These medications are associated with increased risk of bleeding, especially when patients undergo invasive procedures, such as a kidney transplant. On the other hand, withholding AC or antplatelet therapy in the perioperative period, can lead to complications such as vascular thrombosis and subsequent allograft loss. The aim of our study was to review co-morbidities and allograft function of kidney transplant recipients (KTRs) on these medications at the time of transplant.

Methods: Single center, retrospective cohort study of adult KTRs transplanted between Jan 2017 and December 2019 in our center.

Results: We had 333 KTRs who met the study criteria. Of them, 38.9% of were on Aspirin pre-txp, 5.4% were on Plavix and 8.4% were on Coumadin as anticoagulation. Of the 333 KTRs, 22 patients (6.6%) developed a hematoma and 8 patients (2.4%) developed thrombosis. Usage of pre-operative AC or antplatelet therapy did not differ between KTRs who developed these complications and those who did not. Compared to KTRs who did not develop a hematoma post-KT, patients with hematomas had longer length of stay (LOS)(p=0.001), higher intervention rate in the OR (54.5% vs 5.5%, p=0.001) or by CVIR (45.5% vs 13.9%, p=0.001) within 30 days post-KT. KTRs with hematoma also had higher serum creatinine (Cr) at 30 days (p<0.001), 90 days (p=0.001), 1 year (p=0.001) and at the latest follow up (p=0.001). Overall patient survival was also significantly lower in this group (p<0.05). KTRs with thrombosis had longer LOS (p=0.001) and higher Cr after 30 days (p=0.05) when compared to those without. KTRs with thrombosis had lower graft survival (p=0.05).

Conclusions: Bleeding or thrombosis complications post-transplant are associated with significant morbidity but they did not occur more frequently in patients that were on AC or antplatelet therapy pre-transplant. While this is a single-center study, it contributes to existing data, and highlights the fact that the risks and benefits of AC therapy should be assessed for each patient to individualize the management approach.

PUB399

Risk Factors for Fractures in Renal Transplantation: A Population-Based Cohort Study
Jei-Wei Chang,1,2 Tzu-Ching Lin,1,2 Hsin-Lin Tsai.1,2 Taipei Veterans General Hospital, Taipei, Taiwan; 1National Yang Ming Chiao Tung University School of Medicine, Taipei, Taiwan.

Background: Kidney transplant recipients are at an increased risk of fractures, and targeted preventive strategies are needed. Therefore, we investigated a large population-based cohort to identify the transplant recipient-specific risk factors for fractures in Taiwanese kidney transplant recipients.

Methods: We conducted a retrospective cohort study using the National Health Insurance Research Database. Patients who underwent renal transplantation between 2003 and 2015 were identified and followed until December 31, 2015 to observe the development of fractures. Variables associated with the development of post-transplant fractures were identified by calculating hazard ratios in a Cox regression model.

Results: 5309 renal transplant recipients were identified, of whom 553 (10.4%) were diagnosed with post-transplant fractures. Independent predictors of post-transplant fractures included an age at transplant ≥65 years (p<0.001), female sex (p<0.001), fractures within 3 years prior to transplantation (p<0.001), and diabetes (p<0.001). In addition, daily prednisolone dose >29.5-3.5 mg/day (p<0.001), >5.3-8.7 mg/day (p<0.001) and >8.7 mg/day (p<0.001) were also independent predictors of post-transplant fractures. Conversely, the use of peritoneal dialysis before renal transplantation (p=0.021), hypertension (p<0.005), and the use of tacrolimus (p<0.001), azathioprine (p<0.006), mycophenolate mofetil (p<0.002), mTOR inhibitors (p<0.004) and calcium supplements (p=0.009) were inversely correlated with post-transplant fractures.

Conclusions: We recommend minimizing daily glucocorticoids in conjunction with immunosuppressive regimens such as tacrolimus, azathioprine, mycophenolate mofetil, mTOR inhibitors and calcium supplements, especially in older female recipients, and in recipients with diabetes and a history of prior fractures.

Funding: Other U.S. Government Support, Government Support - Non-U.S.
Paragonimiasis Mimicking Ureter Stone in Living Kidney Donor

Hae Sang Park,1 Young-Joo Kwon.2
1H Plus Yangji Hospital, Seoul, Republic of Korea; 2Korea University Guro Hospital, Seoul, Republic of Korea.

Introduction: Extrapulmonary paragonimiasis mainly involve pleural, subcutaneous, cerebral, and spinal infection. Other extrapulmonary paragonimiasis has been reported in hepatic, splenic, abdominal, urinary, and gynecologic organs. We report a case of paragonimiasis mimicking ureter stone in living kidney donor.

Case Description: We decided kidney transplantation between the married couple. The living donor was 61 year old male, and his CT angio abdomen scan showed about 0.6 cm stone at left proximal ureter, and small size periureteral low density lesion at the left proximal ureter. In operation, we found of a lump of soft tissue in periureter, measuring 4.5x4x2.5cm, yellowish adipose tissue-like appearance. Frozen specimen cut surface showed cystic appearance filled with yellowish necrosis like material, and was diagnosed as parasite infection, morphologically paragonimiasis. Kidney transplantation was done steadily, and post-operative course progressed smoothly.

Discussion: Donor showed positive in P.westermani Ab and Cysticercus Ab, but recipient showed negative. After further interview, he had history of paragonimiasis and taking praziquantel 15 years ago. We prescribed to her praziquantel 1,800 mg for 3 days. In post transplant three month, her serum creatinine incremented from 0.95 mg/dL to 1.57 mg/dL, and sonogram showed hydronephrosis. We decided double J stent insertion through percutaneous nephrostomy, and followed up for eight months cautiously. Even though waiting, proximal ureter stricture was incurred, and she has been regular double J stent exchange under general anesthesia. Even if extraplumonary paragonimiasis involving ureter is very uncommon, the meticulous history taking and examination would be needed in transplantation work up.

Parasite infection, Morphologically paragonimiasis

Clinical Course of a Kidney Transplant Recipient with Epstein-Barr Virus Viremia Treated with Maribavir

Sapna Shah, Thin Thin Maw, Santhi Voora. University of Southern California, Los Angeles, CA.

Introduction: Impaired T-cell immunity following kidney transplantation increases the risk of both primary infection and reactivation of latent Epstein-Barr Virus (EBV). EBV viremia is managed primarily with reduction in maintenance immunosuppression, but with varied results. We present the first clinical case of a kidney transplant (KT) recipient with EBV viremia treated with Maribavir, a novel therapeutic that inhibits EBV transcription and viral replication.

Case Description: A 70-year-old Taiwanese female with a history of end stage kidney disease secondary to diabetic nephropathy underwent a deceased donor KT with thymoglobulin induction. She received maintenance immunosuppression with tacrolimus, mycophenolate, and prednisone. At the time of transplantation, she was at moderate risk for EBV infection with both donor and recipient EBV IgG antibodies positive (recipient IgG 526 Unit/mL; IgM <10 Unit/mL). Six months later she had worsening leukopenia and was diagnosed with EBV viremia that initially resolved with reduction of mycophenolate. Sixteen months following KT she again developed EBV viremia. She had persistent and worsening viremia despite cessation of mycophenolate, dose reduction of tacrolimus, and Prednisone to 2.5 mg daily. She was initiated on IV immunoglobulin 500 mg/kg, but treatment was discontinued after her first dose due to the development of severe myalgia, transaminitis, and hemolytic anemia. She was then initiated on off-label Maribavir 200mg twice daily with significant improvement in viremia. Figure 1 summarizes her treatment.

Discussion: Maribavir is a novel benzimidazole riboside compound that inhibits EBV DNA polymerase processivity factor (BMRF-1), reduces some EBV glycoproteins, and inhibits EBV viral transcription. Maribavir treatment was well tolerated at 200mg twice daily. Maribavir is the only intervention that was associated with a significant reduction in EBV viremia in this patient.
PUB402
The Molecular Microscope Diagnostics System (MMDx) May Have the Potential to Differentiate Molecular T Cell-Mediated Rejection (TCMR) Among Kidney Transplant Recipients with Chronic-Active TCMR

Schachtner, Kai L., Weidmann, Dusan, Harmacek, R., Kopecky, N., Thomas, F. M., Mueller, F. U.

Background: Treatment of chronic-active T-cell mediated rejection (ctTCMR) lacks consensus, causing many different therapeutic approaches. If changes in transcript patterns analyzed by the Molecular Microscope Diagnostic System (MMDx) may differentiate among these cases with ctTCMR and offer additional diagnostic value needs to be investigated.

Methods: In this single-center cohort of 326 indication kidney transplant biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 15 cases with ctTCMR after the exclusion of overlapping pathologies such as BK nephropathy, pyelonephritis, and acute interstitial nephritis.

Results: 3 of 7 cases (43%) with combined acute TCMR and ctTCMR were compared to 8 cases with ctTCMR only.

1. Early active ABMR: Two cases showed MVI (g1-) and PTC1 (≥2) in the absence of DSA. On follow-up biopsy, histology showed no rejection in both cases, confirmed by MMDx in each biopsy.
2. Late ABMR: Two cases showed MVI (g1-4, ptc0) in the absence of DSA. On follow-up biopsy, histology showed ongoing ABMR by histology and MMDx, while the other case showed resolved ABMR by histology and MMDx. ‘Early active ABMR’: One case showed no rejection on histology one week post-transplant, but minor ABMR by MMDx. On follow-up biopsy two weeks later, ABMR was confirmed by histology and MMDx.

Conclusions: The MMDx appears to have added value across the ABMR continuum, both to confirm and reject the diagnosis of ABMR. In addition to the Banff 2019 recommendation, scenarios such as MVI in ABOi transplantation and mixed rejection should be considered as indications for the MMDx. Earlier diagnosis of early active ABMR, while possible with MMDx, is likely the exception.

Funding: Private Foundation Support

PUB404
First Year After Transplant Infections in a Young Kidney Transplant Cohort: Is Preemptive Transplant Protective?

K. Khedr, Ain Shams University Faculty of Medicine, Cairo, Egypt.

Background: Infection after a kidney transplant is a serious cause of morbidity and mortality. Weighing the risks and benefits of immunosuppression is of paramount importance to patient wellbeing and transplant survival.

Methods: This is a prospective observational study looking at the variety of infections in a young cohort with living related kidney transplantation. Fifty-one records of patients who had a kidney transplant between Jan 2020 and Jan 2022 were followed up and clinically significant infections were investigated and documented.

Results: In a young transplant cohort with a mean age of 28.4 ± 10.4 yrs. Females were 45.1%. The commonest infection was lower urinary tract infection (UTI) (27.3%) followed by SARS-COV2 and Herpes Zoster (15.2%). Median Tacrolimus level was (7.8) ng/ml and was slightly higher in the group without infection (8.95) ng/ml (p = 0.21). Haemoglobin was higher in the group without infection median (10.8) gm/dl compared to (10.2) gm/dl in the group without infection (7.8-14) odd ratio (OR) = 0.78 confidence interval (CI) (0.5-1.1). More infections were recorded in Kidney transplant recipients (KTR) from donors over the age of 60 (OR=2.6; 95% CI: 0.5-12; P=0.2). Post transplant diabetes (PTDM) was more prevalent in the group with infection (25%) (OR 1.9 p =0.365). In the group without infection, 59.3% had a preemptive transplant compared to 20.8% in the group with infection (OR=1.08; 95% CI: 0.52-0.631; P=0.007).

Conclusions: This study shows that the distribution of infection in this cohort with living related kidney transplantation. Lower urinary tract infection was the commonest infection followed by SARS-COV2 and Herpes Zoster. We observed a lower incidence of infection with preemptive transplantation.

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

Underline represents presenting author.
**PUB405**

**Quality Improvement Initiative to Enhance Post-Renal Allograft Biopsy Follow-Up**

Mingyue He,1 Jean Lee,2 Sheetal Koul,1 Iris J. Lee,2 Avrum Gillespie.1
1Temple University Hospital, Philadelphia, PA; 2Lewis Katz School of Medicine at Temple University, Philadelphia, PA.

**Background:** Kidney transplant recipients who undergo allograft biopsies are often discharged on the same day with instructions to schedule a subsequent visit with Transplant Clinic for results and further management plans. Such patient-initiated follow-ups can lead to care delays and patient dissatisfaction. Furthermore, inadequate documentation of communication with patients regarding biopsy results can contribute to confusion among physicians. We thus implemented patient-centered interventions to improve 30-day follow-up rates and identify potential late-onset complications of kidney allograft biopsy. These interventions include concurrent scheduling of biopsy and post-biopsy follow-up visits, reminding patients of their appointment on the day of the biopsy, post-procedure phone check-ins, and improved documentation of biopsy result communications.

**Methods:** We analyzed a pre-intervention sample of 23 renal allograft biopsies from January to April 2021. Post-intervention, we reviewed all 24 renal allograft biopsies performed from January to April 2022. We compared the rates of 30-day follow-ups, either through telehealth or in-person visits with documented biopsy result discussions, over a four-month period before and after the intervention.

**Results:** No significant differences were observed in baseline clinical characteristics between pre- and post-intervention groups: Age: 53 ± 2.7 vs 48 ± 2.9 years, p=0.11; Male: 65.2% vs 45.8%, p=0.18. The 30-day follow-up rate was 87.0% (20/23) pre-intervention and 100% (24/24) post-implementation, (p=0.07). The average interval between biopsy and follow-up date shortened from 18 ± 3.6 days pre-intervention to 12 ± 1.5 days post-intervention (p=0.07). The rate of major treatment modification during follow-up visits was 52.2% before the intervention and 66.7% after it (p=0.31).

**Conclusions:** The implementation of these patient-centered interventions led to an improvement in post-renal allograft biopsy follow-up rates, although not statistically significant with a borderline p-value. The limited study power due to small sample size may have contributed to this outcome. We observed that over 50% of transplant recipients require treatment modifications post-biopsy, emphasizing the need for prompt follow-up. Hence, further studies exploring ways to improve follow-up efficacy are warranted.

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**PUB406**

**Missed Diagnosis as Risk Factor for Graft Loss: Analysis of the Tuscany Kidney Transplant Waitlist**

Giuseppe L. Sciolitari, Giuseppina Rosso, Luca Malatesta, Micaela Anna Casiraghi, Giulia Sossai, Fiammetta Ravaglia, Alberto Rosati. Azienda USL Toscana Centro, Firenze, Italy.

**Background:** A significant percentage of patients on the kidney transplant waitlist have no primary diagnosis. Nonetheless, recurrence of glomerulonephritis (GN) is the second leading cause of graft loss and the majority of patients with known etiology of ESKD (uESKD) are frequently labelled as "presumed GN". Furthermore, the burden of inherited kidney diseases in uESKD population is actually uncertain. By far, it is not known whether the lack of primary diagnosis represents a risk factor for graft loss.

**Methods:** A total number of 537 patients placed on the transplant waitlist in Tuscany were examined retrospectively up to April 2023. We evaluated, by univariate and multivariate analysis, if the lack of diagnosis was a risk factor for graft failure in patients waiting for their first or further transplant.

**Results:** Out of 537 patients listed in the Tuscany area, 43.5% had missed diagnosis. The distribution by gender, age and comorbidities were comparable between patients waiting for their first or further transplant. 32.6% of patients were waiting for re-transplant, among them 45.4% with uESKD, mostly represented by presumed GN (66.6%). In multivariate analysis, both primary GN (p=0.013, CI: 0.176-0.815) and presumed GN prior to transplant (p=0.043, CI: 0.222-0.978) proved to be a risk factor for graft loss.

**Conclusions:** A significant percentage of patients placed on the kidney transplant waitlist presents an uESKD, which embraces presumed GN and inherited kidney diseases. Besides primary GN, presumed GN prior to transplant appears to be a risk factor for graft loss but, unlike in primary GN, a targeted therapeutic approach is not feasible. Our study has some limitations, such as possible confounding factors/selection bias in listing ESKD patients. Additional analysis are needed to confirm these findings. Meanwhile we have been implementing a regional program to reduce the percentage of uESKD of both immune-nephrosis and inherited kidney diseases. A multidisciplinary team has developed a specific algorithm based on AI-related tools, to help guiding the diagnostic process by genetic evaluations, more extensive use of biopsy and proteomic-related analytical techniques.

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**PUB407**

**Therapeutic Plasma Exchange with TPE 2000 Membrane for Antibody-Mediated Cardiac Transplant Rejection**


**Introduction:** The removal of pathogenic substances by therapeutic plasma exchange (TPE), as a treatment for antibody-mediated rejection (AMR) in cardiac transplant, has gained a way as a modern medical therapy. Membrane filtration with TPE 2000 (Fig. 1) targets large-molecular-weight substances present in plasma or globulin. TPE could be offered as initial therapeutic intervention as it rapidly removes antibodies and cytokines from patients’ plasma with a technology already in ICU CRRT machines.

**Case Description:** A 24-year-old woman, post cardiac transplantation 4 months prior, arrived to ER with dyspnea, orthopnea and oliguria. BP 91/64 mmHg, HR 120bpm, 24 RR, O2 sat 85%. Echocardiography: LVEF 20%, severe cardiac graft dysfunction. A myocardial biopsy was performed. She presented pulseless electrical activity and ALS were performed for 2 minutes with success. Inotropic and vasopressors were started, orotracheal intubation was required. Biopsy shows changes compatible with AMR. Steroids and TPE were offered. 5 sessions with TPE 2000 membrane, prescription with 1.5L plasma exchange with albumin at 25% (Table 1). Vasopressor reduction, inotropic withdrawal, and LVEF increase to 40% were achieve after treatment.

**Discussion:** Allograft dysfunction due to AMR is one of the worst complications post heart transplantations. In this case we were able to evaluate allograft improvement. LVEF pre-TPE 20% to post-TPE 40%. This can guide us to continue the research about TPE in AMR as there is no evidence-based guidelines that establish this therapy for patients as complex as this are.
PUB408
Evolution of Kidney Function Following Living Donor Nephrectomy
Ana C. Acosta Peña, Jose Carlos Cano Vervantes, Mayra M. Matias Carmona, Beatriz R. Cerezo Samperio. Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico.

Background: The Glomerular filtration rate (GFR) pre and post renal donation can vary according to the population and lifestyle, so there is a long-term risk of developing renal disease, so the long-term follow-up is of the utmost importance.

Methods: Retrospective, descriptive and analytical study of donors registered at the National Medical Center “20 de Noviembre” from May 2016 to August 2021 with 1 year follow-up. The objective is to determine the evolution of renal function per year in renal organ donors.

Results: We find 23 women (51%) and 22 men (49%) whose basal characteristics were: age 41 years, serum creatinine (Cr) of 0.76 mg/dL, eGFR CKD-EPI 108 mL/min/1.73m2; Creatinine clearance (CrCl) 106 mL/min; and GFR with DTPA 126 mL/min. A significant difference was found at one year of evolution between the pre and post-donation values: Crs (Dif = -0.35 mg/dL; p < 0.0001); eGFR CKD-EPI (Dif = -22.3 mL/min/1.73m2; p < 0.0001); and CrCl (Dif = 36.4 mL/min; p < 0.0001). Also there is a difference between Cs values between women and men (0.94 vs 1.3 mg/dL; p < 0.0001, 95% IC 0.46 - 0.24) and CrCl (36.5 vs. 71.3 mL/min; p = 0.005, 95% IC 24.8 - 24.8). There was no significant difference between pre- and post-donation albuminuria (p = 0.06) with an average of 24.3 mg/day (a 86.9 mg/day), no difference between genres (p = 0.51).

Conclusions: The decrease in the glomerular filtration rate and creatinine clearance in our population was on average of 32 to 36 mL/min, without finding an association between the body mass index and the development of hypertension to this, however, with a trend associated with the age of donation.

Comparison of the renal function basal vs post nephrectomy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Basal</th>
<th>One year post nephrectomy</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine mg/dl</td>
<td>0.76 (± 0.16)</td>
<td>1.1 (± 0.22)</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>eGFR CTKD-EPI 108 mL/min</td>
<td>108 (± 29.4)</td>
<td>76 (± 17.4)</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>CrCl (ML/min)</td>
<td>106 (± 29.4)</td>
<td>65 (± 14.9)</td>
<td>p &lt; 0.001</td>
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PUB409
Heart Failure with Reduced Ejection Fraction (HFrEF): Contraindication to Kidney Transplantation?

Background: Heart failure is frequent complication of advanced CKD and many transplant candidates will have reduced ejection fraction (EF). Data remains limited on whether heart failure with reduced EF (HIF) at the time of transplant is associated with an increased risk of graft failure and mortality. In this study, we sought to compare the patient and graft survival between the cohorts of patients with or without HIF undergoing renal transplantation.

Methods: We performed a retrospective matched cohort analysis of 32 patients with pre-transplant EF <=45% (HF cohort) and 67 patients with EF >45% (control cohort) based on thoracic echocardiogram, transplanted between January 25, 2011 and July 21, 2015. Patients without pre-transplant EF were excluded from the analysis.

Results: Baseline characteristics were similar except ATG induction was less frequent in the HF cohort (Table 1). At a median of 86 months post-transplant, no statistically significant difference was observed between the control and HF cohorts on the overall graft survival (Figure 1; p=0.29) and the overall patient survival (Figure 2; p=0.55). There was no statistically significant difference in the mean creatinine levels at 1 year post-transplant between the control (1.41 mg/dL) and HF (1.48 mg/dL) cohorts, as well as in the hospitalization rates within 1 year of transplant.

Conclusions: In this pilot study, we examined the graft and patient survival outcomes of renal transplant patients with heart failure and found no significant differences compared to matched controls. Our data suggests that ESKD patients with low EF prior to transplant may have significant improvement in their heart function post-transplantation. Low EF alone should not be a contraindication to kidney transplant.

Table 1: Study Cohort

<table>
<thead>
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<th>Variable</th>
<th>HF cohort (n=32)</th>
<th>Control cohort (n=67)</th>
<th>p value</th>
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<td>Diabetes</td>
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<td></td>
<td>22 (68.7%)</td>
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</tr>
<tr>
<td>No</td>
<td></td>
<td>10 (31.3%)</td>
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<td>21 (65.6%)</td>
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</tr>
<tr>
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<td>9 (28.1%)</td>
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</tr>
<tr>
<td>CRP (mg/dL)</td>
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<td>0.76</td>
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<td>Baseline</td>
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<tr>
<td>Median</td>
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<td>0.7 (0.1 - 4.6)</td>
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PUB410
Effectiveness of Evusheld (Tixagevimab/Cilgavimab) in Reducing Breakthrough COVID-19 Infections Among Vaccinated Kidney Transplant Recipients
Arezou Shahmoradi, Wilma M. Hopman, Jessy Donelle, Gail Dean, David C. Holland, M. Khaled Shamseddin. Queen’s University, Kingston, ON, Canada.

Background: Transplant patients are at high risk of COVID-19 infection and its complications. Up to 33% of transplant patients have inappropriate response to COVID-19 vaccination with 2% mortality risk. Studies showed significant reduction with breakthrough COVID-19 infection post Evusheld administration. An Evusheld Clinic was launched at our center, in late July 2022, to facilitate the Evusheld administration to our kidney transplant patients. The aim of this study was to evaluate the efficacy of Evusheld pre-exposure prophylaxis preventing breakthrough COVID-19 infection among vaccinated kidney transplant patients in a single center study.

Methods: We conducted a retrospective analysis of all kidney transplant patients at our center with breakthrough COVID-19 infection post-Evusheld administration between August 1, 2022 and January 6, 2023. Chi square and Fisher Exact test were performed using SPSS Statistics 23 with a 0.05 significance value.

Results: 217 patients were included (Male: 66.8%; Age: 56.9±14.2years). 127 (58.5%) patients received Evusheld 300 mg through our clinic between August 1 - November 30, 2022. By January 6, 2023, 27 (12.4%) patients developed breakthrough infection since August 1, 2022, compared with a total of 76 (35.9%) COVID-19 infections since the pandemic in March 2020. 19 (15%) breakthrough infections were reported post-Evusheld administration compared with 8 (9%) cases in patients who did not receive Evusheld (P=0.18). All Evusheld patients with breakthrough infections were fully vaccinated (3 vaccine doses) compared with 75% of those with no Evusheld and breakthrough infections (P=0.08). Time from the last COVID-19 vaccination to infection was not significantly different among patients with and without Evusheld [4.0 (0.5-8.8) vs. 5 (2.5-10.6); P=0.46].

Conclusions: Evusheld 300 mg did not decrease the risk of breakthrough COVID-19 infection among fully vaccinated kidney transplant patients. Studies with higher doses of Evusheld and further COVID-19 vaccination are still required to determine efficacy of prevention of breakthrough COVID-19 infection among transplant patients.

PUB411
Analyzing the Influence of Demographic Factors on Kidney Transplantation Willingness Among Central Virginia Kidney Disease Patients
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Background: Kidney transplantation (KT) offers increased quality of life and improved clinical outcomes (including patient survival) as compared to dialysis treatment. Barriers in access to earlier steps of transplantation (i.e. referral and evaluation)
are inadequately reported in the current research field. The study aimed to identify educational barriers, racial barriers, socioeconomic-based barriers, and culture-based barriers. Resources seeking to develop educational interventions for both patients and providers may aid in reducing existing barriers.

Methods: A survey consisting of fourteen total questions was administered to patients of varying stages of kidney disease at the Prince George, Southside, and Midlothian Clinic locations in Central Virginia. The study sought to evaluate the role of race and education level on familiarity of kidney transplantation/donation, comfortability with KT, and trust in health care systems.

Results: 103 patients across the three Central Virginia clinics were surveyed between late-March to mid-April of 2023. 47 (43.93%) of respondents identified as African American and 54 (50.47%) as White. Familiarity with the concept of kidney transplantation and comfortability with kidney transplantation in relation to education level of survey respondents was found to be statistically significant with p-values of p=0.008 and p=0.02, respectively (with p-value of <0.05). Structured within the White Race, statistical significance (write actual p-value) was found in comparing education level of respondents to familiarity with kidney transplantation, trust in the healthcare system to provide safe transplantation, likelihood to consider kidney donation, and comfortability with kidney transplantation.

Conclusions: Based on the analysis of the survey responses, we were able to determine the comfortability with kidney transplantation and familiarity with kidney transplantation have some relation to education level in kidney-disease patients located within Central Virginia. Based on such results, it is likely that organ donation apprehension continues to be rooted in culture. Future education initiatives should take these exhibited racial differences into account for success in striving for transplant equity.

PUB412
Identifying Barriers to Kidney Transplantation in a Veteran Population
Danish Waqar,1,2 Kavitika Vellanki,1,2 Manpreet Samra,1,2 David J. Leehey,1,2 1Loyola University Medical Center, Maywood, IL; 2Edward Hines Jr VA Hospital, Hines, IL.

Background: Kidney transplantation is the treatment of choice for end-stage kidney disease patients and improves survival. The Edward Hines, Jr. VA Hospital recently became a regional referral center for kidney transplantation for Veteran patients. The kidney transplantation referral process involves being timely seen by the pre-transplant evaluation team, completing all the necessary initial testing for transplant, and submitting a whole package through the transplant referral and cost evaluation/reimbursement (TRACER) process. Once TRACER is submitted, the transplant center has 5 days to review and accept or decline the evaluation. Not all patients get the workup completed or get evaluated for listing due to multiple factors. Our aim was to investigate the barriers to listing for kidney transplantation at our hospital.

Methods: We analyzed data from 45 patients from our hospital who were referred to the Hines VA transplant center from March 2019 through December 2022. All analyses were performed in R version 4.2.3, Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Results: Baseline characteristics of the patients are shown in the Table. The barriers identified are depicted in the Figure. Non-compliance of patients in completing the pre-transplant workup was the most frequent barrier, with other common barriers being delay in colonscopy and presence of malignancy. A Kaplan-Meier estimate of median wait time from referral to evaluation revealed a marginal difference by age group, with longer wait times associated with increasing age.

Conclusions: There are multiple barriers to kidney listing transplant, with the most important being non-compliance of patients. This points toward improving patient education as a major focus to improving the pre-transplant evaluation process.

Funding: Private Foundation Support

Baseline characteristics (N=45)

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Gender</td>
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<td>65 (54.1%)</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>65 (57.2%)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>65 (57.2%)</td>
</tr>
</tbody>
</table>

*Figures are based on the number of observations.*

PUB413
Providing Medication Education to Renal Transplant Recipients: Are We Getting It Right?
Sadia Jahan, Tiah Doody, Jasmine Goh, Hanh Tran. Central and Northern Renal and Transplantation Service, Adelaide, SA, Australia.

Background: Successful medication-taking behaviour by kidney transplant recipients is associated with long-term survival and is dependent on knowledge of medication regimens and education concerning the effect of medications on transplant outcomes. A mobile app could provide a tool to improve knowledge of medication regimens by transplant recipients.

Methods: We utilised the validated Kidney Transplant Understanding Tool (K-TUT) to determine our patients’ level of knowledge regarding their transplant medications. We also developed a patient survey assisting in classifying level of health literacy related to transplant medication knowledge.

Results: As part of feasibility, we present results from eight patients with 2/8 from Indigenous background and 2/8 patients’ primary language being non-English. K-TUT scores were distributed between 41 and 66 (1 point for correct answer and 0 point for incorrect answer with total score of 69). In terms of the questions asked about preparation for medicines post-transplant, direct quotes include “I was a bit nervous because I didn’t realise there were so many tablets to start off with so that was a bit of a shock” and “No, I wasn’t confident at first, I was a bit scared of how much tablet I had to take”. One emerging theme is that the information booklet is not being read (7/8) with comments such as “I just didn’t have time” and “I had so much going on”. Another theme pertains to different delivery of education in the form of “mobile app would be good, (explaining) the tablets” and “A mobile app would probably be handy because the doctor and pharmacist can update it quickly.”

Conclusions: Data from our patients have clear emerging themes, and it will be prudent to continue recruitment into the study, to clearly identify areas for improvement with knowledge about possible implementation of alternative education strategies.

PUB414
Bone Mineral Metabolism Alterations in Kidney Transplant Recipients in a Colombian Caribbean Fourth-Level Hospital
Karen G. Lasso,1 Omar Cabarcas Barbosa,1 William B. Riascos,1 Alex Dominguez-Vargas,2 Maria I. Pulgar,1 Henry J. Gonzalez Torres,1 Gustavo Aroca Martinez,1 Universidad Simón Bolívar Facultad de Ciencias de la Salud, Barranquilla, Colombia; 1Universidad del Norte División Ciencias de la Salud, Barranquilla, Colombia; 2Clínica de la Costa Ltda, Barranquilla, Colombia.

Background: Bone mineral disorders are frequent in patients with chronic kidney disease (CKD). Renal transplantation inherits the morbidity burden of the previous subject, including the risk of calcification disorders and cardiovascular diseases. Surveillance of bone mineral metabolism alterations in renal transplant recipients is mandatory.

Methods: A longitudinal study. Patients ≥18 years from the Local CKD Registry Cohort and functional renal allograft with at least 6 months of follow-up in the transplant program were enrolled. Clinical and laboratory variables from pathology follow-up examinations were retrospectively evaluated.

Results: On total of 138 patients, mean age (59%), with a mean age of 43.7±12.3 years were included. A high prevalence of alterations in bone mineral metabolism was found: 78.36% at one-month post-transplant, 66.66% at 3 months, 69.56% at 6 months and 45.65% at 12 months. The most common alterations were: hyperparathyroidism (63%), hypercalcemia, hyperphosphatemia and hypovitaminosis D.
Conclusions: In this study, patients who underwent renal transplantation exhibited a significant prevalence of persistent hyperparathyroidism, irrespective of hypercalcemia. These findings highlight the critical need for diligent monitoring and effective management of bone mineral disorders in post-transplantation patients.

PUB415
Metabolic Profiles in Renal Transplantation: Assessing Hyperglycemia and Dyslipidemia Prevalence in Kidney Transplant Recipients from the Colombian Caribbean
Karen G. Lasso,1 William B. Riascos,1 Omar Cabarcas Barbosa,1 Alex Domínguez-Vargas,2 María I. Pulgar,1 Henry J. Gonzalez Torres,1 Gustavo Aroca Martínez,1 Universidad Simón Bolívar Facultad de Ciencias de la Salud, Barranquilla, Colombia; 2Universidad del Norte Division Ciencias de la Salud, Barranquilla, Colombia; 3Clínica de la Costa Ltda, Barranquilla, Colombia.

Background: The renal transplant patient is at high risk of metabolic complications such as hyperglycemia, dyslipidemia, overweight, obesity and hyperuricemia. These conditions may affect the graft, cause early dysfunction and increase morbidity and mortality. The aim of this study was to determine the prevalence of metabolic disorders in renal transplant recipients in a fourth level hospital from the Colombian Caribbean.

Methods: This was a descriptive cross-sectional study that included patients aged 18 years and older from the Local CKD Registry Cohort with a functional renal allograft. Clinical and laboratory variables from pathology follow-up examinations were retrospectively evaluated.

Results: A total of 138 patients were included, mainly men (59%). The average age was 43.7±12.3 years. Mean paraclinical values were: glycemia 106.3±274.1 mg/dL, total cholesterol 206.5±274.1 mg/dL, LDL cholesterol 206.5±274.1 mg/dL, HDL cholesterol 37.1±8.2, VLDL cholesterol 55.6±25.4 mg/dL, triglycerides 274.1±133 mg/dL. Prevalence of altered lipid profile parameters and altered fasting glycemia were observed at different times during the period evaluated, including as 24-hour proteinuria of 6 grams. They underwent a renal biopsy that demonstrated glomerular capillary loops with frequent spikes and holes, glomerulitis, 30-40% interstitial fibrosis and the presence of pericapillaritis. Immunofluorescence showed strong C4d deposition. Complementation of immunofluorescence with research for podocyte autoantibodies was requested, with positive research for IgG1, and negative for IgG4, PLAR2, THSD7A, NELL1, EX1 and EXT2. DSA research showed the presence of antibody against HLA A1 (MFI: 13029). Intravenous immunoglobulin was administered, with partial improvement in creatinine. The patient evolved with graft loss 1 year after treatment.

Conclusions: In this study, patients who underwent renal transplantation exhibited a significant prevalence of hyperglycemia and dyslipidemia. Early detection and targeted interventions at 12 months post-transplantation are recommended to mitigate the long-term effects of these conditions in post-transplantation patients.

PUB416
De Novo Membranous Nephropathy and Humoral Rejection: A Different Presentation with a Shared Alloimmune Trigger
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Introduction: Membranous nephropathy (MN) is a glomerulopathy that can occur in a primary or secondary form. It is known that the primary form is related to the presence of autoantibodies against podocyte surface antigens, such as phospholipase A2 receptor (PLAR2) in up to 80% of cases. De novo MN has been described and related to humoral rejection, with the presence of circulating donor-specific antibodies (DSA) and biopsy findings of microvascular inflammation and C4d deposition in peritubular capillaries.

Case Description: A 26-year-old patient with CKD of unknown etiology underwent kidney transplantation from a deceased donor. The immunosuppression was tacrolimus and sodium mycophenolate. He had variable serum concentrations of tacrolimus despite maintenance of the dose, due to possible poor adherence. After 7 years of transplantation, he showed a significant increase in creatinine within a 3-month interval, as well as 24-hour proteinuria of 6 grams. They underwent a renal biopsy that demonstrated glomerular capillary loops with frequent spikes and holes, glomerular capillary loops with frequent spikes and holes, glomerulitis, 30-40% interstitial fibrosis and the presence of pericapillaritis. Immunofluorescence showed strong C4d deposition. Complementation of immunofluorescence with research for podocyte autoantibodies was requested, with positive research for IgG1, and negative for IgG4, PLAR2, THSD7A, NELL1, EX1 and EXT2. DSA research showed the presence of antibody against HLA A1 (MFI: 13029). Intravenous immunoglobulin was administered, with partial improvement in creatinine. The patient evolved with graft loss 1 year after treatment.

Discussion: De novo membranous nephropathy after kidney transplantation may be associated with humoral rejection and be induced by alloimmune responses. The case above strengthens this hypothesis, as it fulfills the classic BANFF criteria for humoral rejection: presence of circulating DSA, glomerulitis and pericapillaritis on light microscopy and positive C4d on immunofluorescence. Furthermore, the search for the main autoantibodies involved in the pathogenesis of the primary nephropathy (IgG4, PLAR2, THSD7A, NELL1, EX1 and EXT2) was negative, but positive for the IgG1 subclass that is related to de novo MN. The distinction between both is important for defining the treatment and prognosis.

PUB417
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Background: In 2020, in response to the SARS-CoV-2 pandemic, our center implemented a telehealth (TH) appointment option for kidney transplantation (KT) evaluation. TH has been shown to decrease travel time to clinic appointments and improve healthcare access for patients living in rural locations. It is unknown whether TH impacts KT patients’ access to initial evaluation and waitlisting. We investigated the patient demographics of those who utilized TH for KT evaluation and the impact TH had on the early stages of KT evaluation.

Methods: We performed a retrospective cohort study of adults referred for KT evaluation from 01/31/2020 -12/31/2021. We compared baseline clinical and sociodemographic characteristics between patients who were 1) seen in person (IP) vs. seen via TH for their first KT clinic appointment and 2) whether TH impacted KT waitlisting.

Results: 620 patients were evaluated for KT during the study period, 343 (55.3%) attended their first appointment IP, 277 (44.7%) attended via TH. TH decreased the time from referral to evaluation by 22 days (117 vs 95; p<0.001). Patients who utilized TH lived further from the transplant center (34 vs 28 miles, p<0.01), were younger (55 vs 60 years; p<0.003), were more likely to be English speaking (93% vs 81%; p<0.001) and employed (73% vs 56%; p<0.001) and were less likely to be on dialysis (36% vs 52%; p=0.004). There was no significant difference in the rates of waitlisting between IP vs TH (31% vs 33%; p=0.3).

Conclusions: The use of TH services during early stages of the KT process decreases the time from referral to evaluation, but does not affect rates of waitlisting for KT. Inequities in TH use for KT evaluation are of concern meriting further attention to ensure equitable access.

Funding: NIDDK Support
PUB418
Desensitization Protocol in Pakistan: Is It Worth Doing? A Case Series
Nosheen Anjum, Zahid Nabi, Zahidul Zahideen, Waisif Jamil. Transplant Team, KRL Hospital, Islamabad, Pakistan.

Introduction: Comparing with dialysis treatment for ESRD patients, renal transplant proffers significant survival and quality of life benefits. However, all-inclusive rates of transplantation still remain less for highly sensitized patients. For such cases, advanced approaches include (I) combinations of IVIg, rituximab, PE, bortezomib (II) pair donor exchange (PDE) (III) deceased donor allocation system (DDAS). At present, there are no guidelines for desensitization protocols and most of the published data is based upon * best practices * for desensitization that require individualization among patients. In countries like Pakistan with non-availability of PDE or DDAS, desensitization protocols should be utilized for highly sensitized patients.

Case Description: Methodology: We report two cases of highly sensitized live related renal transplant patients who underwent successful renal transplantation, after application of desensitization protocol using combination of IVIg, rituximab and PLEX in the first case and with addition of bortezomib to previously mentioned combination in second case. Results: Our first patient had positive DSA with MFI of 12000. After desensitization with combination of 2 Rituximab doses, 8 PLEX & IVIg, achieved MFI of 1700, and was therefore proceeded for renal transplant. In our second case, same protocol with addition of 3 doses of Bortezomib IV, DSA decreased significant to 2700 from 13000. Followup DSA at intervals of 1 and 3 months showed values in range of 400-600, Cr of 1.0 to 1.1mg/dl.

Discussion: Desensitization offers a significant improvement in renal transplant rates with impressive outcomes. In third world countries like Pakistan, where mostly adequate dialysis is not available and mortality rate is high, also overall financial burden is also a significant issue, performing renal transplant in highly sensitized population showed a preferable treatment option.

PUB419
Neurocognitive Concerns in Infants and Toddlers Awaiting a Kidney Transplant
Sarah J. Kizilbash, Finola E. Kane-Grade, Danielle Glad, Michael D. Evans, Lidan Gu. University of Minnesota Twin Cities School of Medicine, Minneapolis, MN.

Background: The KDIGO (Kidney Disease Improving Global Outcomes) guidelines suggest neurocognitive assessment in pediatric kidney transplant candidates with end-stage kidney disease (ESKD) before 5 years of age. However, there are limited data delineating the neuropsychological characteristics of infants and toddlers awaiting a kidney transplant.

Methods: Twenty-five infants and toddlers between ages 0 and 2 years completed the Bayley Scales of Infant and Toddler Development (3rd Edition and 4th Edition) at our center as part of their pre-transplant evaluations. Descriptive analyses were performed to summarize the distribution of characteristics within this population. We used one-sample t-tests to compare the standard scores of study participants with the population mean. Pearson correlations were used to examine the correlations between the Bayley scores and age at the evaluation as well as the dialysis duration.

Results: The mean age of this cohort was 1 year (SD 0.76). Within this cohort, 68% of patients were white, 72% were male, and 72% had congenital anomalies of the kidney and the urinary tract (CAKUT). Of all patients, 28% received no dialysis, while 44% received dialysis for more than 1 year. The mean dialysis duration was 432 days (SD 474 days). The mean scores of cognitive assessment (mean 86.7, SD 2.99), language assessment (mean 79.2, SD 2.81), and motor assessment (mean 78, SD 17.3) were significantly lower than the population means (t=-4.43, t=-7.40, t=-5.84, respectively, p<0.001). We found a significantly positive correlation between age and motor scores (r=45, p=0.04) and a significantly negative correlation between dialysis duration and Bayley subscales, including cognitive (r=-0.50, p=0.02), language (r=-0.62, p=0.004), and motor scores (r=-0.63, p=0.003).

Conclusions: We found a significant correlation between dialysis duration and cognitive, language, and motor scores on the Bayley Scales of Infant and Toddler Development among children awaiting a kidney transplant. Moreover, the cognitive, language, and motor scores of infants and children awaiting a kidney transplant are significantly lower than the population means. Infants and children in this group may benefit from early physical therapy, occupational therapy, and speech therapy.

PUB420
Sex Differences in Non-Nephrologist Care Providers’ Knowledge and Perceptions of Female Reproductive Health in CKD: A Survey Protocol
Tina Kim, Cameron Taheri, Sharanaya Ramesh, Sofia B. Ahmed, Victoria J. Richi-Tonn, Karen Fordham, Sandi M. Dumanski. University of Calgary Cumming School of Medicine, Calgary, AB, Canada.

Background: Chronic kidney disease (CKD) affects 12% of females globally and has important implications for reproductive health. Despite recommendations for multidisciplinary care, many females with CKD are managed independently by non-nephrologist care providers. This study aims to assess sex differences in non-nephrologist care providers’ knowledge and perceptions of reproductive health in females with CKD.

Methods: A web-based survey will be developed following a literature review and consultation with experts in the field, as well as patient partners. Non-nephrologist care providers’ knowledge and perceptions of reproductive health in females with CKD will be assessed, specifically as it relates to sexual health, menstruation, fertility, pregnancy, and menopause. Survey validity, clarity, and usability will be evaluated through pre-testing. The survey will be available in the world’s 10 most commonly spoken languages. Snowball sampling will be employed via targeted emails to international and national reproductive healthcare provider organizations, as well as through social media platforms.

Results: Numeric and Likert-scale survey responses will be descriptively analyzed and free-text survey responses will undergo conventional content analysis. All results will be stratified by sex.

Conclusions: An improved understanding of sex differences in non-nephrologist care providers’ knowledge and perceptions of female reproductive health in CKD can help identify gaps in care delivery and optimize reproductive health for this underserved population.

PUB421
Clinicopathological Study of Nine Cases of Proteinuria in Pregnancy, Including Hypertensive Disorders of Pregnancy
Rei Nakazato,1 Akiko Mii,1 Akira Shimizu,1 Yukinasa Sakai,1 Nihon Ika Daigaku Fuzoku Byoin, Bunkyo-ku, Japan; 2Nihon Ika Daigaku, Bunkyo-ku, Japan.

Introduction: Advanced maternal age is a risk factor for prenatal complications including hypertensive disorder of pregnancy (HDP). Furthermore, severe proteinuria during pregnancy suggests the possibility of HDP and/or pregnancy-related renal complications, increasing the risk of worsening maternal renal prognosis.

Case Description: Over the past seven years, we experienced nine pregnant cases with severe proteinuria that required intervention from the internal medicine department. The average maternal age of all cases was 37.6 years old, and seven of the patients were advanced age pregnancy (>35 years old). Among the cases, seven presented nephrotic
syndrome (NS) and eight patients underwent renal biopsy, revealing in IgA nephropathy (n=3), focal segmental glomerulosclerosis (FSGS) (n=3), and membranous glomerulonephritis (n=2). Five patients were diagnosed with HDP and their mean gestational age at diagnosis was 36 weeks, with blood pressure (BP) of 155/86 mmHg, and urinary protein (U-P) level of 9.5 g/g Cr at any time. All HDP cases received antihypertensive therapy. Three of them improved proteinuria through medication alone, one required continuous hemodialfiltration for pulmonary edema after birth, and another case received plasmapheresis for obstetrical DIC and acute kidney injury. The four non-HDP patients were diagnosed at a mean gestational age of 27 weeks, with a BP of 122/74 mmHg, and U-P level of 1.8 g/g Cr at any time. These cases included IgA nephropathy, FSGS (cellular variant and tip variant), and MCNS, respectively, and underwent steroid therapy resulting in remission.

Discussion: We encountered nine cases of proteinuria in pregnancy, including HDP cases. A majority of the patients were of advanced maternal age, which is considered a risk factor for HDP. Our findings suggest that antihypertensive therapy can be expected to improve severe urinary protein levels in HDP cases although their histopathological findings were varied. On the other hand, it was crucial to identify the cause of proteinuria and to treat the underlying disease appropriately. Therefore, it is also important to perform renal biopsies whenever possible.

PUB422
Perceptions of Gynecologic Health and Health Care in Females Living with CKD: A Survey Protocol
Tessa A. Woodside,1 Victoria J. Riehl-Tonn,1 Sofia B. Ahmed,1 Erin A. Brennan,1 Meghan J. Elliott,1 Danica H. Chang,1 Karen Fordham,1 Sandi M. Dumanski,1,2 University of Calgary, Calgary, AB, Canada; 3University of Alberta, Edmonton, AB, Canada.

Background: Chronic kidney disease (CKD) affects more than 12% of females globally and its prevalence is increasing rapidly. CKD is often accompanied by gynecological health complications, with implications for menstruation, menopause, sexual function, and fertility. However, patient perceptions of gynecologic health and healthcare in females living with CKD are poorly understood. This study aims to assess the perceptions of gynecologic health and healthcare of females living with CKD.

Methods: An exploratory web-based survey will be developed following a thorough literature review and after consulting with experts in the fields of nephrology and gynecology, and with the engagement of patient partners. The questions will address patient perceptions of gynecologic health and healthcare-related to menstruation, menopause, sexual health, fertility, pregnancy, and urinary incontinence. Survey pre-testing with patient partners will assess face validity, clarity, length, usability, and technical functionality. The web-based survey will utilize adaptive questioning to help reduce survey complexity. Self-identified adult females with CKD will be invited to participate through national and international CKD patient organizations, as well as through social media platforms.

Results: Numeric responses will be analyzed using descriptive statistics and opened responses will be analyzed using conventional content analysis.

Conclusions: This study will be the first to our knowledge to assess comprehensive gynecologic health and healthcare-related perceptions of females living with CKD, and will aid in the integration of patient perspectives into future research and clinical initiatives.

PUB423
Biomarker Associations with Kidney Failure and Death
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Background: The NURTuRE CKD cohort comprises a wide range of biomarker measurements and outcome data for 2996 CKD patients based in the UK. A comparative study would outline the relative importance of various biomarkers with respect to predicting mortality and kidney failure (KF) of interest in biomarker selection for future studies.

Methods: Using biomarker data from the NURTuRE CKD cohort, we compared the means of patients who suffered KF (defined as dialysis start or transplant) or death within 2 years versus those who did not. A log-transform was applied to biomarkers with skew > 4, and a square root transform to biomarkers with skew between 1 and 4. After these transformations, all skew were within -1 and 1. Mean biomarker differences in the positive and negative groups were then assessed by computing deviations from the negative group means, scaled by the standard deviations of the negative group.

Results: Figure 1 shows mean comparator differences scaled by standard deviation. For example, the first blue bar indicates that eGFR (after normalization) was about 1.25 standard deviations lower on average in patients who suffered kidney failure within 2 years compared with those who did not. Similarly, the first orange bar indicates 0.5 standard deviations lower eGFR in patients who died within 2 years compared with those who did not. The markers associated with the 4 largest differences for kidney failure were eGFR, serum-Creatinine, serum-Cystatin C, and Urine-ACR. The markers associated with 4 largest differences for death were serum-Troponin, Age, brain-natriuretic peptide (BNP), and serum-growth differentiation factor-15 (GDF15).

Conclusions: The top four biomarkers associated with mortality (Troponin, Age, BNP, GDF15) are distinct from the top four biomarkers of kidney failure (eGFR, Creatinine, Cystatin-C, ACR). Perhaps unsurprisingly, the kidney failure markers are all related to kidney failure, whereas the mortality markers are related to cardiac disease.

Funding: Commercial Support - AstraZeneca

Figure 1: Mean biomarker differences in patients who suffered kidney failure or death within 2 years vs those who did not, scaled by standard deviation.

PUB424
The Variation of Estimated Glomerular Filtration Rate (eGFR) with Changes of Body Weight and Body Composition in a Health Check-Up Cohort Without CKD
Soomin Kim,1 So Young Jang,1 Ho Jun Chin,2 1Seoul National University Bundang Hospital, Seongnam, Republic of Korea; 2Seoul National College of Medicine, Seoul, Republic of Korea.

Background: Obesity is well known risk factor to chronic kidney disease, cardiovascular disease, and mortality. However, the effect of weight change within normal weight range on renal function has not been studied, well.

Methods: We enrolled non-CKD participants who had repeated routine health check-up at baseline, one-year, and three-year follow-up period. We measured fat-free weight (FFW) and fat-free percent (FFP) in body weight by InBody test. We analyzed the relationship between changes of body weight, BMI, FFW, and FFP during one-year follow-up period and variation of eGFR during three-year follow-up period. We define rapid decline of renal function as a decrease in eGFR ≥ 5 ml/min/1.73 m²/year.

Results: Enrolled 1837 participants had eGFR of 101.1 (60.2–187.5) ml/min/1.73 m² and urine proteinuria by dipstick test less than one positive. Indicators of body composition were body weight of 66.8 (39.5–117.4) kg, BMI of 23.7 (15.2–36.2) kg/m², FFW of 53.1 (30.9–78.1) kg, and FFP 78.4 (59.4-95.5) % at baseline examination. During one year of change, the eGFR of participants was related to percent change of FFP (factor B=-0.197, p=0.012) and FFW (factor B=0.347, p<0.001), positively. There were 366 participants with rapid decline of eGFR during 3 years. With multiple logistic regression analysis, the factors related to rapid decline of eGFR during 3 years were the percent change of FFW [RR 1.054 (95% CI: 1.011-1.099), p=0.013, Table]. With the quintile group of percent change of FFP, multiple logistic regression to estimate rapid decline of eGFR showed increased relative risk to 1.400 (95% CI: 1.009-1.943, p=0.008) in highest quintile group compared to third and fourth quintile group.

Conclusions: During short-term period, the change of fat-free weight was related to increase of eGFR, however, it was related to decline of renal function in long-term period. That suggested initial rapid renal hypertrophy by increase of fat-free weight would have resulted in decline of eGFR in the end.

PUB425
Prevalence of Asymptomatic Urinary Leptospira Carriage Among Young Adults at Risk of Mesoamerican Nephropathy
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Background: Leptospirosis is a bacterial zoonosis with a range of clinical manifestations including acute kidney injury. Chronic carriage of leptospira is well-described in several species, but it remains unclear whether this occurs in humans. Furthermore, chronic experimental infection with leptospira is associated with progressive
kidney injury in small animal models and asymptomatic carriage of leptospirosis has been proposed as a cause of CKD of unknown aetiology, one form of which is Mesoamerican Nephropathy (MeN). Determining the burden of asymptomatic leptosomal infection is challenging as serological assays may not be sensitive to antibodies against all serovars and immunoassays may wane over time. We therefore explored the evidence for asymptomatic carriage of urinary leptospirosis in a young adult population at risk of MeN.

**Methods:** Samples were analysed at multiple time points per individual from a community-based, longitudinal study of apparently healthy young adults (mean age = 24.2, mean baseline eGFR = 110.5 ml/min/1.73m², % male = 83.2) from rural north-west Nicaragua followed-up annually for 7 years. Serum anti-leptospirosis IgG antibodies were measured in 346 participants using a commercial ELISA kit and an established nested 16S PCR method was used to screen for leptosomal DNA in urine in 94 participants. Sanger sequencing was used to confirm leptosomal species in a subset of 16S PCR positive samples.

**Results:** None of the participants had recent symptoms of acute leptosomal illness. 55 (59%) participants were 16S PCR positive at ≥1 timepoint, 346 of whom had 2 and 18% were positive at 2 timepoints. Subsequent analysis demonstrated 29% of 16S PCR positive samples were consistent with leptosomal DNA, suggesting an overall prevalence of asymptomatic carriage of 17%. Overall, 8.7% (30/346) of participants tested IgG positive for leptospirosis in at least one timepoint of whom 12 seroreverted after follow-up testing. Rates of seroreversion were similar between 16S PCR positive and negative groups.

**Conclusions:** Asymptomatic urinary shedding of leptospirosis is common in a young adult population at risk of MeN which appears to be persistent or recurrent in some cases. Serological assays do not reliably identify individuals shedding urinary leptosomal DNA.

**PUB426**

**Albuminuria and Incident Atrial Fibrillation in Community-Dwelling Adults:** The REGARDS Study

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**Background:** Higher urinary albumin-to-creatinine ratio (ACR) is associated with increased risk of atrial fibrillation (AF). ACR is more strongly associated with incident stroke and coronary heart disease in Black compared to White adults. We aimed to determine whether similar racial differences exist for AF.

**Methods:** Prospective cohort study of community-dwelling adults ≥45 years old enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Modified Poisson regression with robust variance estimates was used to examine the associations of ACR measured at the baseline visit with the validated outcome of incident AF based on electrocardiogram or self-report of physician-diagnosis at the second in-home visit approximately 10 years later. Models were adjusted for demographic variables and AF risk factors including eGFR.

**Results:** Among 11,929 participants (mean age 63 years, 45% male, 36% Black), there were 1,042 (8.7%) with incident AF. In the fully adjusted model (see Figure), compared to ACR <10 mg/g, the association between ACR and incident AF did not differ between Black (RRadj=1.06; 95% CI: 0.76-1.47) and White (RRadj=1.06; 95% CI: 0.89-1.25) participants in the ACR ≥10 and <30 mg/g category. In contrast, compared to ACR <10 mg/g, ACR ≥30 mg/g was associated with greater risk of incident AF in White (RRadj=1.33; 95% CI: 1.08-1.64) but not in Black (RRadj=1.07; 95% CI: 0.77-1.49) participants, although the multiplicative interaction term was not significant (p=0.84).

**Conclusions:** The association between urinary ACR and incident AF did not appreciably differ by race.

**Funding:** Other NIH Support - This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service.

**References:**

RRs and 95% CIs for incident AF among Black and White participants by ACR categories. The model was adjusted for age, sex, and geographic region of residence, education, income, smoking, alcohol consumption, waist circumference, exercise, systolic blood pressure, cholesterol, coronary heart disease, stroke, diabetes, statins, antihypertensives, RAAS inhibitors, and eGFR.

**PUB427**

**Associations of Causes of CKD with Disease Progression and Mortality:** Insights from the Fukuoka Kidney disease Registry (FKR) Study

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**Background:** The Kidney Disease: Improving Global Outcomes guidelines recognize the significance of causes of chronic kidney disease (CKD), glomerular filtration rate, and albuminuria as predictors of kidney outcome and prognosis. However, limited research has explored the relationship between clinically-diagnosed causes of CKD and prognosis, in comparison to biopsy-proven causes.

**Methods:** We examined 3,119 patients with non-dialysis-dependent CKD who participated in the Fukuoka Kidney disease Registry Study, a multicenter prospective cohort study. Patients were divided into six groups: IgA nephropathy, chronic glomerulonephritis (non-biopsy-proven), diabetic nephropathy, hypertensive nephrosclerosis, chronic interstitial nephritis, and polycystic kidney disease. The primary outcomes included a composite kidney outcome, defined by a 1.5-fold increase in serum creatinine and/or development of end-stage kidney disease, and all-cause mortality. The risks for these outcomes were estimated using a Fine-Gray proportional subdistribution hazards model. IgA nephropathy, the most prevalent primary glomerulonephritis, served as the reference group.

**Results:** During the median follow-up period of five years, 1,221 patients developed the composite kidney outcome, and 346 patients died. Compared to IgA nephropathy, the multivariable-adjusted subdistribution hazard ratios (sHRs) for the composite kidney outcome were significantly higher in diabetic nephropathy (sHR 1.45) and polycystic kidney disease (sHR 2.07), while chronic interstitial nephritis showed a significantly lower risk (sHR 0.71). The risk of all-cause mortality was significantly higher in hypertensive nephrosclerosis (sHR 1.90).

**Conclusions:** The causes of CKD were associated with the risks of the composite kidney outcome and all-cause mortality, underscoring their clinical relevance in predicting prognosis. These findings suggest that different causes of CKD have distinct impacts on patient outcomes, emphasizing the importance of tailored management strategies based on the underlying causes.

**PUB428**

**Influence of Consecutive AKI Episodes on CKD Progression**

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**Background:** Is a well-known fact that AKI leads to progression of preexisting CKD. Despite this evidence, we find that some patients after successive AKI episodes progress and some that do not. We aimed to study potential risk factors for worsening CKD stage when suffering from AKI on CKD (AoCKD) besides AKI severity.

**Methods:** Retrospective, study of hospitalized patients that suffered at least 3 AoCKD episodes during a 4-y period. We defined progression as the change to a higher CKD stage compared to the stage of the first AoCKD event, or HD dependence at discharge. In-hospital mortality was not considered an indicator of progression. We defined high Charlson’s (ChI) as Score ≥3, classified AKI with the KDIGO-2012 criteria, compared clinical variables and searched for risk factors for progression.

**Results:** We included 485 AoCKD episodes of 129 individuals. 58 (45%) progressed, 13 were HD dependent at discharge (22% of progressors); they had a higher ChI, were classified in KDIGO-AKI stage 3 and needed acute HD more frequently. We found no statistically significant differences in age, admission in ICU, time to nephrology consultation, KDIGO-AKI stage 2, and in-hospital mortality (Table 1A-B). When analyzing variables, we found risk factors for progression OR: Need for
HD 2.98 (1.22–7.27), KDIGO-3 stage 3.00 (1.46–6.16), High Chl 8.6 (1.10–69.70), and being hospitalized in a Medical Ward 2.22 (1.12–4.40) (Table 2).

**Conclusions:** We found that relatively less patients are progressors, could this finding be explained because CKD confers a physiological adaptation to AKI? We observed that factors that promoted CKD progression were: AKI severity in a dose dependent manner; High Chl ≥3, need for HD and being hospitalized in medical ward, due to a skew of non-progressors being hospitalized in surgical wards? All these factors are not modifiable, so we should be more creative and search for non-traditional factors to try to find modifiable ones, to tackle CKD progression due to AoCKD.

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**Results:**

- **NAFLD incidence:** 89.8%.
- **Obese patients:** 63.1%.
- **Men ≥41%:** 46.6% (Stage 4 severe).
- **Women ≥56%:** 35.8% (Stage 1). UACR: 257.6 (629) vs 265 (638) (NS).
- **Stage distribution:** Healthy: 10.2%; Stage 1: 10.7%; Stage 2: 16.7 (25) vs 14.74 (p<0.001); GFR: 50.09 (26.8) vs 66.14 (32.09) (p<0.001).

**Methods:** The study includes 1143 patients, and 766 (67%) had ≥1 risk factors for hyperkalemia (K≥5.0 mEq/L).

**Results:**

- **Baseline:** Onset of hyperkalemia.
- **ACE-I or ARB:** May affect the acid-base status of CKD patients.
- **Conclusions:** The results provide evidence to guide the management of hyperkalemia in CKD patients, and the impact of ACE-I or ARB on the acid-base status of these patients needs to be further studied.

**Funding:** Commercial Support - AstraZeneca.
Clinical Characteristics, Treatment Patterns, and Renal-Related Events in Patients with Diagnosed CKD: Results from Regional Health Information System in China

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Background: The clinical characteristics, treatment patterns and renal-related events of diagnosed chronic kidney disease (CKD) provide evidence that can improve CKD management. However, the situation in China remains under-investigated.

Methods: We included adults with electronic health records (2020.01-2021.12) in Xuzhou, China. Clinical diagnosis of CKD was defined as having diagnostic keywords and International Classification of Disease (ICD)-10 codes related to primary cause or stages of CKD. All patients with diagnosed CKD were required to have at least one follow up visit after being enrolled, and were further categorized into dialysis and non-dialysis groups. Among the non-dialysis, individuals diagnosed with hypertension and diabetes were categorized as two independent subgroups.

Results: A total of 58,651 patients with diagnosed CKD were identified, including 55,580 non-dialysis and 3071 dialysis individuals. Cardiovascular diseases accounts for 43.8% of all non-dialysis individuals, followed by peripheral vascular disease (25.4%) and diabetes (12.5%). 44.8% of all non-dialysis patients had received CKD-related therapies, including ACEI/ARB (19.2%), SGLT2i (2.8%), glucocorticoids (24.0%), immunosuppressants (3.6%), traditional Chinese medicine for kidney protection (13.3%), et al. A total of 176 renal-related events (0.3%) occurred during follow-up period, including 52 cases of sustained decline in eGFR and 168 cases of progression to ESKD. Besides, 3 patients with advanced MACE events (4.7%). Compared to the general population of non-dialysis patients, individuals with hypertension or diabetes had higher incidence of renal related events (hypertension:0.5%, diabetes:0.7%) and MACE events (hypertension:10.0%, diabetes:11.7%).

Conclusions: Patients with diagnosed CKD in this cohort frequently complicate cardiovascular diseases. Despite being diagnosed with kidney disease, the proportion of individuals receiving CKD-related therapies remains low, and the incidence of renal-related and MACE events should be noticed.

Hospitalizations Among Adults with CKD: Results from KNOW-CKD Study

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Background: Chronic kidney disease (CKD) patients are hospitalized for various causes. Hospitalization increases the readmission rate and mortality rate, seriously deteriorating patients’ quality of life. For this reason, it is crucial to analyze the causes of hospitalization in CKD patients in a broader perspectives according to CKD grades.

Methods: This study was conducted as a prospective cohort of CKD patients, entitled KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). A total of 2,238 patients were examined in this study, and the causes of hospitalization were classified into 16 disease categories. The incidence rate ratio (IRR) of hospitalization in CKD patients in a broader perspectives according to CKD grades.

Results: A total of 193.86, and 310.11 per 1000 person-years. In the hospitalizations for acute kidney injury, endocrine, nutrition, metabolic related cause, nervous system disease, and genitourinary causes. Hospitalization increases the readmission rate and mortality rate, seriously deteriorating patients’ quality of life.

Conclusions: The all-cause hospitalization incidence was 184.96 per 1000 person-years. The most common cause of hospitalization was circulatory system disease, followed by infection and digestive system disease. When analyzing the incidence rate of all-cause hospitalization according to CKD grades, patients had an incidence of 101.99, 143.68, 193.86, and 310.11 per 1000 person-years. In the hospitalizations for acute kidney injury, endocrine, nutrition, metabolic related cause, nervous system disease, and genitourinary system, the IRR increased as the grade advanced. IRR of KNOW-CKD patients was 5.92(95% CI; 5.66-6.19; P-value<0.001) compared to general population.

Funding: Government Support - Non-U.S.
Predictors of Disease Progression in Patients with CKD: Results from a Real-World Study
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Background: Clinical decision making is difficult due to the complex heterogeneous nature of chronic kidney disease (CKD) and its variable rate of progression. We aimed to understand the key predictors of CKD progression and subsequent impact on patients.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a cross-sectional survey of physicians and patients conducted in the USA from Jan-June 2022. Physicians recorded patient demographics, disease characteristics, concomitant conditions treatment history and consultation history. Non dialysis (ND) patients reported their current and most troublesome symptoms. Elastic net regression analysis was conducted.

Results: Physicians provided data for 1525 ND patients, of these 379 also provided data. Mean [SD] age was 61.9 [13.87], 57% were male, and 55% were white. Almost half of patients had progressed (CKD stage) since diagnosis (47%). Regression analysis identified the strongest predictors of CKD progression to include: kidney pain, joint stiffness and shortness of breath, high/very high cardiovascular risk and proteinuria (Figure 1). The strongest predictor, kidney pain, was reported as a current symptom by 10% of patients and of those, 59% reported this to be their most troublesome symptom. Of the patients experiencing joint stiffness (11%) and shortness of breath (13%), approximately a third of these patients reported them to be their most troublesome symptom(s) (31% and 35% respectively).

Conclusions: Presence of kidney pain is a strong predictor of CKD progression and in our study was shown to be most troublesome for over half of the patients experiencing it. In addition to treating the most prevalent symptoms, physicians should aim to control/treat less prevalent symptoms to help slow progression and improve patient outcomes.

Changes in GFRe in a Cohort of Qom Indigenous over a 15-Year Interval
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1Fundacion Renal del Nordeste Argentino, Resistencia, Argentina; 2Universidad Nacional del Nordeste Facultad de Medicina, Corrientes, Argentina.

Background: The Qom ethnic group lives in the province of Chaco, one of the lower incomes in Argentina. In the last 15 years, they access to better living conditions. Illiteracy is 8%. The nutritional transition of poor populations goes from the double burden of malnutrition to obesity. The objective of this work is to describe the changes of eGFR by CKDEpi, and the frequency of proteinuria, obesity, HT, and DM in a cohort of the Qom ethnic group, inhabitants of suburban neighborhoods of the city of Resistencia, Chaco, Argentina, in two cross-sections (2003-2018).

Methods: A descriptive, observational study of two cross-sections was carried out in 2003 and in 2018, visiting each participant’s home, and were included after signing the informed consent. Glycemia was measured by the Hexokinase Enzymatic Method, in 2003 and in 2018, visiting each participant’s home, and were included after signing the informed consent. Glycemia was measured by the Hexokinase Enzymatic Method.

Results: 65 people were studied. The mean age in 2003 was 33.57 ± 12.53 and 49.09 ± 12.40 years old in 2018; 38 (62.3%) were female. The eGFR in 2003 was 101.10 ± 15.39 ml/min and in 2018, 102.10 ± 15.85 ml/min; 19.7% and 23% (p=0.02) respectively presented proteinuria. HT increased from 26.22 to 62.69%; 14.2% developed DM. Obesity increased from 26.2% to 60.6%. Low RR raised from 68.3% to 76, 66%, 10% to 21.66% moderate and high RR only 1.66% in 2018. The correlation between GFRe in 2003 and 2018 is shown in Figures 1 and 2.

Conclusions: This epidemiological study shows that eGFR tends to increase due to obesity and DM and to decrease in patients with HT in a 15 years interval.

Association of Bicarbonate Use and Incident ESKD Among US Veterans with Incident CKD
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Background: Treatment of metabolic acidosis delayed the decline of kidney function in patients with chronic kidney disease (CKD) in small clinical trials, but the effects of bicarbonate therapy on end-stage kidney disease (ESKD) in unselect populations with all stages of CKD remains unclear. We examined the association of sodium bicarbonate use with incident ESKD in a large national cohort of US Veterans.

Methods: In a cohort of 50,540 patients with incident CKD (eGFR <60 mL/min/1.73m²), we examined the association of de novo prescription of bicarbonate containing medications with incident ESKD (defined as initiation of kidney replacement therapy). We examined associations in Cox proportional hazard models adjusted for demographics, major comorbidities, baseline eGFR, urine albumin-creatinine ratio (UACR), and use of renin angiotensin-system inhibitors.

Results: We identified 11,896 incident new bicarbonate users. Overall mean (SD) age was 65 (10) years, with 3.0% female, 15.3% Black, and 5.5% Hispanic, and baseline eGFR of 35 (11). Bicarbonate users were more likely to be male, Black, current smokers, had higher frequencies of diabetes and liver disease and lower eGFR compared to non-users. ESKD developed in 4860 patients (event rate 37.4/1000 patient years, 95% CI: 36.3-38.4). Bicarbonate use (vs. non-use) was associated with higher risk of incident ESKD in the unadjusted (HR: 8.68, 95% CI: 8.17-9.23) and in the fully adjusted model (8.4, 1.38-5.60). Table.

Conclusions: In this large national cohort of US Veterans with long follow-up time, bicarbonate use was associated with higher risk of incident ESKD. Further studies are needed to test the effects of bicarbonate replacement in patients with CKD.
Effect of Dapagliflozin on eGFR Slope in Nondiabetic CKD Patients

Shunsuke Kitamura, Marumi Kitamura, Yoshibumi Miura, Kotaro Oka, Hidetaka Kato, Hidenori Nakamura, Koji Kamiyama, Atsushi Ueda, Yukihiro Inoue

Introduction: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) have been shown to reduce the risk of cardiovascular and renal events. However, the impact of SGLT2i on kidney function has not been fully elucidated. This study aimed to evaluate the effect of dapagliflozin on the estimated glomerular filtration rate (eGFR) slope in patients with chronic kidney disease (CKD) stages 3-5.

Methods: This was a retrospective observational study. Patients with CKD stages 3-5 were included if they were treated with dapagliflozin for at least 1 year. The eGFR slope was calculated as the difference in eGFR between the baseline and follow-up measurements. Multivariable linear regression analysis was performed to adjust for confounders.

Results: A total of 120 patients were included in the analysis. The mean age was 62 years, and 65% were male. The mean baseline eGFR was 50 ml/min/1.73m². Dapagliflozin was initiated at 10 mg daily in 90 patients and 5 mg daily in 30 patients. The mean follow-up period was 23 months. The mean eGFR slope was -0.17 ml/min/1.73m²/year. The adjusted slope was -0.19 ml/min/1.73m²/year (p < 0.001). The eGFR slope was significantly lower in patients treated with dapagliflozin compared to those who were not.

Discussion: Dapagliflozin was associated with a significant reduction in the eGFR slope in patients with CKD stages 3-5. This finding supports the use of SGLT2i in the management of renal disease.

Extrarenal Pelvis: Benign Anatomical Variation Mimicking Hydroureteronephrosis

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Introduction: Extrarenal pelvis is a benign anatomical variant in which the renal pelvis is outside of the renal hilum without affecting kidney function. It can be challenging to differentiate from hydroureteronephrosis. We report a case of a woman with stable kidney function who was referred for an incidental kidney imaging. A kidney ultrasound confirmed the diagnosis of extrarenal pelvis.

Case Description: A 67-year-old woman without proteinuria or stage 2 chronic kidney disease presumably secondary to hypertension presented with chronic low back pain after a motor vehicle accident 1 year ago. She denied lower urinary tract symptoms, bladder or bowel incontinence, or focal neurological deficits. A pelvic CT scan incidentally showed right extrarenal pelvis without calculi or hydronephrosis (Figures 1A and 1B). A kidney ultrasound revealed the right kidney with normal echogenicity and contour and an extrarenal pelvis measuring up to 1.5 cm without hydroureteronephrosis, focal kidney mass or shadowing stones (Figure 1C). The patient remains having no symptoms and signs of urinary tract obstruction and follow-up serum creatinine has been stable at 0.7 – 0.9 mg/dL.

Discussion: While imaging may show similar findings between the extrarenal pelvis and hydroureteronephrosis, which appears as interconnected areas with branching of decreased echogenicity consistent with fluid, normal or stable kidney function without evidence of obstructive uropathy clinically suggests extrarenal pelvis. Reassuring patients with extrarenal pelvis that their condition is benign and does not require therapy is imperative.
Ultrasound Measured Renal Sinus Fat, Parenchymal Thickness, Interstitial Fibrosis, and Their Association with Renal Function

Ana I. Stark, Jafar Alsaid, Mu’ath N. Abdeen. Ochsner Medical Center, New Orleans, LA.

**Background:** Renal ultrasound is valuable for nephrologists in clinical practice to determine the proper management. Measuring renal sinus fat and renal parenchymal thickness was proven to have some clinical implications. In this study we wanted to determine the correlation between ultrasound measured renal sinus fat length, parenchymal thickness and interstitial fibrosis with renal function.

**Methods:** This is a retrospective cross-sectional study for patients biopsied by the Interventional Nephrology division in Ochsner Medical Center over 2 years 2021-2023. Patients without ultrasound reports were excluded. The demographic factors were recorded from the electronic files. The eGFR was calculated by CKD-EPI equation within the time closest to the biopsy. The sinus fat length was measured on longitudinal sagittal US image. The total renal length was measured on the same image. The renal parenchymal thickness was measured by subtracting the longitudinal sagittal length of the sinus fat from the total kidney length. The percentage of sinus fat length was measured by dividing the length of sinus fat over the total renal length using the ipsilateral site of the biopsy. SPSS 25 was utilized for the descriptive statistics. Two tails Spearman correlation was used to calculate the significant correlation. P<0.01 was needed to reject the null hypothesis.

**Results:** Total patients included were 52. Mean age: 50 years (SD 17.5, SE 2.27). Male gender 45%. Mean BMI 29.3 kg/m2 (SD 7.2, SE 0.9) DM was present in 23% of the patients. HTN was present in 55% of the patients. Mean Intestinal fibrosis was 20%. Mean S. Cr. 2.3 mg/dl (SD 2.2, SE 0.28) Mean eGFR: 42 mL/min. (SD 19.3, SE 2.5)

**Conclusions:** There was a significant correlation between ultrasound measured sinus fat length percentage and parenchymal thickness with renal function. Sinus fat and parenchymal thickness were not associated with age, gender, BMI, DM or HTN. Intestinal fibrosis was significantly associated with S.Creatinine and eGFR.

**Association of renal Sinus fat ratio, parenchymal thickness and interstitial fibrosis with renal function**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>eGFR</th>
<th>Significant correlation coefficient (p-value)</th>
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<tbody>
<tr>
<td>Sinus fat ratio</td>
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<tr>
<td>0.79 (0.485)</td>
<td>2.34 (0.422)</td>
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<tr>
<td>Parenchymal Thickness</td>
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<tr>
<td>0.58 (0.005)</td>
<td>(0.31) (0.225)</td>
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<tr>
<td>Interstitial Fibrosis</td>
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**PUB444**

Is the Predicted Skin-to-Kidney Distance by Analytical Method Useful? A Correlation and Association with Ultrasound-Guided Percutaneous Kidney Biopsy


**Background:** Approach techniques and the use of a distance prediction formula (DPF) have been created, using weight and height to estimate the depth of the skin-kidney distance (SKD) in percutaneous renal biopsy (PRB)* ultrasound guided. Its validation and usefulness are still an opportunity area.

**Methods:** Our objective is to correlate SKD derived by DPF in native PRB compared to real-time ultrasound stratified by body mass index (BMI) categories and evaluate its usefulness and sample quality. This is a cross-sectional study spanning data from 2018-2022 in Interventional Nephrology Service of the National Institute of Cardiology Dr. Ignacio Chávez. Sampling was performed in real time guided ultrasound. DPF = (Body weight [hectograms]/height [centimeters]) -0.5 in all cases. Pearson analysis was made and further stratified between BMI categories and by type of biopsy approach. Dispersion analysis was made by Bland-Altman plots at 1.96SD. Binary logistic regression models were fitted to evaluate the association between SKD and the quality of sample.

**Results:** 300 of 501 PRB were analyzed. The mean BMI was 25.7 kg/m². 71% were performed with transverse approach. 45.7% were classified as normal-weight, 34% overweight and 20.3% obese. The mean SKD measured by ultrasound was 4.3 (±0.6) cm and by DPF of 3.61 cm (±0.42), deriving a correlation of 0.42 (95% CI:0.28-0.55, p<0.001). After stratification, subjects with overweight and obesity had a lower correlation and higher variability compared to subjects with normal weight (Fig. 1). Finally, SKD was not associated with the sample quality (OR:1.3, 95% CI: 0.87-1.47, p=0.36).

**Conclusions:** The formula has a moderate correlation in subjects with normal weight, but not with overweight and obesity. There is no association between the depth, sample quality and complications, hence, its further usefulness must be evaluated for other outcome.

**Funding:** Government Support - Non-U.S.
Underline represents presenting author.

**PUB445**

**Assessing Hospice Referral Quality and Length of Stay in Renal Patients at the Iowa City VA**

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Background: Quality assessment of hospice referrals is crucial, but assessment within the Veterans' Health Administration (VHA) and its concurrent care (CC) coverage is understudied. This study evaluates the quality of hospice care at the Iowa City VA (ICVA) in nephrology patients, including LOS, referral patterns, and the effectiveness of a flagging system for hospice enrollment.

Methods: Our objectives were to implement a standardized system for tracking hospice LOS through Electronic Health Records (EHR) flagging, assess hospice LOS, identify gaps in LOS and referral patterns, and evaluate the accuracy of flag placement for hospice enrollment. We identified ICVA patients who died following hospice referral between October 2018 and July 2021 using an internal database. Focused chart reviews provided LOS, hospice diagnosis, referral source, and time lag between hospice enrollment and flag placement. Additional chart review focused on patients with LOS < 7 days to identify potential gaps in care. Median LOS was compared using Kruskal-Wallis, and Chi2 analysis assessed enrollment rates across groups.

Results: Analysis included 661 patients. Common hospice diagnoses were cancer (47.4%), cardiac disease (13.3%), and respiratory illness (13.0%). Among CC patients, cancer was the predominant diagnosis (80.4%). The median hospice LOS was 27.5 days (range: 0-912), while CC LOS was 62 days (range: 4-721). The mean gap between hospice enrollment and flag placement was 3.8 days, with a median discrepancy of 1 day and mode of 0 days (range: 0-514 days). Hospice LOS did not significantly vary by diagnosis, year, or referral source, and CC LOS did not vary by diagnosis. Renal disease patients were underrepresented in both groups and had comparatively shorter median LOS (14 days). Approximately 20% of patients had a short LOS (7 days or less).

Conclusions: Manual flagging of patient charts provides a reliable method to track hospice enrollment date and LOS, with potential implications for the VHA. Our study identified areas for improvement, particularly in the care of nephrology patients with renal disease and those with short LOS. Implementing interventions to address these findings can enhance end-of-life care in nephrology within the ICVA.

**PUB446**

**Molecular and Metabolic Alterations of Lipoproteins and Fatty Acids in CKD**

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Background: Chronic kidney disease (CKD) has a significant impact on lipid and lipoprotein metabolism and homeostasis. These modifications play a crucial role in promoting, modulating, and accelerating CKD and secondary cardiovascular disease (CVD). The changes in lipid and lipoprotein profile encompass variations in protein composition, incorporation of small molecules, and post-translational modifications. Metabolic changes can induce mitochondrial dysfunction and cellular damage, contributing not only to cardiovascular complications but also to the progression of kidney damage.

Methods: An extensive analysis of available literature regarding the alterations in lipid and lipoprotein metabolism in patients with chronic kidney disease was carried out. Relevant studies, research articles, and clinical data were identified through comprehensive searches of databases. The selected information focuses on the modifications in lipid and lipoprotein profiles, including changes in concentration and molecular structure, and their implications for the pathophysiology of CKD and the development of cardiovascular disease.

Results: Lipoprotein abnormalities, such as elevated triglyceride-rich lipoproteins, LDL, and altered HDL, are not only associated with changes in concentration but also exhibit structural changes that impact their biological activity. These modifications can initiate pro-inflammatory and pro-atherogenic processes and induce oxidative stress. Additionally, patients with CKD commonly experience disturbances in serum fatty acid levels, leading to disruptions in fatty acid metabolism, mitochondrial dysfunction, and cellular damage. These lipid and lipoprotein abnormalities interact with the inflammatory and oxidative environment in CKD, further exacerbating cardiovascular risk.

Conclusions: The competing risk of non-atherosclerotic cardiovascular death in individuals with declining kidney function poses additional challenges for therapeutic interventions. Understanding the relationships between lipid and lipoprotein modifications, kidney dysfunction, and the genesis and/or progression of cardiovascular disease in patients with CKD will provide valuable insights for the development of effective therapeutic strategies.

Funding: Government Support - Non-U.S.
PUB447

Alteration of the Gut Microbiota in CKD
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Background: The gut microbiota, consisting of trillions of microorganisms, plays crucial roles in various physiological processes. However, it also contributes to the progression of chronic kidney disease (CKD).

Methods: The information presented in this article is based on existing literature related to gut microbiota in patients with CKD. Relevant studies, research articles, and clinical data were collected from various databases and sources. The selected information focuses on the pathophysiology, clinical consequences, and underlying mechanisms of gut microbiota in CKD.

Results: The human gut microbiome comprises bacterial species from major phyla, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia. Changes in the composition of these phyla result in an imbalance between beneficial and pathogenic bacteria, exacerbating CKD. Additionally, CKD-associated modifications of the gut microbiome lead to metabolic changes and the accumulation of uremic metabolites, such as amines, indoles, and phenols. These metabolites negatively affect renal function and contribute to comorbidities like atherosclerosis and cardiovascular diseases. Uremic toxins were categorized based on known toxicity and experimental evidence, playing a significant role in CKD. Small water-soluble compounds, protein-bound compounds, and middle molecules are representative uremic toxins, with their production influenced by the gut microbiome. Gut-derived uremic metabolites damage the intestinal epithelial barrier, increase gut permeability, and facilitate the translocation of bacteria and endotoxins into the bloodstream. This leads to endotoxemia, inflammation, and further acceleration of CKD progression.

Conclusions: While the importance of the gut microbiome in CKD pathophysiology is recognized, the underlying mechanisms remain incompletely understood. An overview of the current research on CKD, the gut microbiota, alterations in the microbiome, production of uremic toxins, and degradation of the intestinal epithelial barrier would lead to identification of novel therapeutic targets.

Funding: Government Support - Non-U.S.

PUB448

Cortical Iron Deposition Is Associated with Kidney Fibrosis and Can Be Assessed by Magnetic Resonance Imaging
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Background: Iron deposits are associated with fibrosis, and its detection through Magnetic Resonance Imaging (MRI) in a second time, we evaluated prospectively iron deposits through Magnetic Resonance Imaging (MRI) in a cohort of kidney transplant (KT) recipients who underwent a kidney biopsy. We found that patients with high IFTA score presented with significantly higher deposits (p=0.005), than patients with low IFTA score. We also found positive and significant correlation between iron deposits and IFTA (r=0.7357, p=0.00012).

Conclusions: Iron deposits are associated with fibrosis, and its detection through MRI could be considered a non-invasive marker.

Table 1. Analysis considering absence (Negative) or presence (Positive) iron staining in diabetic nephropathy biopsies

<table>
<thead>
<tr>
<th>Variables</th>
<th>Negative</th>
<th>Positive</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFTA score</td>
<td>0-1.0</td>
<td>≥1.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46 (±5.0)</td>
<td>61 (±11.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73m²)</td>
<td>12 (±17.2)</td>
<td>2.1 (±1.5)</td>
<td>0.14</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>2.4 (±3.1)</td>
<td>11 (±8.4)</td>
<td>0.29</td>
</tr>
<tr>
<td>Capillary casters (PLT)</td>
<td>31 (±22.9)</td>
<td>38 (±25.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>Interstitial fibrosis (IF)</td>
<td>6 (±9.9)</td>
<td>0.0 (±0.0)</td>
<td>0.71</td>
</tr>
</tbody>
</table>

eGFR, estimated glomerular filtration rate; SD, standard deviation

PUB449

Not All Controls Are Made Equal: Comparison of Single-Cell Gene Expression in Human Kidney Reference Samples
Rajasree Menon,1,2 Edgar A. Otto,1,2 Jeffrey B. Hodgson,1,2 Abhijit S. Naik,1,2 E. Steve Woodle,3 John R. Sedor,3 Sylvia E. Rosas,4 Sushrut S. Waikar,4 Markus Bitzer,1,3 Petter Bjornstad,4 Matthias Kretzler,1,2 KPMP. University of Michigan Michigan Medicine, Ann Arbor, MI; 3University of Michigan, Ann Arbor, MI; 4Cleveland Clinic, Cleveland, OH; 5 Joslin Diabetes and Endocrinology Research Center, Boston, MA; 6Boston University Medical Campus, Boston, MA; 7University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; 8University of Cincinnati College of Medicine, Cincinnati, OH.

Background: Defining molecular mechanism of kidney disease relies on comparison to healthy reference tissue. With the rapid development of molecular analysis tools understanding advantages and limitations of the different reference tissue sources is critical. Here, we compared single-cell gene expression data from four different reference tissue sources including percutaneous kidney biopsies in healthy volunteers (HV), unaffected parts of tumor-nectropheties (TN) and two sources of living kidney donor biopsies (LD). Diabetic kidney disease data (DKD) (KPMP) was included as a disease comparator.

Methods: Kidney tissue was procured as published (PMIC8330551) with institutional approval and after informed consent of study participants. Single cell data from 10 HV, 16 TN, 18 LD, 27 DKD samples were generated. Integration of single cell data (10x Genomics) from all sample groups was done using reciprocal principal component analysis in Seurat R package. For comparative analyses, each group was down sampled to 15000 cells.

Results: The integrated dataset was annotated to 19 cell types which encompassed major kidney cell types. An adaptive/maladaptive proximal cell state based on markers from the published KPMP kidney atlas study had low representation in HV compared to other groups. Similarly, low expression of injury markers including NGAL and KIM1 and low representation of immune cell types were observed in HV. Principal component analysis clustered HV away from the other reference groups. 155 genes that were common among the over-expressed genes in HV compared to other groups with ion import across plasma membrane as top enriched term. TN had the greatest number of uniquely differentially expressed genes compared to HV with WNT signaling as a top enriched term. mRNA processing and hypoxia are enriched for the few uniquely differentially expressed genes in LD vs HV.

Conclusions: Immune and maladaptive epithelial cell proportion in HV group was lower than the other groups. However, each reference sample group had unique features. The differences could be related to the different tissue types. The integrated dataset is integrated with clinical, demographic and pathologic parameters; these integrated analyses are ongoing.

Funding: NIDDK Support, Private Foundation Support

PUB450

Apolipoprotein C3-Rich Low-Density Lipoprotein (LDL) Induces Human Aortic Endothelial Cells Senescence via FBXO31/p53/p21 Jie S. Wang,1,2 Ping H. Tsai,1,2 Kuo F. Tseng,3 Ming-Yi Shen,3 MYS Lab. 1China Medical University Graduate Institute of Biomedical Sciences, Taichung City, Taiwan; 2China Medical University Hospital, Taichung, Taiwan; 3China Medical University, Taichung, Taiwan.

Background: Apolipoprotein C3 (ApoloC3) delays the catabolism of triglyceride-rich particles. However, the effects of ApoC3 on uremic dyslipidemia progression is unknown. Methods: Plasma samples were obtained from diabetic kidney disease (DKD) patients recruited at our outpatient clinic. Low-density lipoprotein (LDL) was separated from other lipids by sequential potassium bromide density centrifugation. ApoC3-rich low-density lipoprotein (AC3RL) was isolated from plasma LDL with the affinity-purified method. Results: AC3RL induced human aortic endothelial cells (HAEC) senescence in a dose-dependent manner. Reactive oxygen species (ROS) was involved in AC3RL-Induced HAEC senescence. The level of FBXO31, p53 and p21 were markedly increased in AC3RL-induced HAECs. Moreover, silencing FBXO31 attenuated AC3RL-induced DNA damage and reduced cellular senescence. Conclusions: Inhibiting FBXO31 may protect endothelial damage and arrest the progression of DKD by linking AC3RL elevation to aging and uremic dyslipidemia.

Funding: Private Foundation Support

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
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Annika Epithelial Cell Phenotypes in the Context of Progressive CKD
Publication-Only PUB451

Christoph mechanosignaling. for stabilization and regulation of IACs. IPP-KO cell lines failed to form a multilayered studies demonstrated the strong interdependence of individual IPP-complex members. Further characterization using IPP-KO cell lines revealed an altered cytoskeleton, cell members of the IPP complex. Similar alterations were observed in PTs of IRI mice. demonstrated an altered regulation of several matrisome and adhesome genes, including epithelial-to-mesenchymal transition (pEMT) state of hRPTECs. Transcriptome analysis was employed to generate knockout cell lines of the IPP complex (ILK, PARV A and Background: Chronic kidney disease (CKD) is mainly defined by interstitial fibrosis of the renal parenchyma and progressive atrophy of proximal tubules (PT). The latter is characterized by pronounced thickening and multilamellation of the tubular basement membrane, whereas fibrosis is promoted by accumulation of extracellular matrix (ECM) translating into increased matrix rigidity. The role of mechano-transduction via integrin adhesion complexes (IAC) as well as the corresponding signaling programs activated in this context remain elusive. Here, we aimed to elucidate the functional role of the ILK-Pinch-Parvin (IPP) complex as an essential part of the IAC in PT damage response and CKD. Methods: Morphometric assessment of ischaemia-reperfusion injury (IRI) mouse models was performed. Transcriptome studies of human proximal tubular epithelial cells (hRPTECs) under pro-fibrotic conditions were analyzed. CRISPR/Cas9 genome editing was employed to generate knockout cell lines of the IPP complex (ILK, PARVA and PARVA/PARVB double KO), complemented by functional assays. Results: TGFβ treatment (resembling pro-fibrotic conditions) resulted in a partial epithelial-to-mesenchymal transition (pEMT) state of hRPTECs. Transcriptome analysis demonstrated an altered regulation of several matrix and adhesome genes, including members of the IPP complex. Similar alterations were observed in PTs of IRI mice. Further characterization using IPP-KO cell lines revealed an altered cytoskeleton, cell morphology and total number of IACs, as well as an altered distribution of the latter. Interestingly, PARVA/B double KOs lacked the ability to form a proper cytoskeleton, resulting in a significant reduction in cell area and IACs. Further genetic perturbation studies demonstrated the strong independence of individual IPP-complex members for stabilization and regulation of IACs. IPP-KO cell lines failed to form a multilayered and interconnected extracellular matrix, demonstrating a key role of IPP proteins in mechanosignaling. Conclusions: We have established a simplified model to investigate processes of pEMT in hRPTECs resembling hallmark features of tubular remodeling in CKD. In vivo, transcriptome and functional data indicate a central role of the IPP-complex in orchestrating cell-matrix interactions as an underlying theme of tubular atrophy. Funding: Other U.S. Government Support, Government Support - Non-U.S.

PUB452

New Targets for Cardiovascular Disease (CVD) in CKD: Proteomic Analysis of Indoxyl Sulfate-Treated Endothelial Cells and Extracellular Vesicles (EVs)
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Background: CKD is characterized by an accumulation of uremic toxins that promote endothelial damage, generating CVD. The proteome of damaged endothelial cells and the release of extracellular vesicles (EVs), that can function as mediators and/or biomarkers, have been studied to clarify the mechanisms underlying the pathogenesis of cardiovascular complications in kidney disease and identify potential diagnostic and therapeutic targets. Thus, the study aimed to describe changes in the levels of proteins in both endothelial cells and their EVs treated with indoxyl sulfate (IS).

Methods: HUVEC were cultured in two different conditions: control (n=5) and IS-treated (250 µM, 24 h; n=5), and EVs released by the cells were isolated and analyzed using mass spectrometry to identify and quantify their protein patterns.

Results: In the proteomic analysis of a cells, a total of 5871 proteins (5386 groups) were identified, while 3614 proteins (3546 groups) were identified in EVs (FDR<1%). Among these proteins, 145 showed significant differential expression (75 downregulated, 70 upregulated) and 141 differentially expressed in EVs (77 downregulated, 64 upregulated in IS-treated cells vs. control). In addition, reduced levels of proteins involved in replication and mitotic error prevention (MCM2, TACC3), and translation initiation factors (EIF3H, EIF3F, EIF4E) were detected in cells. These changes were accompanied by increased expression of transcriptional inhibitors (ING5, CTCF), caspase 3 and the downregulation of serpin-B3 (apoptosis inhibitor). Additionally, a reduction in extracellular matrix proteins (collagens, ECM1, fibronectin, perlecian) was observed in EVs and an MMP1 increase. Furthermore, elevated levels of complement components (C5, CFI), bacterial protein LYZ, chemotactic protein S100A7, adhesion molecule ICAM-1, and immune activation marker CALM5L were detected.

Conclusions: The study suggests that IS induces cellular endothelial damage and inhibits proliferation. The results show that IS-treated EVs have a proinflammatory effect that may trigger the activation of immune cells. These newly identified molecules are promising as potential diagnostic markers and therapeutic targets for CKD.

PUB453

IL-33-Mediated Mast Cell Activation Promotes Renal Fibrosis by Regulating the Phenotype of Neutrophil
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Background: To investigate the mechanism that IL-33 activates mast cell and promotes its degranulation, which then recruits and regulates the phenotype of neutrophil in the development of renal fibrosis and cardiovascular complications.

Methods: Analyzed the correlation between the density of infiltrating MC in kidney and renal fibrosis. mIL-33, anti-ST2 antibody and Rapamycin were used to clarify the impact of autophagy on mast cell activation and degranulation. Then, the maturation and phenotypic changes of neutrophils were detected. Finally, using MC knockout mice were transfused with mast cells inhibited of autophagy and mIL-33 to detect the maturation and phenotypic changes of neutrophil after kidney injury.

Results: (1)The degree of mast cell infiltration in renal biopsy specimen of IgA nephropathy patients was positively correlated with the degree of renal interstitial fibrosis. Knockout mast cell eliminated UUO-induced renal fibrosis and neutrophil infiltration, while reconstituted with mast cells aggravated UUO-induced renal fibrosis and neutrophil infiltration. (2)Neutrophil infiltration was correlated with the progression of renal fibrosis, and gradually differentiates into pro-inflammatory phenotype. Knocking down neutrophil can significantly inhibit the progression of renal fibrosis. (3)In the early stage of renal injury, renal tubular epithelial cells secreted IL-33, which activates mast cells through its receptor ST2, inhibited autophagy and promoted degranulation, then secreted CXCL1. (4)Both mast cells and CXCL1 can promote neutrophil maturation and differentiate into pro-inflammatory phenotype in vitro. In vivo, reconstituted with mast cells inhibited of autophagy can reduce neutrophil infiltration and alleviate the differentiation. Recombinant IL-33 can enhance neutrophil infiltration in kidney and promote the differentiation of neutrophil into pro-inflammatory phenotype.

Conclusions: In the early stage of renal injury, the injured renal tubular epithelial cells could secrete IL-33, activated mast cells by inhibiting autophagy and then promoted degranulation, which recruited neutrophil infiltration in the kidney and gradually differentiated into pro-inflammatory phenotype. Together, these effects accelerated the process of renal fibrosis.

Funding: Government Support - Non-U.S.
Protective Role of Tulsi (Holy Basil) Extract in Renal Epithelial Wound Repair
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Background: Wound/injury from a resultant reactive oxygen species (ROS) can ultimately lead to chronic kidney disease (CKD). ROS productions are much higher in proximal tubular (PT) cells, which makes them vulnerable to oxidative damage, thus predispose to CKD. We tested the effect of Tulsi Chai (TC) and its ability to protect renal epithelial cells from the ROS in a wound-healing model. We induced CKD-like condition in our model by introducing calcium phosphate (CaP) crystals into PT cells in a scratch wound.

Methods: Hydrothermally extracted Tulsi extracts used as TC to investigate its wound/injury from a resultant reactive oxygen species (ROS) can ultimately lead to chronic kidney disease (CKD). ROS productions are much higher in proximal tubular (PT) cells, which makes them vulnerable to oxidative damage, thus predispose to CKD. We tested the effect of Tulsi Chai (TC) and its ability to protect renal epithelial cells from the ROS in a wound-healing model. We induced CKD-like condition in our model by introducing calcium phosphate (CaP) crystals into PT cells in a scratch wound.

Results: Pretreatment of TC in HK2 cells caused a significant cell-survival and reduction of ROS generation in a concentration dependent manner. Reversal of H2O2-induced HK2 cell death and cytotoxicity by cell viability and extracellular LDH release indicate the protective role of TC. Wound closure and the rate of repair of wound by TC were found to be directly proportional to the amount of TC pretreatment. CaP-induced apoptosis and necrosis as investigated with the HK-2 cells showed reduction in apoptotic, necrotic and cell wall fragmentation for cells preconditioned with TC in a dose dependent manner. TC mitigated the ROS-induced phosphorylation of phospho-P38 (pP38) in our model.

Conclusions: Our study shows that TC has the ability to remediate both mechanical and ROS induced wounds on renal tubular cells, hence, may have the potential for natural regenerative substance for CKD patients.

Subclinical Proximal Tubular Injury in Nonhospitalized Patients with Cirrhosis
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Background: Cirrhosis leads to a reduction in kidney blood flow via splanchnic vasodilation and reflexive neurohormonal activation. These hemodynamic changes may adversely impact tubular health in the absence of clinically apparent kidney injury. We tested the association of cirrhosis with the urine excretion of kidney injury molecule-1 (KIM-1) (KIM-1), a marker of tubular injury, in stable outpatients with end-stage liver disease (ESLD).

Methods: We recruited 39 adult patients with ESLD undergoing outpatient evaluation for liver transplantation. We selected a comparison group of 58 control individuals without liver disease from two previously completed studies, matched to the cirrhosis group by MELD. We selected a comparison group of 58 control individuals without liver disease from two previously completed studies, matched to the cirrhosis group by MELD.

Results: The cirrhosis group was characterized by a mean age of 57 ± 9 years; 28% female; mean eGFR of 66 ± 20 ml/min/1.73m2, and mean Model for End-stage Liver Disease (MELD) and Child-Pugh Scores of 17.4 and 8 ± 2, respectively. The median urine KIM-1 excretion was 1688 pg/ml (IQR 306, 2683 pg/ml) in the cirrhosis group versus 180 pg/ml (IQR 118, 356 pg/ml) in the control group. After adjustment for eGFR, age, and sex, the presence of cirrhosis was associated with an estimated 4-fold greater urine excretion of KIM-1 (95% confidence interval 2.7, 6.2-fold greater; p-value <0.001). Among the cirrhosis group, higher Child-Pugh Scores, international normalized ratios (INR), and the severity of ascites were associated with higher urine excretion of KIM-1.

Conclusions: Cirrhosis is associated with subclinical proximal tubular injury, demonstrated by increased urine excretion of KIM-1, in stable outpatients with ESLD.

PM2.5 induces Epithelial-to-Mesenchymal Transition by Oxidative Stress in Renal Tubular Kidney Cells
Duk-Hee Kang,1 Dal-Ah Kim,1 Chor Ho Jo2. Division of Nephrology, Ewha Womans University School of Medicine, Seoul, Republic of Korea; 2Hanyang University, Seoul, Republic of Korea.

Background: The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide. Recently, the exposure to air pollution, especially particulate matter, PM2.5, was newly identified to be a potential risk factor for CKD, however there are no studies on whether exposure to PM2.5 is a direct cause of CKD occurrence and exacerbation. Epithelial-to-mesenchymal transition (EMT) of tubular cells is one of the early mechanisms of progression of renal disease. Therefore, the identification of association between fine dust and EMT may allow to reveal the causality toward CKD.

Methods: Fine dust collected by PM2.5 filter (Ulaanbaatar, Mongolia) was dissolved in DMSO by sonication. Renal tubular kidney cells (NRK) were treated with dissolved PM2.5 (2 and 5 µg/mL). EMT was evaluated by morphological changes of NRK cells and the expression of E-cadherin, α-SMA, and vimentin after the stimulation with PM2.5 and TGF-β (5 ng/mL) by WB and immunostaining. ROS generation was assessed by DCF-DA and Mito-Sox staining. RNA-seq analysis (Ebiogen, Korea) was performed to investigate which upregulated/downregulated-genes are associated with PM2.5-induced phenotype transition in NRK cells.

Results: The concentration of 2 and 5 µg/mL did not alter LDH release and cell proliferation up to 48 hours of exposure. PM2.5 induced EMT of NRK cells assessed by morphologic changes associated with a decreased E-cadherin expression and de novo expression of α-SMA and vimentin. PM2.5 also increased DCF-DA and Mito-Sox staining. EMT was evaluated by morphological changes of NRK cells and the expression of E-cadherin, α-SMA, and vimentin after the stimulation with PM2.5 and TGF-β (5 ng/mL) by WB and immunostaining. ROS generation was assessed by DCF-DA and Mito-Sox staining. RNA-seq analysis demonstrated the differences in gene expression related to EMT (16.1% upregulated [15.9% of which is MDA/MDR1 (17.8%) and oxidative stress (12.8%)]. Among them, lipocalin 2 (LCN2), Interleukin-11 (IL-11), and hypoxiaislaactone 2 (HAS2) expression showed the highest fold difference (2.7-folds, 2.5-folds, and 2.0-folds, respectively) between control and PM2.5-treated NRK cells.

Conclusions: This data suggest that exposure to PM2.5 induces EMT and oxidative stress in NRK cells, which may be one of the possible mechanisms for the association between fine dust exposure and the development of renal disease.

PM2.5 induces Epithelial-to-Mesenchymal Transition by Oxidative Stress in Renal Tubular Kidney Cells
Duk-Hee Kang,1 Dal-Ah Kim,1 Chor Ho Jo2. Division of Nephrology, Ewha Womans University School of Medicine, Seoul, Republic of Korea; 2Hanyang University, Seoul, Republic of Korea.

Figure: Associations of measures of liver disease with urine KIM-1 excretion in patients with cirrhosis: (a) Child-Pugh Score, (b) INR (c) Ascites, categorized as none (0), slight (1), and moderate/severe (2); IRR = incidence rate ratio.
uACR (P=0.01), a 1.5% decline in eGFRcys (P=0.02), but not significantly associated with cross-sectional eGFR (b=−0.004, P=0.5) or CKD (OR=1.31, 95% CI 1.1-1.73, P=0.05).

**Conclusions:** GRP78 is relatively intolerant of genetic variation consistent with selection against heterozygous variation. Nevertheless, GWAS and rare variant analysis show a nominal association of variants around GRP78 with kidney phenotypes. In contrast, genetically-predicted variation in GRP78 expression was not associated with kidney phenotypes.

**PUB458**

**Growth Restriction, but Not Prematurity, Is Associated with Renal Microinflammation in Early Adulthood**

Liangjian Lu,1 Chang-Yien Chan,2,3 Chian Chau Lee,3 Isaac Desheng Liu,1 Hui Kim Yap,2,4 Khoo Teck Puat-National University Children’s Medical Institute, National University Health System, Singapore, Singapore; 2National University of Singapore Yong Loo Lin School of Medicine, Singapore, Singapore; 3National University of Singapore, University Health Centre, Singapore, Singapore.

**Background:** Low birth weight (LBW), i.e. birth weight <2.5kg, is associated with an increased risk of adult-onset chronic kidney disease and kidney failure, but the mechanistic basis of this association is unknown. We hypothesize that reduced nephron endowment in these patients results in chronic glomerular hyperfiltration, which eventually leads to renal immune cell infiltration and inflammation, creating a pro-fibrogenic milieu. We aimed to characterize the urine immune cell and cytokine composition in young adults born LBW, and compare them with normal birth weight controls.

**Methods:** We recruited a cohort of 40 LBW participants, comprising 25 participants born prematurely and 15 born growth-restricted (IUGR) at term, as well as 16 age- and sex- matched normal birth weight controls. Urine immune cells were quantified by flow cytometry (markers: CD45, CD3, CD56, CD19, CD14) and urine cytokine composition by multiplex ELISA. The 3 participant groups were first compared using ANOVA, and if significant with p≤0.05, post-hoc tests were then performed with Tukey’s HSD test.

**Results:** The 3 participant groups were comparable in terms of serum creatinine (p=0.206), Cystatin C (p=0.709), as well as urine albumin:creatinine ratio (p=0.485). Of the cell markers studied, urine CD3+ T-cell (p=0.048) and CD14+ macrophages (p=0.007) differed between groups. This was due to Term IUGR participants having a higher level of urinary CD3+ T-cells (9.5±2.2% vs 3.6±0.7%, p=0.041) and CD14+ macrophages (0.17±0.04% vs 0.05±0.01%, p=0.005) compared to controls. Participants also differed in urine IL-6 concentrations (p=0.009), with Term IUGR participants having higher urinary IL-6 compared to controls (1.1±0.3 vs 0.43±0.1 pg/mg creatinine, p=0.047).

**Conclusions:** Young adults who were born growth-restricted at term displayed incipient nephropathy characterized by renal microinflammation. If validated, indices of renal microinflammation can be used to identify high-risk patients for long-term follow-up, and provide a basis for early intervention using targeted immunological therapies.

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

immunology and pathology

immunohistochemistry

interventional nephrology

intoxication

intracellular signal

intravenous immunoglobulin

ion channel

ion transport

ischemia

ischemia-reperfusion

ischemic renal failure

kidney anatomy

kidney biopsy

kidney disease

kidney function

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pharmacokinetics

progression of renal failure

proteinuria

pulmonary edema

progression of renal failure

pulmonary fibrosis

pulmonary embolism

pulmonary hypertension

pulse wave velocity

pure red cell aplasia

purity

purine metabolism

pseudosarcomatous spindled matrix cell tumor

pseudoglandular

pseudohypoparathyroidism

pseudohypothyroidism

pseudohypoparathyroidism type Ia

pulmonary edema

pulmonary hypertension

pulmonary fibrosis

pure red cell aplasia

purity

purine metabolism

pseudosarcomatous spindled matrix cell tumor

pseudoglandular

pseudohypoparathyroidism

pseudohypothyroidism

pseudohypoparathyroidism type Ia
water-electrolyte balance .......... TH-PO373, TH-PO526, FR-PO132, FR-PO505, FR-PO508, FR-PO523, FR-PO525, FR-PO608, SA-OR38, SA-OR42, SA-PO125, SA-PO543, SA-PO705, SA-PO712, SA-PO717, SA-PO718, SA-PO723, SA-PO727, SA-PO734, SA-PO740, PUB190


women's health (continued) .......... FR-PO864, FR-PO865, FR-PO866, FR-PO867, FR-PO869, FR-PO871, FR-PO872, FR-PO875, FR-PO876, SA-OR31, SA-OR32, SA-PO039, SA-PO712, SA-PO713, PUB420, PUB422
FR-OR108
Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Focal Segmental Glomerulosclerosis (FSGS): Results from the Phase 3 DUPELX Trial
Michelle N. Rheaume,1 Howard Trachtman,2 Ulysses Diva,2 Radko Komers,3 On behalf of the DUPRO steering committee and DUPRO investigators.
1Division of Pediatric Nephrology, University of Minnesota Medical School, Minneapolis, MN; 2Traver Therapeutics, San Diego, CA

Background: SPAR is a dual endothelin angiotensin receptor antagonist (DEARA) that reduced proteinuria in patients with FSGS in the phase 2 DUPELX trial. DUPRO evaluated the antiproteinuric and nephroprotective potential of SPAR vs active control IRB in patients with FSGS. DUPELX met its interim efficacy endpoint (FSGS partial remission remission [PPI]), with 42% of patients achieving PPI with SPAR vs 26% with IRB and 16% with placebo (P<0.05). Here, we present results from the primary analysis.

Methods: In this phase 3 randomized trial, patients (ages 8-75 y) with FSGS, within 110 wk. Safety and tolerability data will be presented.

Results: A total of 404 pts were randomized to SPAR (n=202) or IRB (n=202). We will present eGFR chronic and total slopes over 2 years, incidence of the kidney composite endpoint, percent change from baseline in urine protein-creatinine ratio through wk 110, and proportion of pts who achieved partial or complete proteinuria remission at any time within 110 wk. Safety and tolerability data will be presented.

Conclusions: The DUPELX trial results on kidney function and outcomes, proteinuria, and safety with SPAR vs IRB over 2 years may significantly impact the treatment landscape of pts with IgAN.

Funding: Commercial Support - Travere Therapeutics

FR-OR110
AYAME Study: Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Bardoxolone Methyl in Diabetic Kidney Disease (DKD) Patients
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Background: Bardoxolone methyl (BARD) is an activator of the Keap1-Nrf2 pathway. Previous studies demonstrated that BARD improves the estimated glomerular filtration rate (eGFR) and reduces adverse events in patients with type 2 diabetes mellitus (T2DM) and diabetic kidney disease (DKD). However, the effects of BARD on kidney disease progression in patients with CKD and DKD have not been fully evaluated. The AYAME study is an open-label, randomized, double-blind, placebo-controlled phase 3 study that evaluated the efficacy and safety of BARD in patients with DKD.

Methods: The AYAME study randomized 466 patients with T2DM and DKD to receive BARD (25 mg, n=154), 50 mg (n=151), or placebo (n=161) for 48 weeks. The primary endpoint was the percentage of patients with a ≥30% reduction in urine albumin-creatinine ratio (UACR) from baseline to week 48. Secondary endpoints included the percentage of patients with a ≥30% reduction in UACR from baseline to week 48, the percentage of patients with a ≥30% reduction in eGFR from baseline to week 48, and the percentage of patients with a ≥30% increase in estimated glomerular filtration rate (eGFR). Safety and tolerability data will be presented.

Results: The study reached its primary endpoint. The percentage of patients with a ≥30% reduction in urine albumin-creatinine ratio from baseline to week 48 was 51.1% in the 25 mg group, 60.9% in the 50 mg group, and 39.2% in the placebo group. The percentage of patients with a ≥30% reduction in eGFR from baseline to week 48 was 41.3% in the 25 mg group, 44.1% in the 50 mg group, and 40.0% in the placebo group. The percentage of patients with a ≥30% increase in eGFR from baseline to week 48 was 43.8% in the 25 mg group, 45.5% in the 50 mg group, and 53.0% in the placebo group. Adverse events were reported in 73.8% of patients in the 25 mg group, 74.3% in the 50 mg group, and 72.8% in the placebo group. The most common adverse events were gastrointestinal events, including diarrhea, nausea, and vomiting.

Conclusions: The AYAME study demonstrated the efficacy and safety of BARD in patients with T2DM and DKD. BARD was well tolerated and showed significant improvements in urinary protein excretion and eGFR. These results suggest that BARD may be a promising treatment option for patients with DKD.

Funding: Commercial Support - Kyowa Kirin Co., Ltd.

FR-OR109
Pivotal Results of the Phase 3 PROTECT Trial of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Immunoglobulin A Nephropathy (IgAN)
Brad H. Rovin,1 Jonathan Barratt,2 Ulysses Diva,2 Radko Komers,3 Vladimir Petkovic,4 On behalf of the DUPRO steering committee and PROTECT investigators. 1Division of Nephrology, Ohio State University Wexner Medical Center, Columbus, OH; 2Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; 3Traver Therapeutics, San Diego, CA; 4Faculty of Medicine & Health, University of New South Wales Sydney, Sydney, NSW, Australia

Background: SPAR, a dual endothelin angiotensin receptor antagonist (DEARA), showed a significantly greater reduction in urine protein excretion vs IRB in patients (pts) with biopsy-proven IgAN in an interim 36-wk analysis of the PROTECT phase 2 DUPELX trial (−49% vs −15.1%, respectively; P<0.001) (Heerspink et al. Lancet. 2023). Based on these data, SPAR was granted accelerated approval in the US for adults with primary IgAN at risk of rapid disease progression. We will present the pivotal double-blind PROTECT trial results on the efficacy and safety of SPAR vs IRB. These results will be available after database lock in Sep 2023.
The primary endpoint was change from R2 baseline (BL) in urine albumin:creatinine ratio (UACR) from the first morning void on Week 14. A secondary endpoint was UACR ≥30% reduction from R2 BL at Week 14.

Results: Of 714 pts randomized in R1, 586 were randomized in R2. At R2 BL, mean (SD) age was 63.8 (11.3) years, 58.4% of pts were White, 66.6% were male, and 70.6% had type 2 diabetes. BL median (IQR) UACR was 426.3 (205-889) mg/g and mean (SD) eGFR was 51.9 (17.7) mL/min/1.73m. BI 690517 dose-dependently reduced UACR (Figure). Largest median (95%) CI PBO corrected-change was −39.5% (~5.1 ~−24.0) for BI 690517 10 mg on EMPA BG. Among BI 690517 3–20mg pts, changes in UACR ≥30% were achieved by 53.5% on EMPA BG and 43.2% on PBO EMPA BG.

Conclusions: BI 690517 was well tolerated and dose-dependently reduced UACR on top of BI RASI and EMPA/PBO EMPA in pts with CKD. BI 690517 and EMPA showed additive anti-albuminuric efficacy that may translate into greater kidney protection.

Funding: Commercial Support - Boehringer Ingelheim

Percentage change from R2 BL in UACR up to Week 14 following BI 690517 treatment administered with A) EMPA-matched placebo or B) EMPA 10 mg.

FR-OR112

ZENITH-CKD: A Phase 2B Study of Zibotentan in Combination with Dapagliflozin and Dapagliflozin Alone in Patients with CKD

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Background: Despite treatment of CKD with RAS and SGLT2i, many patients have residual albuminuria which may be associated with rapid CKD progression. The albuminuria lowering efficacy and safety of a selective ETA receptor antagonist, were examined when administered concomitantly with an SGLT2i in a phase 2b dose-ranging trial.

Methods: ZENITH-CKD, a randomized, double-blind, active-controlled trial, was conducted in 170 clinical sites in 18 countries. Adults with a urinary albumin-creatinine ratio (UACR) of 150 to 5000 mg/g and eGFR ≥20 mL/min/1.73m2 not on SGLT2i were randomized to 1 of 6 treatment arms. Enrollment to 5 mg zibotentan monotherapy, 5 mg zibotentan/10 mg dapagliflozin, and placebo was discontinued at 62 participants. Enrollment continued across 3 other treatment arms: 0.25 mg/10 mg zibotentan, 1.5 mg/10 mg zibotentan/dapagliflozin, dapagliflozin/placebo 10 mg. The primary efficacy endpoint was change from baseline to week 12 in log-transformed UACR, assessed using mixed model repeated measures (in patients who received at least 1 dose of study treatment). Adverse events were recorded as safety endpoints.

Results: From April 28, 2021, to January 17, 2023, 447 patients were enrolled and received 0.25 mg/10 mg zibotentan/dapagliflozin (n=91), 1.5 mg/10 mg zibotentan/dapagliflozin (n=179), or 10 mg dapagliflozin/placebo (n=177). Overall, 58.4% of patients had type 2 diabetes, mean baseline eGFR was 46.7 mL/min/1.73m, and geometric mean UACR was 538.3 mg/g. At week 12, vs dapagliflozin alone, adjusted percentage mean change in UACR was greater in the 0.25 mg/10 mg and 1.5 mg/10 mg zibotentan/dapagliflozin groups (27.0% [90% CI 38.4% -13.6%] and -33.7% [90% CI -42.5%, -23.5%]). No increase in BNP, body weight, or total body water was seen for the 0.25 mg/10 mg zibotentan/dapagliflozin group; modest increases were observed in the 1.5 mg/10 mg zibotentan/dapagliflozin group. One SAE of heart failure occurred in the 0.25 mg/10 mg zibotentan/dapagliflozin and group and two occurred in the 1.5 mg/10 mg zibotentan/dapagliflozin group.

Conclusions: ZENITH-CKD confirmed 0.25 mg/10 mg zibotentan/dapagliflozin is highly effective in reducing albuminuria, is well tolerated, and could be an attractive option to further delay CKD progression.

Funding: Commercial Support - AstraZeneca (NCT04724837)

FR-OR113

ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST): Primary Results

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Background: There is currently no strong evidence-based pharmacological therapy to improve the excessively poor cardiovascular (CV) prognosis in chronic hemodialysis patients (HD). We aimed to investigate the effects of the steroidal mineralocorticoid receptor antagonist, spironolactone on CV outcomes in a high-risk HD population.

Methods: We conducted an international, multicenter, double-blind, randomized, placebo-controlled event-driven trial in HD patients with at least one CV comorbidity, abnormality or risk factor. Spironolactone 25 mg every other day was first administered open-label during a 4-week run-in period. Patients were excluded prior to randomization if serum potassium was greater than or equal to 5.5 mmol/l on two occasions during this run-in period or on the day of randomization. Randomized patients received spironolactone or placebo, both titrated up to 25 mg/day according to a pre-specified algorithm based on serum potassium monitoring. The primary outcome was the time to first MACe-adjudicated event (cardiovascular death or non-fatal myocardial infarction (MI), acute coronary syndromes (ACS), stroke or hospitalization for heart failure (HHF)). The win ratio including 1. all-cause death 2. Time to a CV event (HHF, non-fatal MI, ACS or stroke) was tested in a hierarchical statistical strategy as secondary endpoint. We assumed that a total of 750 randomized patients followed for 2 years would provide 80% power to determine a risk reduction of the primary endpoint by 30% with a alpha risk of 5%. Assuming a 10% run-in withdrawal rate, 825 patients would have to be included in the run-in phase. Safety endpoints included incidence of severe hyperkalemia >6 mmol/L, as monitored at pre-specified visits, and as reported by investigators as serious adverse event ( Clinicaltrials.gov NCT01848639.

Results: First visit in first patient occurred on June 2013 and last visit in last patient occurred on November 2022. 823 patients were recruited. ALCHEMIST primary results will be presented at the ASN 2023 annual meeting.

Conclusions: ALCHEMIST was the first international double-blind randomized CV outcome trial of spironolactone vs placebo in high-risk HD population.

Funding: Government Support - Non-U.S.

FR-OR114

Effect of a Multi-Component Intervention to Improve Patient Access to Kidney Transplantation and Living Kidney Donation

Amir X. Garg,1,2 Seychelle Yohanna,1 Kyla L. Naylor,4 Susan Q. Mckenzie,4 Istvan Mucsii,1 Stephanie N. Dixon,4 Bin Luo,2 Jessica M. Sontrop,4 Peter G. Blake,3,4 Enhancement Access to Kidney Transplant and Living Kidney Donation (EnAKT LKD) Investigators, 1Medicine, Western University, London, ON, Canada; 2ICES, Toronto, ON, Canada; 3McMaster University, Hamilton, ON, Canada; 4Lavson Health Research Institute, London, ON, Canada; 5Kidney Patient and Donor Alliance Canada, Stratford, ON, Canada; 6University of Toronto, Toronto, ON, Canada; 7University Health Network, Toronto, ON, Canada; 8Ontario Health, Toronto, ON, Canada.

Background: Patients with advanced chronic kidney disease (CKD) have the best chance for a longer and healthier life if they receive a kidney transplant. However, many barriers prevent patients from receiving a transplant.

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

Underline represents presenting author.
Methods: We conducted a pragmatic, two-arm, parallel-group, cluster-randomized trial with a sample size designed to detect several differences between the intervention and usual care. The trial included 16 CKD programs in 13 intervention and 13 usual care centers across Europe. The primary outcome was a composite of all-cause mortality and 2-year graft survival (GS). The trial was designed with a factorial design incorporating two interventions: (1) a computer-based decision support system (Computer-Based Decision Support System, CBDDS) and (2) a computer-based electronic medical record (EMR) upgrade. The CBDDS provided real-time feedback to the transplant team based on electronic patient records, while the EMR upgrade included enhancements to improve documentation and communication. The trial was conducted from April 2017 to March 2019, and the follow-up period was 2 years.

Results: The trial enrolled 1,529 KTRs from 16 centers, with 795 and 734 in the intervention and usual care arms, respectively. The baseline characteristics were well balanced between the two groups. The primary composite outcome was met in 86% of the intervention group and 82% of the usual care group (p = 0.14). The 2-year GS was 95.0% (95% CI: 93.4%, 96.5%) in the intervention group and 93.0% (95% CI: 91.2%, 94.7%) in the usual care group (p = 0.05). The improvement was driven by a reduction in acute rejection episodes in the intervention group.

Conclusions: This study demonstrated that a computer-based decision support system can improve clinical outcomes in kidney transplantation, particularly in the management of acute rejection episodes. Further research is needed to evaluate the impact of the EMR upgrade on clinical outcomes.
age were 52±14 and 52±15 yrs respectively. Other baseline characteristics were similar between groups. The mean period of follow-up time after randomization was 9.6±3.6 months. In Predigraf, 39% iBox alerts were recorded among which 232 (58%) were deemed clinically relevant by physicians and 133 (33%) were followed by a change in clinical management. However, there is limited experience with DOACs in HD patients and concerns about the impact of residual diuresis did not show higher apixaban levels. A close temporal relationship between apixaban plasma concentrations and AXA was observed across the dosing intervals. No bleeding events were observed. 

Conclusions: Our results have significant clinical implications, as they provide P/KD data that justifiy the use of 2.5 mg BD in patients with atrial fibrillation on hemofiltration. Our findings emphasize the importance of considering inter-subject variability in drug response and adopting individualized treatment approaches.

Funding: Government Support - Non-U.S.

TH-PO1118
NAVIKIDS® Trial: A Multi-Centre, Waitlisted, Mixed Methods, Randomized Controlled Trial of a Patient Navigator Intervention in Children with CKD
Germaine Wong, NAVIKIDS® Trial Steering Committee, Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia.

Background: Inequitable access to care is a major impediment to optimal health in children with chronic kidney disease (CKD). Patient navigators help patients and caregivers to navigate complex health systems, with the goal of improving accessibility to healthcare and community support. However, the role of patient navigation in improving the overall health of children with CKD is unknown.

Methods: In this multi-center, waitlisted, randomized control trial, we randomly assigned children with CKD (aged 0-16 years, of low socioeconomic backgrounds) to surgery. Patients were followed at 1 and 3 month visits and had a protocol biopsy at 14 and 52 ± 3 years old.

Conclusions: For the first time, the effect of SGLT2i in a large number of young patients with AS was investigated; patients were much younger than non-diabetic CKD patients in EMPA-Kidney (37 vs. 64 years), had a similar BMW and blood pressure, a much better eGFR (63 vs. 39 ml/min/1.73m^2), and a four times higher UACR (1822 vs. 461 mg/gCrea). Patients with AS showed an intermediate response in UACR reduction. In month 12 and 21, the positive effect on long-term eGFR scope declined from -1.36 (V1), -8.4 (V2), 7.7 (V3), to -4.1 ml/min/year at V4. At a total of 50 patient-years at risk, adverse drug reactions occurred in 7/66 patients (11%).

Funding: Government Support - Non-U.S.

TH-PO1116
Exploring the Pharmacokinetics, Pharmacodynamics, and Safety of Apixaban in Hemodialfiltration: Insights from the HEMOCIONA Study
Miguel Hueso,1 Aurena Otero,2 Elena Roselló-Palmer,3 Juan Peris Vidal,4 Sergio Codina Sanchez,5 Yurema Martinz Vilar,5 Raúl Rigo-Bonnin,5 Nuria Lloberas,6 Sebastián Videla Casés,7 HEMOCIONA: 1Nephrology, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain; 2Nephrology, Institut d’Investigació Biomèdica de Bellvitge, Barcelona, Spain; 3Thrombosis and Haemostasis Unit, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Spain; 4Clinical Pharmacology, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Spain; 5Clinical Research Support Unit, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Spain; 6Clinical Laboratory, Hospital Universitari de Bellvitge, L’Hospitalet de Llobregat, Spain.

Background: Atrial fibrillation (AF) is common among hemodialysis (HD) patients, and increases the risk of stroke. Since vitamin K antagonists increase the risk of bleeding and vascular calcifications, direct oral anticoagulants (DOACs) has attracted considerable attention. However, there is limited experience with DOACs in HD patients and concerns have been raised about potential accumulation. Consequently, DOACs are currently not recommended in HD patients. Our study aims to assess the safety of low-dose of apixaban, based on long-term their pharmacokinetic profile, for patients with nonvalvular AF undergong hemodialfiltration.

Methods: We conducted a single-center phase 2 clinical trial to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of apixaban at a dose of 2.5 mg twice daily (BID) over a period of 4 weeks. Plasma levels were obtained during the middle dialysis session of the week, as well as the day before and after for PK/PD assessments. Concentration of apixaban was directly measured in plasma, urine and dialysis wasted liquid using a validated liquid chromatography-mass spectrometry/mass spectrometry (LC/MS/MS). Blood samples for the determination of Anti-Xa activity (AXA) were collected at the same time points as the PK samples.

Results: A total of 11 patients (8 male, 3 female) with a mean age of 67±3 years old were enrolled. The main result was the demonstration of the absence of accumulation of apixaban since daily exposure (mean (%CV) AXA) appeared similar the day of dialysis of the first week (1030 ± 580 ng/ml), and after 4 weeks (921 ± 432 ng/ml). Hemodialfiltration had no impact on apixaban plasma concentration and patients without residual diuresis did not show higher apixaban levels. A close temporal relationship between apixaban plasma concentrations and AXA was observed across the dosing intervals. No bleeding events were observed.

Conclusions: For the first time, the effect of SGLT2i in a large number of young patients with AS was investigated: patients were much younger than non-diabetic CKD patients in EMPA-Kidney (37 vs. 64 years), had a similar BMW and blood pressure, a much better eGFR (63 vs. 39 ml/min/1.73m^2), and a four times higher UACR (1822 vs. 461 mg/gCrea). Patients with AS showed an intermediate response in UACR reduction. In month 12 and 21, the positive effect on long-term eGFR scope declined from -1.36 (V1), -8.4 (V2), 7.7 (V3), to -4.1 ml/min/year at V4. At a total of 50 patient-years at risk, adverse drug reactions occurred in 7/66 patients (11%).

Funding: Government Support - Non-U.S.
We analysed repeated measures of the primary outcome from baseline to six months post-randomisation using cumulative logistic mixed effects models. Semi-structured interviews were analysed thematically to understand caregivers’ perspectives on the intervention.

Results: Of 398 children who were screened, 162 were enrolled (mean age (standard deviation): 8.8 (4.8) years, boys (64.8%)), with 80 and 82 assigned to the immediate and waitlist groups, respectively. There were no differences in the child’s SRH between the immediate and waitlist groups at baseline (p=0.92). There were also no cumulative differences in the child’s SRH between the immediate and waitlist groups over the 6 months period (p=0.70). Caregivers reported five themes: easing mental strain, facilitating care coordination, strengthening capacity to provide care, reinforcing care collaborations, alleviating family tensions.

Conclusions: In children with CKD, the child’s SRH did not differ significantly between the immediate and waitlist groups over time. However, caregivers may have gained skills and capacity related to care from the program.

Funding: Government Support - Non-U.S.

**TH-PO1119**

The TRANSNephro Study Examining a New Transition Model for Post-Kidney Transplant Adolescents: A Multicenter, Randomized Controlled Trial

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Background: Allograft loss is highest in adolescents due to non-adherence and transfer of health care. This multicenter, randomized controlled trial aimed to evaluate whether support by a central case manager and a corresponding app during transition may improve the outcome.

Methods: Adolescent patients in 18 German and Austrian centers one year before planned transfer were randomized 1:1 to a control group that received transition as by center standard or to an intervention group. The intervention consisted of a central case manager, a communication app, and joined transition rounds for one year before and one after transfer. Primary endpoint was the coefficient of variation (CoV) of the trough level of the Calcineurininhibitor as a surrogate marker for medication adherence. Important secondary endpoints were acute rejections, graft loss, eGFR, and quality of life. For the assessment, least square (LS) mean differences and corresponding 95% confidence intervals (CIs) were estimated within an analysis of covariance (ANCOVA) model.

Results: A total of 220 patients was assessed for eligibility. Of these, 102 patients were randomized, 49 to the intervention and 53 to the control group. We analyzed 84 patients in the modified intention-to-treat (mITT) analysis (38 intervention vs 46 control patients) and 60 patients in the per protocol (PP) analysis (25 intervention vs 35 control patients). No difference in CoV was observed between the two groups, neither in the mITT (LS mean difference [95% CI]:0.01 [-0.17, 0.18], p=0.9574) nor in the PP analysis (LS mean difference [95% CI]: [-0.01 [0.19, 0.16], p=0.8748). We observed a trend for a lower mean eGFR at adult clinic outpatient phase in the intervention group. We saw only low numbers of graft-related events and observed no differences between the groups with respect to quality of life.

Conclusions: The addition of our case-manager-based intervention to standard of care transition, did not improve adherence and other outcome parameters in adolescent kidney graft recipients. We assume that non-adherent patients may have decided not to take part in the trial, as adherence was already good at study start. It thus is a future challenge to design multicenter trials on transition that include multiple interventions for a better transition in order to stop the long-term decrease in graft function.

**TH-PO1120**

Limited Antiproteinuric Efficacy of Dapagliflozin (DPG) in Adolescents with Proteinuric CKD

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Background: While reducing proteinuria is renoprotective in CKD, it might persist despite renin-angiotensin-aldosterone (RAAS) blockade. SGLT2 inhibitors, known to be antiproteinuric in adult-onset CKD, have not been tested in children.

Methods: This single-center trial examined the antiproteinuric efficacy & safety of DPG in adolescents with CKD (CTR1/21/2020). After written consent & baseline evaluation, consecutive eligible patients, 11-19 yr old with eGFR >45 ml/min/1.73 m² & proteinuria >0.5 g/m²/d despite optimal RAAS blockade, received Dapavel® at 5 mg/d x 2-wk, followed by 10 mg/d x 10-wk. Biochemistry & 24-hr urine protein/albumin were repeated at 4, 8 & 12-wk, and ambulatory blood pressure at 12-wk.

Results: Of 49 screened, 25 patients (76% boys, chiefly glomerular CKD), were enrolled at median eGFR 93 ml/min/1.73 m² & proteinuria 1.4 g/m²/d (Table 1). Fig. 1 shows outcomes at 4 & 12-wk. At 12-wk, proteinuria declined by median 1.3% and eGFR by 13.4%; 4 (16%) patients achieved the FSGS proteinuria reduction endpoint. 3 patients noted giddiness; none had serious adverse events.

Conclusions: Therapy with DPG for 12-wk has limited antiproteinuric efficacy in adolescents with CKD. Controlled studies should examine the antiproteinuric effect and optimal dose & duration of SGLT2 inhibitors in children.

**Table 1: Baseline characteristics n=25**

<table>
<thead>
<tr>
<th>Boys, %</th>
<th>19 (76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset, yrs</td>
<td>8 (5-11)</td>
</tr>
<tr>
<td>Age at enrollment, yrs</td>
<td>16 (13-18)</td>
</tr>
</tbody>
</table>

**Diagnosis**

| CNI-resistant FSGS | 11 (44) |
| Prednisolone; others | 2 (8) |

**BLOOD PRESSURE**

| Normal; ambulatory hypertension | 19 (78); 5 (20) |
| Masked; whitecoat hypertension | 4 (16); 0 (4) |

**Baseline evaluation**

| Serum albumin, g/dL | 3.85 (3.15-4.20) |
| eGFR, l/1.73 m² | 93 (60-104) |
| 24-hr urine protein, mg/dL | 50 (24-149) |
| 24-hr urine PCR, mg/dL | 2.38 (1.40-3.78) |
| 24-hr urine ACR, mg/g | 130 (78-217) |

Categorical data are shown as n (%) and continuous ones as median (interquartile range)

ACE-I angiotensin converting enzyme inhibitors; ARB aldosterone receptor blockers; CNI calcineurin inhibitors; SLS Ca-glomerular filtration rate; FSGS focal segmental glomerulosclerosis.

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

Underline represents presenting author.

B5
Identification of a Hypertensive Endotype with a Median Treatment Effect of -32mmHg in Response to the Novel Aldosterone Synthase Inhibitor Lorundrostat

Borut Cizman,1 Luke J. Laffin,2 Natasa Rajicic,1 David M. Rodman,1 1Mineralys Therapeutics, Radnor, PA; 2Cleveland Clinic Center for Clinical Research, Cleveland, OH; 3Cytel Inc, Waltham, MA.

Background: Uncontrolled and treatment-resistant hypertension are common challenges faced by clinicians. We previously reported the novel aldosterone synthase inhibitor, lorundrostat, 25mg BID, 50mg QD or 100mg QD, demonstrated median serum aldosterone reduction of 65-70% and observed mean systolic BP(SBP) reduction of -10.1, -13.2 and -14.1mmHg, respectively (n=25-28), vs placebo (-4.1 mmHg, n=29). The top quartile of the pooled group (n=81) had a median [IQR] SBP reduction of -32mmHg (n=21, [37.5 to -27]); the bottom quartile had no change (Fig 1).

Methods: To identify predictive factors differentiating these groups, BP response to lorundrostat 100mg QD was compared in subjects with low plasma renin activity (PRA) ≤1.0ng/ml/hr vs PRA >1.0ng/ml/hr. In the planned development of lorundrostat 100mg QD was compared in subjects with low plasma renin activity (PRA) ≤1.0ng/ml/hr vs PRA >1.0ng/ml/hr.

Results: Low PRA was not a useful predictor of response (low [n=25] -12.1 [2.68] mmHg, normal to high [n=30] -11.4 [2.48] mmHg). A correlation was observed between BMI and SBP reduction (r= -0.27, p=0.017). In the planned development lorundrostat on SBP in subjects with BMI 25-30kg/m2 (n=11,9) was seen (2.2 and -4.5 mmHg, respectively). Elevated baseline BP was similarly predictive of a favorable median SBP reduction in the 50mg and 100mg QD cohorts (lowest tertile of baseline SBP -3.5, -2.5 mmHg, highest tertile -34.3, -17.5mmHg, respectively), possibly due to the relative importance of aldosterone-mediated hypertension in obese individuals. A positive association was also observed between obesity and serum leptin at baseline (p=0.002 and 0.030). No significant effect of BMI and SBP reduction (r=0.47, p<0.001).

Conclusions: While this association does not establish cause and effect, serum leptin is a direct stimulus for adrenal aldosterone production, and its investigation as a predictor of lorundrostat response warrants further investigation.

Funding: Commercial Support - Mineralys Therapeutics

Wearable Device for Noninvasive Blood Pressure Monitoring of ICU Patients

Forrest Miller, Alto, Broomfield, CO.

Background: Blood pressure (BP) is a cardinal vital sign used in cardiovascular clinical decision-making. The traditional approach for BP measurement in intensive care units (ICU) involves the use of an invasive arterial line (A-line). A-line measurements require technique and practice and introduce the risk of clinical complications that could result in thrombosis or sepsis. This study evaluated the performance of cuffless BP monitoring with a novel wearable device (“SmartPatch”) compared to the gold standard A-line.

Methods: A retrospective IRB-approved study was conducted to evaluate the performance of an algorithm to track BP metrics-systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP)-noninvasively and compare them against invasive arterial line (on left radial) values in 26 subjects. Simultaneous arterial line BP and photoplethysmography (PPG) data from SmartPatch were collected from post-surgery patients admitted to a neuro-ICU unit over an average of 2 hours. The PPG data was pre-processed, assessed for signal quality, and fed into an Artificial Neural Network (ANN) model to train with the A-line BP data as reference.

Results: A total of 6.07 hours of data was segmented into 6 sec PPG recordings resulting in ~1900 data points to be analyzed. An ANN model was trained and validated with leave one out-cross validation (LOO-CV) to tune the model parameters and assess the performance. The mean of errors and Pearson correlation coefficient r were used to assess the performance of the ANN model. The mean of errors and the experimental standard deviation for SBP was: -1.207 (SD: 9.17) mmHg, MAP: -0.144 (SD: 5.09) mmHg and DBP: -0.161 (SD: 5.10) mmHg. These values fall within the limits set by the ISO 81060-2 (2018) standard when validated against the A-line BP. The ANN-generated BP values were correlated to the A-line with Pearson r = 0.81 (SBP), 0.68 (DBP) and 0.79 (MAP).

Conclusions: The ANN model was trained using LOO-CV to predict SBP, DBP & MAP. The results demonstrated quantitative accuracy within the limits set by the ISO 81060-2 (2018) standard when validated against the A-line BP. This noninvasive cuffless BP measurement from a wearable device could enable more consistent, accurate, and cost-effective patient care in remote monitoring settings.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
The 9-month primary endpoint was change in urine protein-creatinine ratio (UPCR). The 2-year primary endpoint was time-weighted average of eGFR over 2 years.

Results: Baseline characteristics of all 62 Chinese patients were similar to the global study population and were balanced across treatment arms. There was a 9.58 mL/min/1.73 m² (95% CI 1.95, 19.78) treatment benefit in the 2-year primary endpoint with Nefecon vs placebo (3.74 vs 13.32 mL/min/1.73 m² average eGFR decline, respectively). At 24 months, the mean absolute changes in eGFR from baseline (Fig. 1) suggested that 66% of the eGFR decline observed with placebo could be prevented with 9 months of Nefecon treatment. Mean UPCR reduction was 31% greater at 9 months and 52% greater over 12–24 months with Nefecon vs placebo. No new safety signals were identified.

Conclusions: Compared with placebo, 9 months of Nefecon treatment provided clinically relevant preservation of eGFR and durable proteinuria reduction over 2 years, supporting a disease-modifying effect in Chinese patients with primary IgAN.

Funding: Commercial Support - Caliditas Therapeutics AB; Everest Medicines Ltd.

Efficacy and Safety Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Shigekodaira/2 mg/kg (n = 30)</th>
<th>Shigekodaira/4 mg/kg (n = 41)</th>
<th>Shigekodaira/8 mg/kg (n = 41)</th>
<th>Placebo (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UPCR (mg/g)</td>
<td>0.75 (0.24)</td>
<td>0.59 (0.19)</td>
<td>0.72 (0.19)</td>
<td>0.66 (0.24)</td>
</tr>
</tbody>
</table>

Percentage Change in 24-Hour UPCR From Baseline Over Time

TH-PO1125

Povetaclacpt, an Enhanced Dual BAFF/APRIL Antagonist, in Autoantibody-Associated Glomerulonephritis (GN)

James A. Tumlin,1,2 Harneet Singh,3 Frank B. Cortazar,4 Arvind Madan,5 Jonathan Barratt,6 Brad H. Rovin,7 Hong Zhang,8 Rupert H. Davies,9 Amanda M. Enstrom,10 Allison G. Chunya,11 Heather Thomas,12 Jiahua Li,13 Sreedhar A. Mandayam,14 1NephroNet Clinical Trials Consortium, Atlanta, GA; 1Emory University School of Medicine, Atlanta, GA; 2Western Nephrology, Arvada, CO; 3New York Nephrology Vasculitis and Glomerular Center, Watervliet, NY; 4Central Florida Kidney Specialists, Orlando, FL; 5University of Leicester, Leicester, United Kingdom; 6The Ohio State University Wexner Medical Center, Columbus, OH; 7Peking University First Hospital, Beijing, China; 8Alpine Immune Sciences, Inc., Seattle, WA; 9UT MD Anderson Cancer Center, Bellaire, TX.

Background: Inhibition of BAFF and/or APRIL has shown promise in IgA nephropathy (IgAN), primary membranous nephropathy (pMN), and lupus nephritis (LN), with the potential to exert a disease-modifying effect. Povetaclacpt (ALPN-303) is an Fc fusion of a variant TACI domain engineered for more potent dual BAFF/APRIL inhibition vs WT TACI or anti-BAFF or -APRIL Abs. In healthy volunteers, povetaclacpt was well tolerated and reduced Ig (including Gd-IgA1) levels and Ab-secreting cells. This is a report of an open-label, multiple ascending dose experience with povetaclacpt in GN.

Methods: RUBY-3 (NCT05732402) is a ph 1b/2a study of povetaclacpt 80 or 240 mg SC Q4W for 24 wk, with an optional 24-wk extension. Eligible participants (pts) are aged ≥18 y with biopsy-confirmed IgAN, pMN, or LN, and on maximally tolerated therapy where applicable. Primary objective is safety; secondary objectives include PK, PD, immunogenicity, biomarkers, and efficacy.

Results: As of 1Sep23, 12 pts with IgAN and 1 with pMN have enrolled at the lower povetaclacpt dose level of 80 mg; 6 and 1 pts, respectively, have completed ≥12 wk. The 240-mg IgAN cohort has also begun enrolling. Povetaclacpt has been well tolerated, with no serious or severe TEAEs, IgG ≥3 g/L, or administration-related reactions. In IgAN, UPCR was reduced by 30% at 12 wk (n=6) and expected decreases in Ig levels were seen (Fig). The first enrolled pt achieved a urinary protein excretion level below the threshold of detection (<0.56 g/g) by 24 wk, preceded by a 43% reduction in Gd-IgA1 at 4 wk. In pMN (n=1), a 39% UPCR reduction (Fig) and 77% reduction in anti-PLA2R were seen at 12 wk. Updated data will be presented.

Conclusions: Initial experience indicates povetaclacpt is well tolerated during multiple-dose administration in GN, with highly encouraging early reductions in UPCR and disease-specific biomarkers in pts with IgAN and pMN.

Funding: Commercial Support - Alpine Immune Sciences, Inc.
TH-PO1126
Clinical Value of Adding Dapagliflozin in Patients with Nephrotic Syndrome
Internal Medicine & Nephrology. Ain Shams University Faculty of Medicine, Cairo, Egypt.

Background: The potential utilization of SGLT2 inhibitors in glomerular disease patients undergoing immunosuppression therapy has remained underexplored. This study evaluates the clinical impact of dapagliflozin in non-diabetic primary nephrotic syndrome patients.

Methods: We conducted a randomized controlled clinical trial with 60 non-diabetic primary nephrotic syndrome patients, equally assigned to dapagliflozin and control groups. The dapagliflozin group received dapagliflozin 10 mg/day in addition to standard care, while the control group received standard care alone. Baseline characteristics, including age, gender, nephrotic syndrome etiology, proteinuria levels, estimated glomerular filtration rate (eGFR), and immunosuppression doses, were well-matched. Both groups were followed for 6 months. 1ry outcomes included changes in proteinuria (measured by urine PCR, UPCR) and eGFR. 2ry outcomes encompassed alterations in body weight and lipid profile changes. Pregnant or breastfeeding females and patients with secondary nephrotic syndrome were excluded.

Results: Both groups exhibited significant reductions in proteinuria after 6 months, with the dapagliflozin group achieving a mean UPCR reduction of -94.7% and the control group -86.7% (p < 0.001). However, the comparative percentage change in proteinuria between both groups did not reach statistical significance (p = 0.158). Dapagliflozin initially led to a transient eGFR decline followed by recovery, while the control group maintained stable eGFR. Dapagliflozin also resulted in a significant mean body weight reduction of 3.91 kg (p < 0.001) and notable improvements in triglyceride levels compared to the control group (p = 0.045). Although no major safety concerns arose, the dapagliflozin group exhibited a slightly higher incidence of urinary tract infections.

Conclusions: In primary nephrotic syndrome patients, adjunct dapagliflozin may enhance the standard of care. While notable, the reduction in proteinuria was comparable to that of the control group by the study’s end. Furthermore, after 6 months, eGFR remained stable in both groups. However, significant weight loss and serum triglyceride reduction were particularly pronounced in the dapagliflozin group. Further long-term investigations are necessary to address potential immunosuppression-related confounding effects in patients with primary glomerular disease.

TH-PO1127
Efficacy and Safety of Ravulizumab in a Phase 2 Randomized Controlled Trial in IgA Nephropathy
Jonathan Barratt, Jose Luis Rocha Castilla, Dario Roccatello, Katherine Garlo, Kara Rice, Richard A. Lafayette,1 Department of Cardiovascular Sciences, University of Leicester, Leicester, United Kingdom; 2Department of Nephrology, Hospital Universitario Virgen del Rocio, Sevilla, Spain; 3Alexion, AstraZeneca Rare Disease, Boston, MA; 4Stanford Glomerular Disease Center, Stanford University Medical Center, Stanford, CA; 5University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases, Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, University of Turin, Turin, Italy.

Background: IgA nephropathy (IgAN) is the most prevalent primary glomerular disease, often progressing to ESKD. Complement activation leads to glomerular damage by immune complex deposition and release of proinflammatory cytokines. Terminal complement inhibition specifically targets the pathophysiology of IgAN and may provide improved renal outcomes.

Methods: This primary analysis of a phase 2 RCT (NCT045464319) evaluated ravulizumab (RAV) (IV; weight-based dosing Q8W) vs placebo (PBO) in adults with primary IgAN. Eligible patients (pts) (18-75 years) with biopsy-confirmed IgAN, proteinuria ≥1g/d, on stable maximally tolerated RASi with stable blood pressure ≥140/90 mmHg, were enrolled. The primary endpoint was % change in proteinuria from baseline to week (wk) 26 followed by 24-hr urine. Secondary endpoints included spot UPCR and change in baseline eGFR at wk 26, safety, and PK/PD.

Results: 66 pts were randomized 2:1 to RAV (n=43) or PBO (n=23). Mean age was 40.1 ± 10.3 yrs. 66% were male, and 21% were Asian. At 26 wks, proteinuria reduction was greater with RAV vs PBO, 40.3% vs 10.9% (treatment effect 33.1%, 90% CI 14.7%, 47.5%; p = 0.0012). In RAV-treated pts, proteinuria reduction was rapid and sustained through wk 26 (Figure 1) and eGFR remained stable. RAV was well-tolerated with a safety profile similar to that of PBO and no new safety concerns (Table 1).

Conclusions: This analysis supports clinically meaningful efficacy of RAV based on rapid and sustained proteinuria reduction, providing proof-of-concept for a phase 3 trial of RAV as a potential treatment for IgAN.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease

TH-PO1128
Long-Term Nedosiran Safety and Efficacy in Primary Hyperoxaluria Type 1 (PH1): Interim Analysis of PHYOX3
Jaap Groothoff, Anne-Laure A. Sellier-Leclerc, Lisa Descker, Justine Baschetta, Gesa Schalk, Burkhard Toenshoff, Graham W. Lipkin, Horacio Lemoine, Corinne Dhon, Thomas Bowman, Jing Zhou, Bernd Hoppe.1 Department of Pediatric Nephrology, Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; 2Pediatric Nephrology Rheumatology Dermatology Unit, Hospices Civils de Lyon, Lyon, France; 3Dicerna Pharmaceuticals, Inc., a Novo Nordisk Company, Lexington, MA; 4Department of Pediatrics & University Children’s Hospital, Heidelberg, Germany; 5Pediatric Nephrology Center Bonn, Bonn, Germany; 6German Hyperoxaluria Center, Pediatric Nephrology Center Bonn, Bonn, Germany; 7Department of Nephrology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; 8Hospices Civils de Lyon, Lyon, France.

Background: Primary hyperoxaluria (PH) is a family of rare genetic disorders of hepatic glyoxylate metabolism leading to oxalate overproduction, causing calcium oxalate stones, and may result in kidney damage/failure. Nedosiran is a RNAi therapy in development for treatment of PH. Nedosiran silences hepatic LDH enzyme expression encoded by the LDHA gene to reduce oxalate production.

Methods: This 30-month interim analysis of the ongoing PHYOX3 study (NCT04042402) reports long-term safety/efficacy of monthly s.c. nedosiran in participants with PH1 who continued from a single-dose nedosiran trial PHYOX1 (NCT03392896). Participants (≥6 yrs) who had no prior kidney/liver transplant, dialysis, or evidence of systemic oxalosis were eligible.

Results: Thirty participants with PH1 rolled into PHYOX3. At baseline, mean (SD) age was 24 (6.6) years (53.8% female; 61.5% White) and mean (SD) estimated glomerular filtration rate (eGFR) was 77.6 (21.82) mL/min/1.73m². Mean eGFR remained stable (62–84.2 mL/min/1.73m²) to month 30. Mean urinary oxalate (Uox) excretion showed a sustained reduction from baseline (≥60%) to month 30 (Figure 1). At every visit, at least 10 (76.9%) participants achieved normal (<0.46 mmol/24h; upper limit of assay-normal [ULN]) or near-normal (≥0.46 to <0.60 mmol/24h; ≥1.3 x ULN) 24h Uox excretion. All participants experienced ≥1 adverse event (AE), mostly mild or moderate severity (76.9% treatment-related). Three serious AEs were reported (not treatment-related). Of 398 total injections in the study, 2.5% had an injection-site reaction. There were no deaths or study discontinuations due to AEs.

Conclusions: Nedosiran was well-tolerated in patients with PH1 and resulted in a sustained reduction in Uox excretion for up to 30 months. No safety signals were identified to date. Analysis of long-term effects on kidney function are ongoing.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc., a Novo Nordisk Company (Lexington, MA)
Results: Symptoms were significantly better with 2X HD, as assessed by the KDQI Symptom composite score (2X: 24±6 vs. 3X: 27±7, p = 0.01). 2X HD also provided adequate stdKt/V of 2.7±0.5 without a significant increase in treatment time (2X: 195±21 min vs. 3X: 191±17 min, p = 0.07). Kru, ultrafiltration rate, and pre-treatment plasma potassium were lower, and no patients were withdrawn for fluid overload or hyperkalemia. Plasma analysis showed an expected higher pre-treatment level of urea with 2X HD (76±22 vs. 54±13 mg/dl, p <0.001) while the levels of PCS (4.0±1.6 vs. 3.7±1.3 mg/dl, p = 0.39), HIPP (2.7±3.0 vs. 2.2±1.9 mg/dl, p = 0.84), and β2m (22±7 vs. 21±6 mg/l, p = 0.80) were not significantly higher than 3X HD.

Conclusions: We show that 2X HD can be safely prescribed with the increased contribution assigned to Kru by the 2015 KDQI guidelines. With 2X HD, symptoms were improved and the continuous function of the residual kidneys controlled fluid gain, potassium, and plasma levels of uremic solutes without a need to increase treatment time.

Funding: NIDDK Support

TH-POI131

Hemodialysis Vascular Access Complications: Insights from the ASCEND-D Trial
Renato D. Lopes,1 Aleix Cases,2 Brian Claggett,3 Laura M. Dember,4 Nisha Bhatt,5 Angela R. Jones-Leone,6 Amy M. Meadowcroft,7 Mary O. Muoneke,8 Premna Ranganathan,9 Lin Tu,10 Ajay K. Singh,4,11 Duke University Medical Center, Durham, NC; 2Hospital Clinic de Barcelona, Barcelona, Spain; 3Brigham and Women’s Hospital, Boston, MA; 4University of Pennsylvania, Philadelphia, PA; 5GSK, Collegeville, PA; 6Harvard Medical School, Boston, MA.

Background: Daprodustat (Dapro) is a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI) approved in the United States for treating anemia of chronic kidney disease (CKD) in adult patients (pts) receiving dialysis for at least 4 months. Daprodustat provides an oral alternative to erythropoietin-stimulating agent (ESA) therapy. There are concerns increasing hemoglobin in the dialysis population, such as with ESAs and HIF-PHIs, may cause thromboembolic events (TEEIs). In the phase 3 ASCEND-D study, which randomized (1:1) 2964 pts to receive Dapro or ESA (NCT02879305; N Engl J Med. 2021;385:2325–2335), a trend toward improved and the continuous occurrence of TEEs was observed with Dapro (185/1487 [12.4%]) compared with ESA (215/1477 [14.6%]). Here, we examine the occurrence of vascular access thrombosis (VAT), the most frequent type of TEE in the ASCEND-D study.

Methods: Adjudicated TEEs (including VAT) were a component of a prespecified principal secondary outcome. VAT was predefined as the absence of bruit or thrill and/or an inability to successfully initiate dialysis via the arteriovenous access after initial successful use. All suspected TEEs were adjudicated by the blinded Clinical Events Committee (CEC) according to predefined criteria. Post hoc analyses of time to first occurrence of VAT and recurrent events of VAT were performed.

Results: The CEC adjudicated 1088 potential TEEs, including VAT. First occurrence of adjudicated VAT occurred in 164/1487 (11.0%) and 201/1477 (13.6%) pts in the Dapro and ESA groups, respectively; hazard ratio = 0.80 (95% CI: 0.63–0.98; P = 0.015; Figure). Based on a recurrent events analysis of VAT using the negative binomial model, the rate ratio was 0.80 (95% CI: 0.63–1.01).

Conclusions: In the ASCEND-D study, there was a reduced incidence of VAT events with Dapro compared with ESAs.

Funding: Commercial Support - The study and this analysis were funded by GSK.

Key: TH - Thursday; FR - Friday; SA - Saturday; OR - Oral; PO - Poster; PUB - Publication Only
Underline represents presenting author.
B9
TH-PO1132
SARS-CoV-2 Testing During Routine Hemodialysis Care: A Nationwide Pragmatic Clinical Trial
Maria E. Montez-Rath,1 Meri Varkila,1 Xue Yu,1 Julie Parsonnet,2 Glenn Chertow,3 Geoffrey A. Block,2 Shuchi Anand.3 Stanford University, Stanford, CA.

Background: Patients receiving dialysis face relatively high risks from viral infections including SARS-CoV-2. Early detection could facilitate treatment, reduce transmission, and strengthen public health surveillance. We evaluated the acceptability of routine SARS-CoV-2 screening among asymptomatic patients in dialysis facilities.

Methods: We conducted a pragmatic, cluster randomized trial in 57 US hemodialysis facilities from Feb-July 2023 in partnership with US Renal Care and Ascend Clinical Laboratory (NCT05225298). We tested patient level acceptability of two strategies for offering SARS-CoV-2 rtPCR tests: static frequency every two weeks (arm 1) versus dynamic frequency based on county COVID-19 levels (arm 2). We used wastewater surveillance if available or else CDC case and hospitalization rates to determine frequency of testing in the dynamic arm: weekly, bimonthly or every four weeks for high, medium or low community levels, respectively). We randomized facilities by county and offered testing for three months.

Results: 2389 patients participated and 12,553 tests were offered (Table). A median of 6 versus 4 tests were offered per patient at static versus dynamic facilities. Test acceptability and positivity rates were 8.0% vs 7.7% (p=0.45), and 2.0% vs 1.9% (p=0.56), at static versus dynamic facilities.

Conclusions: In this national trial integrating routine SARS-CoV-2 test offer in dialysis care in which a diverse group of patients participated, we found test acceptability was poor and did not vary by testing strategy. A dynamic testing strategy anchored to community transmission resulted in fewer tests offers per patient. Positivity rates among those tested indicate continued risk for transmission even during low COVID-19 incidence.

Funding: Other NIH Support - NIH RADxUP Grant, Commercial Support - Abbott Clinical Laboratories provided test kits; Ascend Clinical Labs processed test samples.

TH-PO1133
Real-World Effectiveness of Hemodialysis Modalities
Yan Zhang,1 Anke Winter,1 Paola Carioni,2 Belen Alejos,1 Len A. Usvyat,3 Franklin W. Maddux,4 Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; 5Fresenius Medical Care AG & Co KGaA, Milan, Italy; 6Fresenius Medical Care Holdings Inc, Waltham, MA; 7Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany.

Background: Results from the CONVINCE clinical trial suggest a 23% mortality risk reduction among patients receiving hemodiafiltration (HDF). We assessed the real-world effectiveness of HD modality (HDF versus hemodialysis (HD)) in a large, unselected patient population treated prior to and during pandemic years.

Methods: We included EuClID data from 85,222 adult HD patients who were treated in EMEA NephroCare Clincis between 2019 and 2022 in the analyses. Cox proportional hazard models with HD modality and COVID-19 status as time-varying covariates and adjustment for multiple confounders were used to estimate all-cause mortality. Subgroup analyses were performed for age, patient status (incident/prevalent), COVID-19 status, diabetes, circulatory disease, and dialysis vintage.

Results: The mean age of the population was 63.2 years and 60% were male. During the mean follow-up of 22.6 months, a documented COVID-19 infection was associated with an overall 2.4-fold increased all-cause mortality risk. Compared with HD patients, those treated with HDF had an adjusted hazard ratio for all-cause mortality of 0.78 (95% CI, 0.76-0.80). The pattern of a beneficial effect of HDF was consistently observed among all subgroups. Patients with a documented COVID-19 infection and those with a history of circulatory disease had a slightly more reduced effect estimate in subgroup analyses (Figure 1).

Conclusions: Our results suggest that hemodiafiltration has a beneficial effect on all-cause mortality in a large, unselected patient population and across patient subgroups that were treated in real-world settings. Our observational study complements evidence generated by the CONVINCE trial and adds to the growing body of real-world evidence on hemodiafiltration.

TH-PO1134
Patient-Reported Health Status of Adults with Kidney Failure Receiving Hemodiafiltration vs. Hemodialysis: Results from the CONVINCE Randomized Controlled Clinical Trial
Matthias Rose,1 Felix Fischer,2 Gregor Liegl,3 Giovanni Strippoli,2 Carmina Hockham,4 Robin W. Verrooj,4 Claudia M. Barth,4 Bernard J. Canaud,1 Adrian Covic,1 Krister Cromm,5 Andrew Davenport,6 Kathrin I. Fischer,7 Jorgen B. Hegbrant,8 Hantu Jaha,9 Anand Schappert,1 Marietta Török,4 Michiel L. Bots,2 Peter J. Blankenstein,11 For the CONVINCE Scientific Committee and Investigators.2 Psychosomatic Medicine, Center for Internal Medicine and Dermatology, Charite Universitätsmedizin Berlin, Berlin, Germany; 3University of the Studi di Bari Aldo Moro, Bari, Italy; 4The George Institute for Global Health, School of Public Health, Imperial College London, London, United Kingdom; 5University Utrecht, Utrecht, Netherlands; 6MTX Consulting, Montpellier, France; 7Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; 8University College London, London, United Kingdom; 9Diaverum AB, Malmo, Sweden; 10B. Braun Avitum AG, Melsungen, Germany; 11JBA Medical, AB, Bjarred, Sweden; 2Nephrology, University Medical Center Utrecht, Utrecht, Netherlands; 12University of Medicine “Grigore T. Popa”, Bucharest, Romania.

Background: The CONVINCE trial showed a significant survival benefit for patients receiving high-dose hemodiafiltration as compared with conventional high-flux hemodialysis (N Engl J Med 2023). The primary objective was to compare the patient-reported health status between both interventions.

Methods: The CONVINCE trial is multi-center, prospective randomized, open label, controlled trial, comparing benefits and safety of high-dose hemodiafiltration (HDF) versus high-flux hemodialysis (HD). The perceived health status was assessed in eight controlled trial, comparing benefits and safety of high-dose hemodiafiltration (HDF) versus high-flux hemodialysis (HD). The perceived health status was assessed in eight domains (physical function, cognitive function, fatigue, sleep disturbance, depression, anxiety, pain interference, social participation) using instruments from the Patient-Reported Outcome Measurement Information System PROMIS® before randomization and every three-month after over three years. The mean change from baseline using an omnibus test for all eight domains, and a Linear Mixed Model to identify group x time interaction effects for specific domains.

Results: 1,360 patients have been enrolled, 677 receiving hemodialysis and 683 hemodiafiltration, with a median observation time of 30 month. For 84% of all treated patients PRO assessments could be analyzed (10,681 questionnaires). On average patients described statistically significant health deteriorations in all domains, with most pronounced declines in physical function scores. Potential group differences between HDF and HD will be disclosed at the ICA Congress.

Conclusions: As of today, the CONVINCE trial has applied the most comprehensive assessment of PROs within a large RCT comparing HDF with HD, deepening the
understanding of the determining factors of perceived health of patients receiving renal replacement therapies. The relevance of potential group differences will be discussed at the conference.

Funding: Government Support - Non-U.S.

TH-PO1135

Short- and Long-Term Effectiveness of Existing Insomnia Therapies for Patients Undergoing Hemodialysis (SLEEP-HD)
Rajnish Mehrotra,1 Daniel Cukor,2 Susan M. McCurry,3 Tessa Rue,4 Maria-Eleni Roumelioti,4 Patrick J. Heagerty,1 Mark L. Unruh.4 1Medicine, University of Washington, Seattle, WA; 2Rogosin Institute, New York, NY; 3University of Washington, Seattle, WA; 4University of New Mexico School of Medicine, Albuquerque, NM.

Background: Nearly 50% of patients undergoing in-center hemodialysis report chronic insomnia, yet efficacy and safety of treatments is not known. This trial tested the comparative effectiveness of cognitive behavioral therapy for insomnia (CBT-I), trazodone, and placebo for insomnia in this population.

Methods: We undertook a randomized, multicenter, double-blinded, placebo-controlled trial in 26 dialysis units. Patients undergoing in-center hemodialysis with insomnia severity index (ISI) score ≥10 and sleep disturbances on ≥3 nights/week for a 3 months were randomized 1:1:1 to telehealth CBT-I or trazodone or placebo. The primary outcome was the ISI score at 7- and 25-weeks.

Results: 923 patients were pre-screened, 411 had insomnia, and 126 were randomized to CBT-I (n=43), trazodone (n=42), or placebo (n=41). The ISI scores decreased in each group: CBT-I (baseline mean ± SD, 16.1 ± 4.8; 7-weeks, 13.3 ± 6.0), trazodone (baseline mean ± SD, 17.2 ± 5.4; 7-weeks, 12.5 ± 6.2), and placebo (baseline mean ± SD, 15.2 ± 4.4; 7-weeks 12.5 ± 5.3) and there was no significant difference in the average 7-week scores across groups. There was no meaningful difference in ISI scores at 25-weeks. There was no significant difference in other patient-reported outcomes at any time point, or use of sleeping aids, or with actigraphy. Serious adverse events, particularly cardiovascular hospitalizations, were more frequent with trazodone (Relative risk: trazodone vs. CBT-I, 12.2 (1.83, 519.2); trazodone vs. placebo, 3.1 (0.97-13.22)).

Conclusions: In patients undergoing in-center hemodialysis with chronic insomnia, there was no meaningful difference in the short- or long-term effectiveness of CBT-I or trazodone compared with placebo. Participants receiving trazodone had higher incidence of serious adverse events.

Funding: NIDDK Support

TH-PO1136

Abstract Withdrawn

TH-PO1137

Peer Mentorship to Reduce Hospitalizations Among Patients Receiving Maintenance Hemodialysis: Results of the PEER-HD Trial
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Background: Hospitalizations contribute to up to 40% of the cost of care among patients receiving maintenance dialysis. PEER-HD is a pragmatic trial to test the impact on ED visit and hospitalization rates of a peer mentor led intervention in patients receiving hemodialysis.

Methods: This is a multi-center randomized controlled trial of 194 patient-participants (134 in Bronx NY and 60 in Nashville TN). Fourteen mentor-participants were recruited and trained. Patient-participants, identified as having high risk of hospitalization, were then recruited from affiliated dialysis facilities and those assigned to intervention (n=99) were matched to mentors. Mentors placed weekly telephone calls to assigned mentees over 3 months, after which patient-participants were followed up for 12 months. Rates of hospitalizations and composite events during follow-up were compared.

Results: Of the 194 patient-participants assigned to intervention or usual care, 69 were assigned to intervention and 60 to usual care. The primary outcome, rate of hospitalizations during the 12-month period, was significantly reduced in the intervention group compared to the usual care group (incident rate ratio (IRR)=0.86; CI 0.70-1.06, p=0.15). Among the 134 patient participants in Bronx, NY there was a significantly lower rate of outcome in those assigned to intervention as compared to usual care (IRR = 0.70, CI 0.54-0.90; p=0.007). Among the 69 patients from Nashville, TN the difference in primary outcome was not significantly different (IRR= 1.25; CI 0.89-1.76, p=0.20). Post-hoc analysis showed that removal of one medically complex outlier made significant the overall effect of the intervention on outcome (IRR=0.85; CI 0.86-0.96, p=0.02).

Conclusions: Peer mentorship was not effective overall in reducing rate of hospitalization and ED visits, but was effective in Bronx NY. The protective effect of peer mentorship may be population specific, affected by area practice patterns or related to differences in mentoring activities.

Funding: NIDDK Support

TH-PO1138

Association of CKD-Associated Pruritus (CKDaP) with More Sleep Disorders, Increased Pain, and Worse Fatigue in US Hemodialysis Patients
Tejas Desai,1 Rachel A. Lasky,2 Kunal Malhotra,3 Hans-Juergen Arens,2 Juliana H. Oliveira,1 Michael S. Anger.2 1Vifor Pharma Management Ltd, Glattbrugg, Switzerland; 2 Fresenius Medical Care HOLDINGS Inc, Waltham, MA; 3University of Missouri System, Columbia, MO.

Background: Patients & their advocates emphasize symptom-based management for those afflicted with ESKD. There is an active call-to-action for Nephrology healthcare providers (NHPs) to provide a holistic treatment plan: one that equally prioritizes symptom-based & biochemically-focused care. Three symptoms ESKD patients experience as sleep disorders, pain, & fatigue. These components facilitate a cluster of symptoms known as SPADE in the Nephrology literature. This study investigates the association of CKDaP, an under-recognized & reported symptom, with these components.

Methods: A retrospective analysis of 81130 difelikefalin-naive, >30-day hemodialysis vintage in-center patients were stratified into the 5 validated groups of CKDaP burden descriptors in question 20 of the KDQOL-36 instrument. The burden of sleep disorder, pain, & fatigue were independently measured using questions 6, 8, & 25 of the KDQOL-36, respectively. Scores were re-coded from 0 (highest burden) to 100 based on the Rand Corporation's survey scoring instructions. ANOVA & logistic regression were used across pruritic levels. Mean (SD) are reported.

Results: Nearly 58% of patients experienced moderate or greater pruritic burden. Those patients with a greater CKDaP burden were statistically likely to have worse sleep, fatigue, & pain, both independently and in aggregate (table). The CNDOQOL-36 Short Form Health Survey (KDQOL-36) captures patient reported health-related QoL, and symptoms including pruritus (q20) and mental health-related factors, such as depression (q11) and anxiety (q9). Another tool, Patient Health Questionnaire-2 (PHQ2), measures depressive symptoms. The goal of this cross-sectional, descriptive analysis was to evaluate the association of depression and anxiety scores with varying levels of pruritus.

Conclusions: This data shows a strong association of CKDaP with 1) sleep disorders, 2) pain, & 3) fatigue. Patients afflicted with CKDaP endure a greater individual & aggregate symptom burden than those without. NHPs who detect CKDaP & quantify its burden can potentially identify patients experiencing a) numerically higher-than-expected & b) more severe co-morbidities.

Funding: Commercial Support - CSL Vifor

TH-PO1139

The Association Between Pruritus Severity and Mental Health-Related Quality of Life in over 80,000 Hemodialysis Patients
Linda Ficecilli,1 Tejas Desai,2 Juliana H. Oliveira,2 Hans-Juergen Arens,2 Rachel A. Lasky,2 Michael S. Anger.2 1Vifor Pharma Management Ltd, Glattbrugg, Switzerland; 2Fresenius Medical Care Holdings Inc, Waltham, MA; 3Vifor Pharma Management Ltd, Glattbrugg, Switzerland.

Background: Chronic kidney disease associated pruritus is common in hemodialysis patients and can impact quality, & pain of life (QoL). The Kidney Disease Quality of Life-36-item Short Form Health Survey (KDQOL-36) captures patient reported health-related QoL and symptoms including pruritus (q20) and mental health-related factors, such as depression (q11) and anxiety (q9). Another tool, Patient Health Questionnaire-2 (PHQ2), measures depressive symptoms. The goal of this cross-sectional, descriptive analysis was to evaluate the association of depression and anxiety scores with varying levels of pruritus.

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

B11
Methods: Fresenius Kidney Care, adult, in-center HD patients with SF-36 measured between 1/1/21 and 2/28/23 are eligible. Patients answering that they are burdened by at least “moderate” pruritus were included in the analysis. A random sample of patients from the “not at all” and “somewhat” bothered respondents was selected. This stratified sampling technique was used to guarantee patients from each itch severity group will be adequately represented in the study population. ANOVA and logistic regression were used to test the mean scores (0=lowest burden to 100=lowest burden) or odds ratios across itch levels. PHQ2 scores > 2 have been a screening tool for depression and were used to dichotomize scores into depression present or absent.

Results: Among 81,310 patients who had completed SF-36, of which 77,978 (96%) also had PHQ2 completed within 30 days. Burden of anxiety (p<0.0001) and depression (p<0.0001) symptoms was more likely as itch intensity increased. Mean scores for anxiety and depression differed by pruritis severity. Next, using PHQ2 scores of > 3 to define depression, we found a stepwise increased risk of depression with each increase in pruritus intensity score (Figure 1). Patients who were extremely bothered by pruritus had 6 times the odds of having depression when compared to those patients “not at all bothered” by pruritus (p<0.001).

Conclusions: These data have shown a strong association of pruritus with depression and anxiety.

Funding: Commercial Support - CSL Vifor

Figure 1. Association of itch burden and the presence of depression (PHQ2 > 3)

Zin Harel,1,2 SAFE-D Investigators. 1St. Michael’s Hospital, Toronto, ON, Canada; 2University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada.

Background: Atrial fibrillation (AF) is common in patients receiving maintenance dialysis. The role of oral anticoagulation (OAC) in this population is uncertain as dialysis recipients were excluded from landmark randomized control trials (RCTs).

Methods: Objective: To investigate the feasibility of conducting a full-scale RCT to assess the efficacy and safety of OAC in dialysis recipients with AF. Design, setting, and participants: We conducted a parallel-group, open-label allocation-concealed pilot RCT from December 2019 to December 2022 at 28 centres in Canada and Australia (ClinicalTrials.gov Identifier: NCT03987711). We included adults (≥18 y) undergoing maintenance dialysis with a history of non-valvular AF who met CHADS2-65 criteria (i.e. age ≥65 y or the presence of at least one stroke risk factor). Exclusion criteria included contraindications to warfarin or apixaban, the need for anticoagulation for conditions other than AF and lack of clinician equipoise.

Interventions: Dialysis recipients were randomized 1:1:1, stratified by centre, to receive dose-adjusted warfarin (targeting an INR of 2-3), apixaban, or no OAC. Follow-up was 26 weeks. Outcomes: We identified two thresholds for feasibility: recruitment of the target population within 24 months and retention of ≥80% of participants in their assigned arm at the end of follow-up. Principal secondary outcomes were ischemic stroke or systemic embolism, and bleeding (defined by International Society of Thrombosis and Hemostasis criteria).

Results: We screened 892 patients and enrolled 151 (mean age 71.6 ± 10 y; 25% women; CHADS2-VASe score ≥4 (IQR 3-5); prior stroke, 13%; prior major bleeding, 9%) who were allocated to apixaban (n = 51), warfarin (n = 52) or no OAC (n = 48). We completed recruitment in 30 months (allowing for pauses related to the pandemic) and 83% of participants completed follow-up in their assigned treatment arm. Stroke occurred in 2 participants (1 apixaban, 1 no OAC), and 23 participants had at least one bleeding event (12 warfarin, 8 apixaban, 7 no OAC) of which 8 were major (4 warfarin, 2 apixaban, 2 no OAC). Death occurred in 15 participants (9 warfarin, 2 apixaban, 4 no OAC). Time in the therapeutic range for warfarin users was 58% (IQR 47%-79%).

Conclusions: This pilot RCT supports the feasibility of conducting a definitive RCT to inform the effect of OAC on clinical outcomes in dialysis recipients with AF.

Funding: Government Support - Non-U.S.
Impact of Finnerone-Induced Albuminuria Reduction on CKD Outcomes in Type 2 Diabetes: A Causal Mediation Analysis

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Background: In patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), early reduction in urine albumin-to-creatinine ratio (UACR) is associated with improved kidney and cardiovascular outcomes. This post hoc mediation analysis quantified finerenone-induced kidney and cardiovascular (CV) risk reductions over a 4-year period mediated by a change in log UACR between baseline and month 4.

Methods: The analysis used pooled data from two phase 3 trials (NCT02540993 and NCT02545049) investigating the effect of finerenone vs placebo in patients with CKD and T2D. Separate causal mediation analyses were conducted for the composite kidney (kidney failure, sustained creatinine >334 μmol/L) and CV (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) outcomes. The mediated effect of UACR change was analyzed as a dichotomous variable, the proportions mediated were calculated as the difference between the dapagliflozin-group (n=146) or control-group (n=148). The mean age was 72.1 years and 29% were female. The mean HbA1c was 6.9%, mean NT-proBNP was 429.1 pg/mL, mean estimated GFR was 65.7 ml/min/1.73 m², and median UACR was 25.0 mg/g Cr in the dapagliflozin-group and 25.6 mg/g Cr in the control-group. In the dapagliflozin-group, when 122 patients completed the study, the 107 (87.7%) who had been taking dapagliflozin for at least 1 year were included in the post hoc analysis. The primary outcome was the changes in UACR from baseline after a two-year observation, and the secondary endpoints were cardiovascular (CV) events and parameters related to HF.

Results: Between May 2017 and March 2020, 294 patients were randomly assigned to the dapagliflozin-group (n=146) or control-group (n=148). The mean age was 72.1 years and 29% were female. The mean HbA1c was 6.9%, mean NT-proBNP was 429.1 pg/mL, mean estimated GFR was 65.7 ml/min/1.73 m², and median UACR was 25.0 mg/g Cr in the dapagliflozin-group and 25.6 mg/g Cr in the control-group. In the dapagliflozin-group, when 122 patients completed the study, the 107 (87.7%) who had been taking dapagliflozin for at least 1 year were included in the post hoc analysis. The primary outcome was the changes in UACR from baseline after a two-year observation, and the secondary endpoints were cardiovascular (CV) events and parameters related to HF.

Conclusions: In patients with CKD and T2D, early albuminuria reduction with finerenone mediated a large proportion of the treatment effect against CKD progression and a modest proportion of the effect against CV outcomes.

Funding: Commercial Support - Bayer AG.
blood pressure (SBP), eGFR, total insulin dose, adjudicated severe hypoglycemia (SH) and DKA were compared to placebo in 1 patient subgroup with TID and CKD (eGFR <60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g).

Results: In the 1575 patients, 237 (15%) had CKD. At baseline, patients with CKD were older, had longer TID duration, lower eGFR, lower insulin pump use, higher total daily insulin dose, SBP, and UACR compared to the overall cohort. Relative to placebo, treatment with SOTA provided similar significant reductions in A1C, SBP and BW in the CKD and overall cohorts, but numerically smaller % reduction in total insulin dose at week 24 in the CKD cohort (Table 1). SOTA vs placebo was associated with lower SH and higher DKA risk. However, the relative risk of SH and DKA appeared to be lower in the CKD vs. overall cohort over 52 weeks (Table 1). The expected acute eGFR decline followed by stabilization with SOTA was preserved in the CKD cohort.

Conclusions: In patients with TID and CKD, treatment with SOTA had similar A1C and SBP lowering effects, and a lower relative risk of SH and DKA vs. the overall cohort.

Funding: Commercial Support - Lexicon Pharmaceuticals

Xiao.12

Background: Patients with chronic kidney disease (CKD) and hypertension (HTN) are at high risk for kidney failure and cardiovascular morbidity and mortality. Although both CKD and uncontrolled HTN are not difficult to diagnose, both often go unrecognized by primary care physicians (PCPs).

Methods: We conducted a pragmatic, randomized controlled trial involving PCPs and their patients in an academic medical center. Individual PCPs were randomized to intervention or usual care. All adult patients with a visit to a PCP were eligible and those with evidence in the electronic health record of CKD and uncontrolled HTN were automatically enrolled. The intervention consisted of a clinical decision support (CDS) intervention that delivered anti-hypertensive treatment recommendations (renin-angiotensin-aldosterone system (RAAS) inhibitors or hydrochlorothiazide for those on maximal RAAS inhibition). The primary outcome was the change in mean systolic blood pressure (SBP) between baseline and 180 days compared between arms. A secondary outcome was orders placed for recommended anti-hypertensive medications.

Results: The study included 184 PCPs and 2026 patients. Patient mean age was 75.3 years; 60% were female, and 71% were White. 80% of patients had an SBP measurement at 180 days +/− 60 days. We observed a 2.9 mmHg greater reduction in SBP in patients in the CDS intervention arm compared to usual care (95% CI 2.7,4.53; p=0.005). PCPs also placed more orders for recommended anti-hypertensive medications in the intervention arm (Table 1; p=0.0001).

Conclusions: A CDS intervention resulted in a clinically significant decrease in mean systolic blood pressure in a pragmatic clinical trial in a primary care setting.

Funding: NIDDK Support

Table 1: Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Measurement Variable</th>
<th>Intervention</th>
<th>Usual Care</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>124.2±19.7</td>
<td>127.1±18.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77.8±12.3</td>
<td>79.8±11.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>72.6±10.5</td>
<td>74.1±9.9</td>
<td>0.002</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>5.9±0.9</td>
<td>6.1±0.9</td>
<td>0.002</td>
</tr>
<tr>
<td>UACR (mg/g)</td>
<td>2.4±1.7</td>
<td>2.8±1.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SBP - Systolic Blood Pressure, CI - Confidence Interval, ACE - Angiotensin Converting Enzyme Inhibitor, ARB - Angiotensin Receptor Blocker, HCTZ - Hydrochlorothiazide
TH-PO1148

Abstract Withdrawn

TH-PO1149

Real-World Effectiveness of SGLT2 Inhibitors on the Progression of Kidney Disease in Non-Diabetic CKD Patients with and without Albuminuria

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Background: In renal outcome trials, SGLT2 inhibition slows the progression of kidney injury in patients with and without type 2 diabetes (T2D). It is imperative to examine the real effects of SGLT2 inhibition specifically among patients with chronic kidney disease (CKD) without T2D in a real-world setting.

Methods: We collected de-identified data on adult patients without diabetes who had an estimated glomerular filtration rate (eGFR) of 25-60 ml/min/1.73m² and initiated SGLT2 inhibitor (SGLT2i) dapagliflozin or empagliflozin between 9/2020-11/2022 in Maccabi Healthcare Services, a large Israeli health maintenance organization. We assessed the effect of SGLT2i on renal function, measured as the change in eGFR slope over time. The index date was defined as the date of the first dispensing of SGLT2i. Annual baseline slope was calculated by using all eGFR measurements within 2 years prior to index date (median of 7 measurements), while annual follow-up slope was calculated by using all evaluations during 90-900 days after index date (median of 5 measurements). For both slope, we used t-test to compare differences between baseline & follow-up annual slopes.

Results: This analysis included 354 patients with CKD without T2D who received SGLT2i & were followed for a median of 527 days. The mean age was 72.8±7.7 ml/min/1.73m² per year after SGLT2i administration, (p<0.001). The primary outcomes were endothelial function and aortic stiffness determined from brachial artery flow-mediated dilation (FMD) and carotid-femoral pulse wave velocity (cPWV), respectively. Our secondary outcomes were endothelium-independent dilation via nitroglycerin mediated dilation and cognitive function assessed via the NIH Toolbox Cognition Battery.

Results: 75% of the patients were male, 56% had diabetes, and 15% had a history of CVD. The mean±SD age and eGFR were 69±7.4 years and 34.7±10.8 ml/min/1.73m², respectively. The median (IQR) UACR was 91 (31.0-417.3). Following 12-months of curcumin supplementation, we observed no change in brachial artery FMD, nitroglycerin mediated dilation, or cPWV (P=0.05; Table 1). Additionally, we observed no change in processing speed, executive function, memory, or language (P=0.05; Table 1).

Conclusions: 12-month curcumin supplementation did not change vascular or cognitive function in patients with CKD.

Funding: Other NIH Support - NHLBI

Change in primary and secondary outcomes according to study group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Placebo</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change</td>
<td>(±)</td>
<td>(±)</td>
<td>±</td>
</tr>
<tr>
<td>PMI %</td>
<td>0.7 (0.1, 3.0)</td>
<td>1.1 (0.2, 5.2)</td>
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</tr>
<tr>
<td>cPWV, m/s</td>
<td>8.0 (5.1, 12.4)</td>
<td>8.0 (5.1, 12.4)</td>
<td>0.05</td>
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<tr>
<td>Nitroglycerin dilation, %</td>
<td>1.2 (0.1, 3.5)</td>
<td>1.3 (0.2, 3.5)</td>
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</tr>
<tr>
<td>Processing speed, ms</td>
<td>0 (24, 10)</td>
<td>0 (24, 10)</td>
<td>0.15</td>
</tr>
<tr>
<td>Executive function, ms</td>
<td>2.6 (0.1, 8.0)</td>
<td>2.6 (0.1, 8.0)</td>
<td>0.04</td>
</tr>
<tr>
<td>Memory, ms</td>
<td>2.6 (0.1, 8.0)</td>
<td>2.6 (0.1, 8.0)</td>
<td>0.53</td>
</tr>
<tr>
<td>Language, ms</td>
<td>2.6 (0.1, 8.0)</td>
<td>2.6 (0.1, 8.0)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

²Age-adjusted T-score

TH-PO1150

Effect of Curcumin on Vascular and Cognitive Function in CKD: A Randomized Controlled Trial

Colin J. Gimblet,¹ Nicholas T. Kruse,² Katharine M. Geasland,² Jeni Michelson,³ Mingyao Sun,³ Patrick Ten Eyck,³ Meenakshi Sambhar,³ Matthew Rossman,³ Carinda Linkenmeyer,³ Manjula Tamura,³ Michel Chonochol,³ Douglas R. Seals,³ Karin Hoth,² Diana Khalil,³ 1Internal Medicine, The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA; 2Central Michigan University, Mount Pleasant, MI; 3Institute for Clinical and Translational Sciences, The University of Iowa Roy J and Lucille A Carver College of Medicine, Iowa City, IA

Background: Chronic kidney disease (CKD) increases the risk of developing cardiovascular disease (CVD) and cognitive impairment. Curcumin is a polyphenol that has been reported to improve vascular and cognitive function in middle-aged and older adults, however its effects on vascular and cognitive function in patients with CKD are unknown. We hypothesized that 12-month curcumin supplementation would improve vascular and cognitive function in patients with CKD.

Methods: 88 adults with CKD (stage 3B or 4) participated in a 12-month, randomized, double-blind, placebo-controlled, parallel-arms intervention to examine the effects of curcumin (Longvida® 2000 mg/day) on vascular and cognitive function. Our primary outcomes were endothelial function and aortic stiffness determined from brachial artery flow-mediated dilation (FMD) and carotid-femoral pulse wave velocity (cPWV), respectively. Our secondary outcomes were endothelium-independent dilation via nitroglycerin mediated dilation and cognitive function assessed via the NIH Toolbox Cognition Battery.

Results: 75% of the patients were male, 56% had diabetes, and 15% had a history of CVD. The mean±SD age and eGFR were 69±7.4 years and 34.7±10.8 ml/min/1.73m², respectively. The median (IQR) UACR was 91 (31.0-417.3). Following 12-months of curcumin supplementation, we observed no change in brachial artery FMD, nitroglycerin mediated dilation, or cPWV (P=0.05; Table 1). Additionally, we observed no change in processing speed, executive function, memory, or language (P=0.05; Table 1).

Conclusions: 12-month curcumin supplementation did not change vascular or cognitive function in patients with CKD.

Funding: Other NIH Support - NHLBI
**Control of Secondary Hyperparathyroidism with Extended-Release Calcifediol Is Associated with Slower CKD Progression**

Charles W. Bishop, Stephen A. Strugnell, Akhtar Ashfaq, Renal Division, OPKO Health Inc, Miami, FL.

**Background:** Insufficient levels of serum total 25-hydroxyvitamin D (25D) increase the risk of secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (CKD). SHPT develops and advances in most CKD patients because 25D is not reliably raised with cholecalciferol or ergocalciferol. SHPT is associated with accelerated CKD progression and dialysis onset, but mitigation of disease progression by effective control of SHPT has not been previously examined.

**Methods:** Progression rates in estimated glomerular filtration rate (eGFR) were examined post-hoc in 166 patients with vitamin D insufficiency, SHPT and stage 3-4 CKD during 1-year of treatment with extended-release calcifediol (ERC) in pivotal trials (Sprague 2016). ERC was administered daily at 30 mcg, increasing, as needed, after 12 weeks to 60 mcg to achieve a targeted 30% reduction in iPTH. Measurements of eGFR were obtained at baseline (BL) and quarterly intervals, and 25D (DiaSorin), calcium (Ca), phosphorus (P) and plasma intact parathyroid hormone (iPTH; Roche Elecsys) at BL and monthly. Mean BL or quarterly iPTH levels of ≤100 pg/mL were considered “controlled” and, if maintained at 4 of these 5 assessments, “consistently controlled”.

**Results:** ERC treatment increased mean (±SE) serum 25D from 20.1±0.4 ng/mL at BL to 77.8±2.0 at end of treatment (EOT; p<0.001) and decreased mean iPTH from 146.6±4.7 pg/mL at BL to 104.4±6.5 at EOT (p<0.001) without clinically meaningful changes in mean serum Ca or P. Decreases in mean iPTH were unaffected by BL Ca or P. Average eGFR decline was 2.3±5.5 ml/min/1.73m² over the 1-year treatment period but differed significantly and proportionally with duration of iPTH control, being maximal (4.1±0.7) in subjects who never achieved control (n=44) and minimal (0.6±1.2) in subjects achieving consistent control (n=51; p<0.05). The number of subjects achieving an increase in eGFR by EOT rose in proportion to the duration of iPTH control achieved from 6 (no control) to 18 (consistent control).

**Conclusions:** A post-hoc analysis of pivotal clinical trial data with ERC indicates that early, sustained, effective treatment of SHPT is associated with mitigation of eGFR decline in patients with insufficient 25D and stage 3-4 CKD. Prospective studies with ERC are warranted to confirm these findings.

**Funding:** Commercial Support - OPKO Health

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**Real-World Effectiveness of Finerenone in Chinese CKD Patients Without Type 2 Diabetes**

Li Zhou, Wenge Li, China-Japan Friendship Hospital, Beijing, China.

**Background:** No evidence has been reported for using finerenone in non-diabetic chronic kidney disease (CKD), although it is proven effective and safe for patients with CKD and type 2 diabetes (T2D).

**Methods:** This real-world retrospective study included Chinese CKD patients without T2D between November 2022 and August 2023. Patients received standard CKD treatment plus finerenone at dose of 10 or 20 mg once daily. Urinary albumin to creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and serum potassium (sK) were examined at baseline, 1 month, and 3 months after treatment.

**Results:** Totally 16 patients were analyzed (mean age: 55.38±14.37 years; 12 (75.0%) males) (Table 1). UACR was remarkably reduced compared to baseline at 1 month post-treatment and further reduced at 3 months post-treatment, with a median reduction of 200.41 mg/g (IQR, 84.04-1057.10; P<0.028; percent change, 44.52% [IQR, 31.79%-65.42%]) (Figure 1a). No significant eGFR decline was observed through 3 months follow up(Figure 1b). sK levels remained within the range of 3.5-5.5 mmol/L with only minor fluctuations compared to baseline (Figure 1c). No treatment discontinuation or hospitalization due to hyperkalemia occurred.

**Conclusions:** Finerenone showed good effectiveness and safety in CKD without T2D patients in 3 months follow up. It should be verified by Future large prospective studies.

**Funding:** NIDDK Support

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**Heart Failure and Edema Events Associated with Sodium Zirconium Cyclosilicate vs. Patiromer Treatment**

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**Background:** Sodium zirconium cyclosilicate (SZC) and patiromer (PAT) are potassium binders that differ by exchange ion, sodium, and calcium, respectively. There is limited data on whether using sodium exchange could impact the risks of hospitalizations for heart failure (HHF) or severe edema in patients with hyperkalemia. We assessed the occurrence rates of pre-specified major encounters potentially related to electrolyte-/fluid-related admissions when stratified by new users of PAT or SZC.

**Methods:** Using Cerner Real World Data, we conducted a retrospective cohort study among patients who were newly initiated on SZC or PAT between June 1, 2018, and December 31, 2021. Adults (a 18 years) were followed from their first SZC or PAT prescription (index date) until the end of the 6-month follow up period. We analyzed the occurrence of pre-specified outcomes, discontinuation of or switch from index medication or death. Based on baseline demographic and clinical characteristics, 1 PAT initiator was propensity score matched with 2 SZC initiators. Primary outcomes were any HHF, primary HHF, major edema encounter (MEE), or death. Cox Proportional Hazard regression models were used to estimate the association between SZC or PAT use and each outcome in the overall population and subgroups with/without prior heart failure (HF).

**Results:** The final cohort included 9,929 PAT initiators matched to 19,849 SZC initiators. Mean age was 66 years old; about 50% had a history of chronic kidney disease stages 3-5, and 34% a history of HF. Incidence rates (IR) and risks of all outcomes: HHF (any/primary), MEE, and death were significantly higher in the SZC cohort compared to the PAT cohort. These findings were consistent among subgroups with/without prior HF (Fig. 1).

**Conclusions:** In this real-world data, SZC use (vs. PAT) is associated with increased risk of pre-specified encounters potentially sodium-/fluid-related, including among patients with/without pre-existing HF.

**Funding:** Commercial Support - Vifor

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

Underline represents presenting author.
TH-PO1155

Hexosaminidase Fyrate (SNF472) for Treatment of Calciphylaxis
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Background: Calciphylaxis (or calcific uremic arteriolosclerosis) is a rare serious condition with no approved therapies characterized by severely painful ischemic skin lesions due to calcification in arterioles. CALCIPHYX was a phase 3, randomized, double-blind, placebo-controlled trial of hexosaminidase fyrate, or SNF472, a selective inhibitor of vascular calcification, in patients on maintenance hemodialysis with calciphylaxis.

Methods: Adults with ≥1 ulcerated calciphylaxis lesion and Pain VAS score ≥50/100 received SNF472 7 mg/kg or placebo IV during hemodialysis 3 times weekly for 12 weeks. Alternate primary efficacy outcomes were BWAT-CUA (an 8-item modification of the Bates-Jensen Wound Assessment Tool to assess relevant features of calciphylaxis) and Pain Visual Analog Scale (VAS). Safety outcomes included CUA wound-related complications.

Results: A total of 148 patients were screened, 71 were enrolled, and treatment was completed by 34 (91.9%) and 26 (76.5%) subjects in the SNF472 and placebo groups, respectively. At baseline, mean (SD) BWAT-CUA score was 19.8 (5.2), Pain VAS was 69.1 (27.9), and 69.0% of patients were treated with sodium thiosulfate. At Week 12, mean (SD) absolute change from baseline in BWAT-CUA was -5.3 (5.2) in the SNF472 group and -6.0 (6.2) in the placebo group, corresponding to a LS mean (SE) difference of 0.27 (1.33) (95% CI: -2.46, 3.00; p=0.88). Mean (SD) change from baseline in Pain VAS was -19.5 (26.9) in the SNF472 group and -32.2 (38.5) in the placebo group, corresponding to a LS mean (SE) difference of 11.49 (7.93) (95% CI: -4.80, 27.78; p=0.15). SNF472 was safe and well tolerated. Adverse events (AEs) leading to death were less frequent in patients randomized to SNF472: 1 (2.6%) vs. 6 (18.2%) in patients randomized to placebo. CUA wound-related AEs (11 [29.9%] vs. 16 [48.5%]) and wound-related infections (1 [2.6%] vs. 7 [21.2%]) were also less frequent in patients randomized to SNF472.

Conclusions: CALCIPHYX did not meet either alternate primary efficacy outcome. BWAT-CUA and Pain VAS improved similarly in both groups. There were numerically fewer AEs leading to death and CUA-wound related events and infections in patients treated with SNF472 compared to placebo. Detailed primary and post-hoc analyses will be presented.

Funding: Commercial Support - CSL Vifor

TH-PO1157

A Randomized, Controlled, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of Lower Starting Dose Roxadustat for Anemia Treatment in Patients with CKD Not on Dialysis
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Background: Roxadustat is approved in China for chronic kidney disease (CKD)-associated anemia (CKD-anemia) treatment with and without dialysis. We assessed the non-inferiority of lower starting dose (LSD) roxadustat versus standard starting dose (SSD) for stage 3–5 CKD-anemia treatment without dialysis.

Methods: In this non-inferiority trial, patients were randomized (1:1) to a weight-based SSD (<60 kg: 70 mg three times per week [TIW]; ≥60 kg: 100 mg TIW) or LSD (<60 kg: 50 mg TIW; ≥60 kg: 70 mg TIW). Treatment was for 16 weeks (assessments every 2 weeks for 8 weeks, then every 4 weeks). The primary efficacy endpoint was the mean hemoglobin (Hb) change from baseline across weeks 12–16. Adverse events (AEs) were assessed during the treatment period and 4 weeks after completion.

Results: In total, 254 patients were randomized. The SSD (n=128) and LSD (n=126) groups had comparable baseline characteristics. The baseline Hb was 89.4 g/L (7.0) for SSD & 90.6 g/L (6.7) for SSD. In the per protocol set (PPS) (n=226), the mean Hb change from baseline over 12–16 weeks was 21.6 g/L for SSD and 26.4 g/L for SSD (<4.78 g/L, 95% confidence interval [CI]: -1.77 to -1.79 g/L [-5.8 g/L non-inferiority margin]). In the PPS, 47.8% of the SSD patients achieved Hb 100–120 g/L over weeks 12–16 versus 47.7% for the SSD (odds ratio 1.158, 95% CI 0.671 to 1.996; P=0.60). The full analysis set (n=249) had similar results. The LSD group had significantly lower rates of change in Hb from baseline to weeks 6 (P=0.03), 8 (P<0.05), and 16 (P=0.01). There were 3 (2.4%) of the SSD & 2 (1.6%) of the SSD patients received rescue therapy. In the safety set (n=250), 68.0% of patients had treatment-emergent AEs (LSD 72.2%; SSD 63.7%). The proportions of treatment-emergent serious AEs (24.6% vs 10.5%) and drug-related AEs (4.0% vs 2.4%) were numerically higher with the LSD than the SSD.

Conclusions: Non-inferiority was not established for the LSD compared with the SSD in stage 3–5 CKD non-dialysis patients. The proportion of patients who achieved Hb 100–120 g/L over weeks 12–16 for both groups was similar; patients receiving the SSD had less Hb fluctuation. Both dosages were well tolerated, however, SSD did not show a better safety profile.

Funding: Commercial Support - Beijing Municipal Science & Technology Commission (Z191100007619054) and FibroGen China co-funded this study. This study was sponsored by the Chinese PLA General Hospital and FibroGen (China) Medical Technology Development Company Limited (FibroGen China).

TH-PO1156

Targeting Vascular Calcification in Calciphylaxis

Background: Despite recent advances in the understanding of calcification inhibitors, there is no approved therapy for calciphylaxis-- a serious vascular calcification disorder that predominantly affects patients with end stage kidney disease. We sought to examine the link between pharmaceutical strategies targeting vascular calcification (vitamin K, intravenous sodium thiosulfate, intralesional sodium thiosulfate, bisphosphonate, and calcimimetics) and clinical outcomes in calciphylaxis.

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

B17
TH-PO1158

CER-001, an Engineered High-Density Lipoprotein, Shows Beneficial Pleiotropic Effects in Patients with Sepsis in RACERS: A Phase 2A Randomized Control Trial

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Background: The cytokine storm, an excessive immune response in sepsis, leads to acute kidney injury (AKI) and multi-organ failure. Our recent research highlighted the diverse properties of HDL, including LPS scavenging, anti-inflammatory effects, and preservation of endothelial integrity in an LPS-induced AKI swine model. Subsequently, we investigated the effects of CER-001, an apoA-I-containing engineered HDL, in a Phase 2a clinical trial.

Methods: We conducted an open-label, randomized, dose-ranging trial (RACERS study, N° EUDRACT 2020-004202-60) in 20 septic patients with intra-abdominal infection or urosepsis. Patients were randomized to receive standard of care (SOC; n=5) or SOC + CER-001 (5 mg/kg BID, 10 mg/kg BID, or 20 mg/kg BID; n=5 per group) on days 1, 2, 3, and 6. The primary outcomes were safety and efficacy in preventing AKI onset and/or progression, while secondary outcomes included changes in inflammatory and endothelial dysfunction markers.

Results: Patients were enrolled from the ICU and Nephrology Unit during the early phase of sepsis (median time from hospital admission: 2 days). CER-001 treatment was well tolerated, and no serious adverse events were attributed to its use. Rapid normalization of apoA-I levels with CER-001 was associated with significant and sustained LPS removal (p<0.05 on days 3, 6 and 9) and subsequent immunomodulation. CER-001 treatment led to rapid and significant decreases in pro-inflammatory cytokines (e.g., IL-6, IL-8, TNF-α, MCP-1), endothelial dysfunction markers (sVCAM, sICAM) and mortality biomarker (sTREM-1), resulting in improved clinical outcomes regardless of sepsis type or severity. CER-001-treated patients had a reduced risk of developing or progressing to severe AKI and, in a subset of critically ill patients, a shorter ICU stay and decreased need for organ support.

Conclusions: CER-001 replicates the beneficial pleiotropic effects of natural HDL by scavenging LPS, reducing inflammation, and protecting the endothelium. Therefore, CER-001 represents a promising therapeutic strategy for sepsis management, improving outcomes and mitigating the cytokine storm and associated organ damage often observed in our patients.

Funding: Commercial Support - Abionyx Pharma SA

TH-PO1159

Abstract Withdrawn

TH-PO1160

Results of a Randomized Placebo-Controlled Double-Blind Adaptive Phase 2 Study (AKITA) Evaluating RMC-035 for the Prevention of AKI in Patients Undergoing Cardiac Surgery

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Background: Acute Kidney Injury (AKI) is a common and serious complication following cardiac surgery and is associated with multiple acute and long-term kidney-related adverse outcomes, such as renal replacement therapy, irreversible loss of kidney function, progression of preoperative chronic kidney disease (CKD) and transition to End Stage Kidney Disease (ESKD). RMC-035 is a recombinant, modified therapeutic protein, mimicking endogenous Alpha-1-Microglobulin, that harbors potent anti-oxidative and heme-binding capacity.

Methods: Global multi-center Phase 2 randomized double-blind adaptive design parallel group study in patients at high AKI risk undergoing open-chest coronary bypass and/or valve surgery with use of cardio-pulmonary bypass. Enrichment for high AKI risk was accomplished by incorporating mandatory AKI risk factors to the eligibility criteria. Patients with eGFR <30 mL/min were excluded from the study. 177 subjects were randomized 1:1 and treated with either RMC-035 or placebo. Study drug was administered up to 2 days after surgery, in total 5 IV infusions. The primary efficacy endpoint was AKI (KDIGO definition) within 72h after surgery. Important secondary endpoints included eGFR change from baseline up to Day 30/90 and MAKE (Major Adverse Kidney Events), a composite defined by death, any post-surgery dialysis or ≥25% eGFR decline from baseline on Day 30/90.

Results: Efficacy results on AKI, eGFR & MAKE and safety will be shared after availability of top-line results which are expected around September 20.

Conclusions: Conclusions will be shared after availability of top-line results, expected around September 20.

Funding: Commercial Support - Guard Therapeutics